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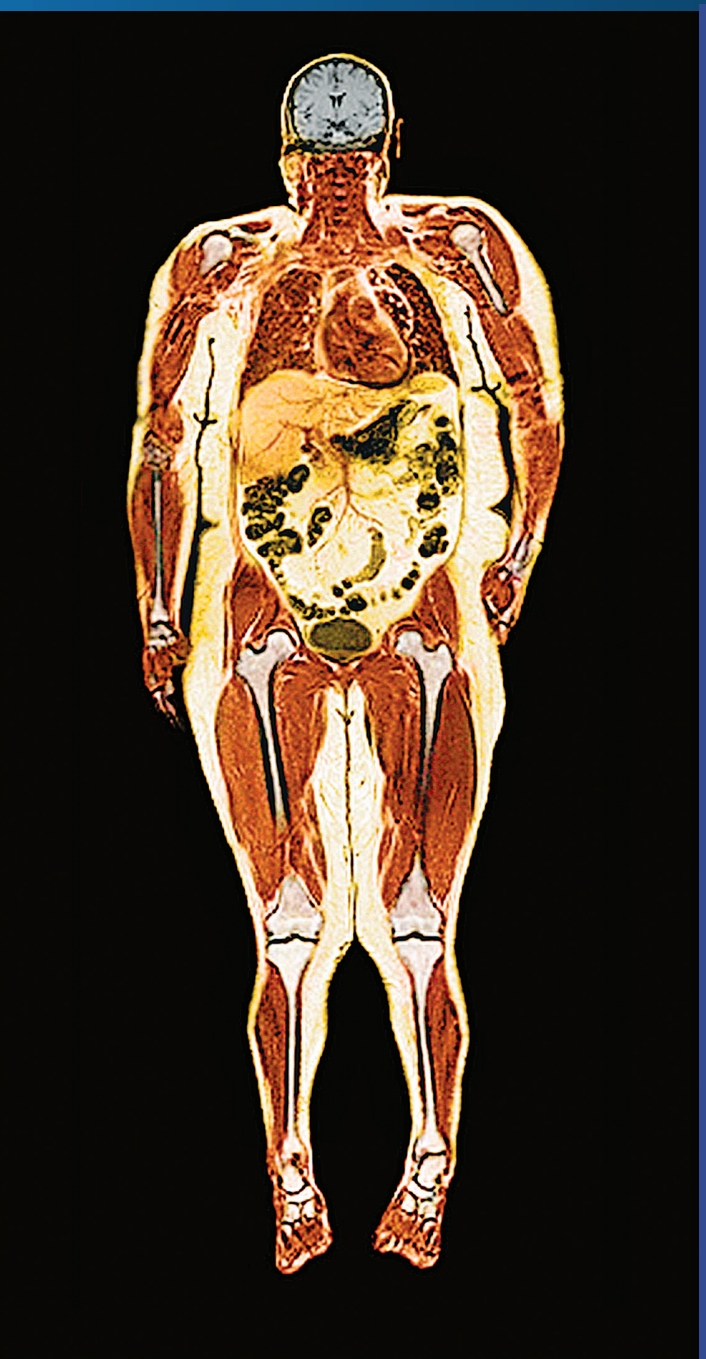
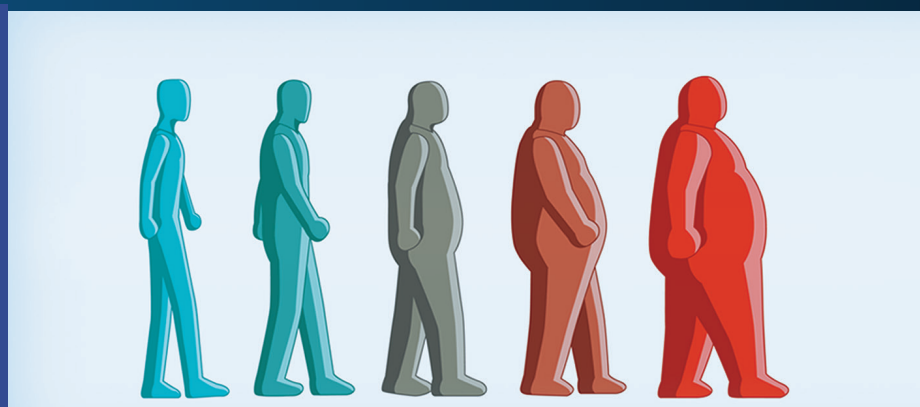
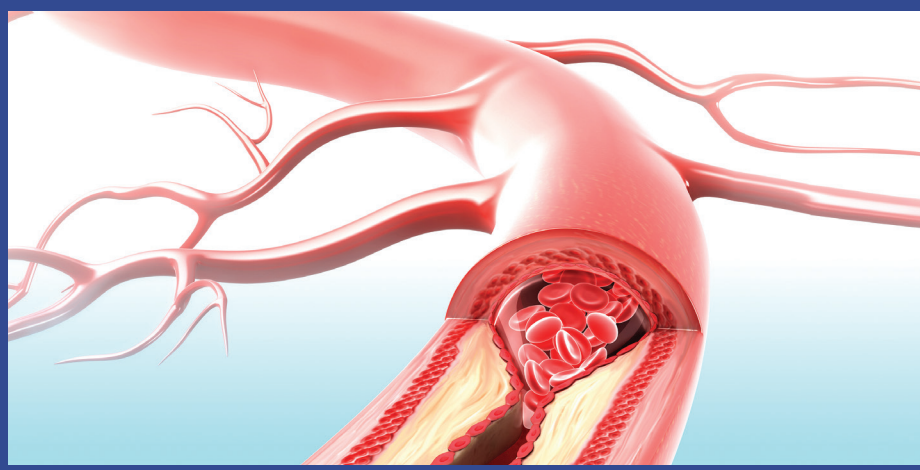
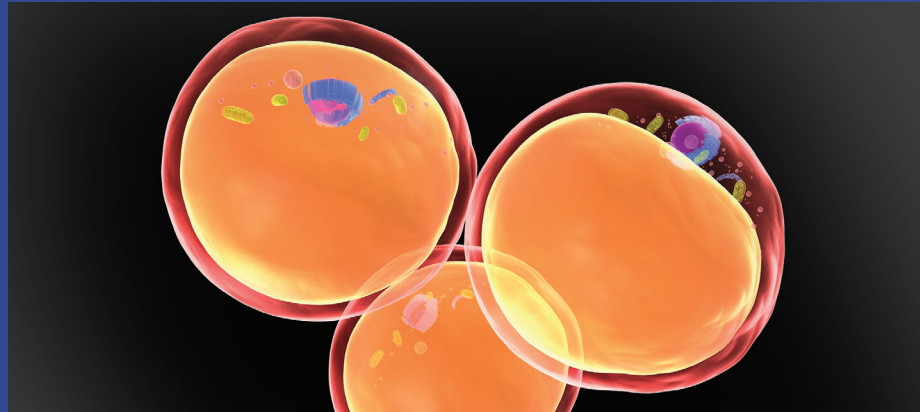
HANDBOOK OF OBESITY

Epidemiology, Etiology, and Physiopathology









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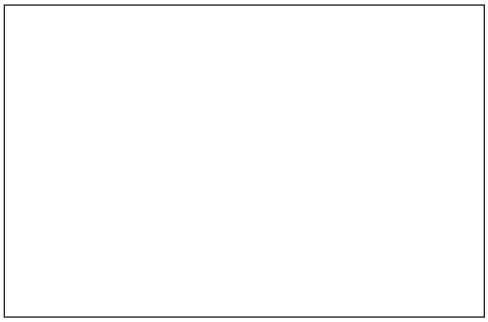

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Preface

It has been 15 years since the first edition of the *Handbook of Obesity* was published, and these years have seen enormous progress in our understanding of the etiology and the causes of obesity as well as innovative approaches to its treatment. We are thus pleased to publish this update of the *Handbook of Obesity* in the form of two coordinated and comprehensive volumes. Shortly after the first edition, translational research took hold and it became evident that the "therapeutic" strategies for treatment of obesity would need more space, and this was accomplished by splitting the second edition into two volumes; subsequently, the therapeutic volume was updated and published separately without the basic science volume. By 2012, the growth of the science underlying the increase in the prevalence of obesity and the emphasis on translation research led to the need for a new edition of each volume with many new authors and entirely new content. For instance, many drugs that were available in 1998 are no longer available now, and new ones have come on the market. In brief, Volume 1 covers the epidemiology, etiology, and physiopathology of obesity and Volume 2 covers the clinical applications associated with translation of basic science into treatment strategies for obesity. With these two volumes, we believe that the reader has access to the latest research and clinical practice in the field.

We are indebted to the authors for maintaining a tight writing schedule so that all chapters would appear in a reasonably short time after submission. We also want to thank Robin Post and Allison Templet for their hard work on the editorial side of this publication. They have facilitated the rapid accretion of chapters and turnaround of the edited papers so that they could get into line for publication. We also thank the publisher, especially Claire Bonnett, senior editor at CRC Press, for helping us move this book from manuscript to the published *Handbook of Obesity* rapidly.

George A. Bray and Claude Bouchard
Pennington Biomedical Research Center

Introduction

The second edition of the *Handbook of Obesity*, Volume 1, published in 2004, included 43 chapters covering the basic science of obesity. In this new edition, Volume 1 covers all the basic science aspects under the broad topic areas of epidemiology, etiology, and pathophysiology of obesity. The content of the volume is detailed in 60 chapters organized around 5 parts. Important advances have occurred over the past decade, and the reader will notice that some of the early topics have been merged and are now addressed together in a single chapter. Some areas have enjoyed significant growth and are now dealt with in multiple chapters; one example is the genetic basis of obesity. The attentive reader will also appreciate that there are many chapters devoted to basic science topics that were not even considered for the 2004 edition. For instance, the current version of Volume 1 includes chapters on epigenetics, the gut microbiome, ectopic fat deposition, viral infection, sleeping habits, transportation policies, environmental pollutants, and inflammation and immune function.

In 2008, on the occasion of the 20th anniversary of the opening of the Pennington Biomedical Research Center, a conference was held with a focus on the 20 most important advances in the field of obesity science that had occurred in the preceding 50 years. A committee of experts (C. Bouchard, G.A. Bray, L.P. Kozak, and E. Ravussin) was given the task of identifying these 20 scientific discoveries or advances in the field. The list of these topics and the papers presented at the Baton Rouge conference can be found in Supplement 7, December 2008, of the *International Journal of Obesity*. As one could predict, many of the topics identified by the committee of experts are now addressed in this new edition of Volume 1 of the *Handbook of Obesity*, but new and exciting topic areas have arisen over the past 4 years and they are also addressed in Volume 1.

It is always a problem for a publication of the magnitude of the *Handbook of Obesity* to be as current as possible. We believe that we have met this challenge successfully in the new edition. The chapters of Volume 1 are organized as follows.

PART I: HISTORY, DEFINITIONS, AND PREVALENCE

Part I is organized around seven chapters. Chapter 1 by George A. Bray identifies the historical references to excess weight or corpulence and the changes surrounding the notion of obesity that have taken place from the early days of *Homo sapiens* to our current era. Chapters 2 and 3 deal with direct and surrogate measurements of traits for adiposity. Chapters 4 through 6 focus on the epidemiology of obesity around the world, in children, and in the elderly. Chapter 7 on gender, ethnic, and geographical variation completes this part of the volume.

PART II: BIOLOGICAL DETERMINANTS OF OBESITY

There are 20 chapters in this part of the volume. Chapters 8 through 10 are devoted to genetic and epigenetic evidence, and they are followed by Chapter 11 on fetal life and early postnatal influences on obesity. Chapters 12 and 13 provide information on nonhuman primates and rodents as models for obesity research, along with discussion on how to address mechanistic questions using these resources. They are followed by Chapters 14 through 16 on the regulation of energy balance at multiple levels. The relationships between the sympathetic nervous system, insulin resistance, and other endocrine determinants are addressed in Chapters 17 and 18. Chapters 19 through 21 examine various aspects of adipogenesis and adipose tissue metabolism. The topics of skeletal muscle biology and molecular aspects of bioenergetics are subsequently addressed in Chapters 22 and 23. In addition, Chapters 24 through 26 cover metabolic rates, energy expenditure, and energy partitioning, respectively. Finally, Chapter 27 reviews the evidence on viral infection and adiposity.

PART III: BEHAVIORAL DETERMINANTS OF OBESITY

Nine chapters in this part are devoted to the behavioral determinants of obesity. Among them, Chapters 28, 29, and 32 relate to food and ingestive behavior. Chapters 30, 31, and 36 deal with smoking and smoking cessation, breastfeeding, and sleep duration and pattern, respectively. To complete this part of the volume, Chapter 33 focuses on sedentary behavior, Chapter 34 on occupational work, and Chapter 35 on leisure-time physical activity and obesity.

PART IV: ENVIRONMENTAL, SOCIAL, AND CULTURAL DETERMINANTS OF OBESITY

Part IV comprises eight chapters. Chapter 37 discusses the role of agriculture and the food industry in the current obesity epidemic in the United States. It is followed by Chapter 38 on transportation policies, Chapter 39 on the urban environment, Chapter 40 on social and economic aspects of obesity, and Chapter 41 on ethnic and cultural differences. The issues of bias and discrimination are considered in Chapter 42. Chapter 43 is devoted to the complex question of environmental pollutants and how they can lead to enhanced fat deposition and obesity. Part IV concludes with Chapter 44 on the direct and indirect economic costs of obesity and associated morbidities.

PART V: CONSEQUENCES OF OBESITY

Part V concludes with 16 chapters dealing with the health consequences of obesity. Chapter 45 focuses on obesity and mortality rates. It is followed by Chapters 46 through 52 addressing the topics of obesity and heart disease, hypertension, lipoprotein metabolism, diabetes, metabolic syndrome, cancer, and inflammation and immunity. The topics of obesity and gallbladder disease, hepatic biology, pulmonary functions, and arthritis and gout are covered in Chapters 53 through 56. Chapters 57 and 58 are focused on mental health and quality of life. Obesity and pregnancy outcomes are addressed in Chapter 59. Finally, the trilogy of obesity, sedentary lifestyle, and low fitness as an unhealthy combination, which dramatically increases the risk of morbidities and premature death, is examined in Chapter 60.

Editors

George A. Bray, MD, MACP, MACE, is former executive director and current Boyd Professor at the Pennington Biomedical Research Center of Louisiana State University in Baton Rouge, Louisiana. He is also a professor of medicine at the Louisiana State University Medical Center in New Orleans, an adjunct professor of physiology in the School of Veterinary Medicine, and an adjunct professor of food science in the College of Agriculture at Louisiana State University. He was the first executive director of the Pennington Biomedical Research Center in Baton Rouge, a post he held from 1989 to 1999. Dr. Bray is a master in both the American College of Physicians and the American College of Endocrinology. He founded the North American Association for the Study of Obesity (NAASO now The Obesity Society), and was the founding editor of its journal, *Obesity*, as well as founder and the first editor of *International Journal of Obesity*, official journal of the International Association for the Study of Obesity, and of *Endocrine Practice*, the official journal of the American College of Endocrinologists.

Professor Bray has received many awards during his medical career. They include the Johns Hopkins Society of Scholars, Honorary Fellow from the American Dietetic Association, Joseph Goldberger Award from the American Medical Association, the McCollum Award from the American Society of Clinical Nutrition, and the Osborne–Mendel Award from the American Society for Nutrition. He has also received the TOPS Award from NAASO, the Weight Watchers Award, the Bristol-Myers Squibb/Mead Johnson Award in Nutrition, and the Stunkard Lifetime Achievement Award. The Obesity Society has even named an award after him—The George A. Bray Founders Award!

Claude Bouchard, PhD, is professor at Pennington Biomedical Research Center, Baton Rouge, Louisiana, and the John W. Barton, Sr. Endowed Chair in Genetics and Nutrition. His research focuses on the genetics of obesity and its comorbidities, as well as on the genetics of adaptation to regular exercise in terms of cardiovascular and diabetes risk factors. Dr Bouchard has authored or coauthored more than 1000 scientific publications and several books and monographs. He is a past president of The Obesity Society from 1991 to 1992 and of the International Society for the Study of Obesity from 2002 to 2006. He also served as president of the Canadian Society for Applied Physiology, and directed the Physical Activity Sciences Laboratory at Laval University, Quebec City, Canada, for over 20 years.

Dr. Bouchard has received numerous awards over the years, including the TOPS, George A. Bray, and Friends of Albert J. Stunkard awards from The Obesity Society; the E.V. McCollum Award from the American Society of Nutrition; the Willendorf Award from the International Society for the Study of Obesity; the Albert Creff Award in Nutrition from the National Academy of Medicine of France; the Honor Award from the American College of Sports Medicine; and the W. Henry Sebrell Award from the Weight Watchers Foundation. He was awarded honoris causa doctorates in science from the Katholieke Universiteit Leuven in 1998, from the University of South Carolina in 2009, from Brock University in 2011, from the University of Guelph in 2011, and from the University of Ottawa in 2012. He was elected Fellow of the American Association for the Advancement of Science.

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Part I

History, Definitions, and Prevalence

1 Obesity Has Always Been with Us
A Historical Introduction

George A. Bray

CONTENTS

We do not live in our own time alone; we carry our history within us.

Gaarder
Sophie's World. A Novel about the History of Philosophy [1]

The history of truth is neither linear nor monotone.

Canguilhem
Ideology and Rationality in the History of the Life Sciences [2]

1.1 INTRODUCTION

Obesity is more evident now than ever before. Its prevalence has been increasing for the past 30 years. People in every country are three to five times fatter now than ever before in history. Yet, historically, obesity has always been with us [3–5]. It thus seems appropriate to begin this *Handbook of Obesity* by tracing the problem of obesity from before the time when words were written down to the present time and to sketch some of the key events in our understanding of this important and timely public health issue. To provide an overview of historical changes related to obesity, I have summarized a number of them in Table 1.1.

Two hundred years ago, Wadd (1776–1829) [6] made this comment about obesity:

> If the increase of wealth and the refinement of modern times, have tended to banish plague and pestilence from our cities, they have probably introduced the whole train of nervous disorder, and increased the frequency of corpulence.

He went on to say:

> It has been conjectured by some, that for one fat person in France or Spain, there are an hundred in England. I shall leave others to determine the fairness of such a calculation.

In the historical records, there is abundant evidence that obesity was a medical and health concern as long as medicine has been practiced, and even before. Treatment for obesity has a similarly long history, although the number of people who might need treatment was smaller than today and probably came from the upper class of society where obesity seems to accompany increased wealth, leisure time, and easier access to food. It is also clear that the type of diet is irrelevant to the development of obesity as it is evident in all cultures, independent of diet.

1.1.1 Obesity in Prehistory

Human obesity is clearly depicted in Stone Age artifacts. The earliest of these Stone Age statues dates from 35,000 years ago [7]. Figurines from 20,000 to 25,000 years ago have been found within a 2000 km band crossing Europe from southwestern France to southern Russia. These Paleolithic or Old Stone Age statuettes were made of ivory, limestone, or terra-cotta. The most famous is the "Venus of Willendorf," an 11 cm figurine that was found in Austria. Typical of many such figurines, this Venus shows marked abdominal obesity and pendulous breasts. Anne Scott Beller [8] has suggested that "obesity was already a fact of life" for Paleolithic humans, although one can only speculate about the purpose or significance of these artifacts.

The New Stone Age or Neolithic period, spanning the interval between 8000 and 5500 BC, saw the introduction of agriculture and domestication of animals, as well as the establishment of human settlements. This era has also yielded numerous statuettes depicting obesity, notably the "mother goddess" artifacts found in the Mediterranean basin. Anthropological studies indicate

TABLE 1.1
Short Summary of Events in the History of Science and Obesity Since 1500 AD

	World Scene	Science and Technology	Biology and Medicine	Obesity
Fifteenth century		Printing		
Sixteenth century		Copernicus (heliocentric theory)	Vesalius (anatomy)	
Seventeenth century		Galileo (telescope)	Harvey (blood circulation)	Santorio (metabolic balance)
		Boyle (laws of temperature and pressure)	Malpighi (pulmonary circulation)	Benvieni (fat dissection)
			Hooke (*Micrographia*)	
	1649: English Civil War	Watt (steam engine)		
Eighteenth century		Photography	Morgagni (first pathology text)	1727: Short (first monograph on corpulency)
		Electrical cell	Lind (*On Scurvy*)	
		Atomic theory	1780: Cullen (classification)	1760: Flemyng second monograph
		Electromagnetism	Oxygen and hydrogen discovered	
	1776: American Revolution			1780s: Lavoisier (oxygen theory of metabolism)
	1789: French Revolution			1810: Wadd (*On Corpulency*)
Nineteenth century	Napoleon	Wohler (urea synthesized from inorganic molecules)	Jenner and vaccination	1826: Brillat-Savarin (*Physiologie du Gout*)
	1861: U.S. Civil War	Mendeleev (periodic table of elements)	Laennec (stethoscope)	1835: Quetelet (BMI)
		Bernard (liver glycogen)	Schwann (cell theory)	1848: Helmholtz (conservation of energy)
		Morphine, cocaine, quinine, amphetamine	Morton (ether anesthesia)	1849: Hassal describes fat cell
		Ions hypothesized	Helmholtz (ophthalmoscope)	1863: Banting (first diet book)
		Internal combustion engine	Darwin (*On the Origin of the Species*)	1866: Sleep apnea described
		Salvarsan	Semmelweis (puerperal fever)	1870: Fat cell identified
Twentieth century		Wright brothers' flight	Lister (antiseptic surgery)	1896: Atwater (room calorimeter)
	Spanish-American War	Vacuum tube	Mendelian genetics	1900: Babinski
		Theory of relativity	Sherrington and reflex arc	1901: Frohlich describes hypothalamic obesity
		Sulfonamides	Secretin—first hormone	1912: Cushing's syndrome
		Nylon	Pavlov identified conditioned reflexes	1914: Gastric contractions and hunger
		DDT	1921: Banting isolates insulin	1932: Garrod and Inborn errors
Twenty-first century	World War I	Vitamins	1928: Fleming finds penicillin	Family study of obesity
		$E = mc^2$—atomic bomb	Operant conditioning	Genetically obese animals
		Quantum physics	Salk/Sabin polio vaccine	Amphetamine used to treat obesity
		Rockets		
	World War II	Transistor		CT/MRI scans for visceral fat
		Laser	Watson Crick DNA hypothesis	DXA and density for body fat
	Vietnam War	CT/MRI scans	AIDS	Doubly labeled water
	Iraq War		Genetic engineering	Leptin 1994
	Afghanistan War		Human genome	Laparoscopic surgery
			Genome-wide screens	Combination therapy
			Functional brain imaging	

that hunter-gatherers are typically lean and that overt overweight is unusual [9], although the enhanced ability to store energy as fat might have clear survival advantages. This fact makes these representations of severe obesity all the more striking.

Almost all of these obese figures are female or their sex could not be identified. Only one male, from Laussel in France, has been noted. Although these figures have been touted as examples of mother goddesses, others interpret them as examples of glandular or endocrine disease evident before recorded history. These figures are distributed worldwide and in all cultures except Africa. The reason for the lack of such figures from Africa is unknown. It could be that obesity did not appear in these cultures because of increased heat. It may be that artists had other things to represent. The high prevalence of obesity in the pre-Columbian statues from Central and South America is consistent with the high prevalence of this problem among the descendents of these pre-Columbian peoples of North and South America. In careful surveys, the prevalence of obesity in Latinos, many of whom are descendants of these early indigenous American peoples, is higher than in those with European ancestry. Although this survey shows us that obesity has a long history, we have no information on how or if it was treated in these early periods.

1.1.2 Obesity in Medical Traditions

Obesity and its sequelae have long figured in the medical traditions of many diverse cultures. Ancient Egyptian stone reliefs show occasional obese people, such as a cook in Ankh-ma-Hor's tomb (Sixth Dynasty; 2340–2180 BC) and a fat man enjoying food presented to him by his lean servant in Mereruka's tomb. Studies of the reconstructed skin folds of royal mummies suggest that some were fat, including Queen Inhapy, Hatshepsut, and King Rameses III [10]. Overall, it appears that stout people were not uncommon in ancient Egypt and were present among the higher classes [11].

1.1.3 Ancient Greece and Rome

The health hazards associated with obesity were well known to the ancient Greek physician Hippocrates (460–377 BCE), who stated that "sudden death is more common in those who are naturally fat than in the lean" [12]. Greek physicians also noted that obesity was a cause of infrequent menses and infertility in women.

To treat obesity, Hippocrates, the "father of medicine," suggested the following:

> [o]bese people and those desiring to lose weight should perform hard work before food. Meals should be taken after exertion and while still panting from fatigue and with no other refreshment before meals except only wine, diluted and slightly cold. Their meals should be prepared with sesame or seasoning and other similar substances and be of a fatty nature as people get thus, satiated with little food. They should, moreover, eat only once a day and take no baths and sleep on a hard bed and walk naked as long as possible. [13]

Some 500 years after Hippocrates, Galen (ca. 130–200), the leading Roman physician of the time, distinguished "moderate" and "immoderate" forms of obesity, the latter perhaps anticipating the "morbid" category of some current classifications.

Obesity was also familiar to Abu Ali Ibn Sina (Avicenna in the westernized version of his name) (980–1037), one of the most prominent figures of the Arabic medical tradition. Avicenna was a prolific and influential author who published the most influential textbook of the Middle Ages called *The Canon of Medicine in Avicenna* [14].

The Hindu physicians Sushrut (Susrata) and Charak (500–400 BC) are credited with very early recognition of the sugary taste of diabetic urine, and they also observed that the disease often affected indolent, overweight people who ate excessively, especially sweet and fatty foods. The seventeenth-century Tibetan medical treatise entitled *The Blue Beryl* recognized obesity as a condition that required treatment through weight loss. The author, Sangye Gyamtso, a noted scholar and the regent of Tibet, wrote that "overeating … causes illness and shortens life span." He made two suggestions for treating obesity, namely, the vigorous massage of the body with pea flour and eating the gullet, hair, and flesh of a wolf (which was also recommended to treat goiter and edematous states):

> [O]vereating … causes illness and shortens life span. It is a contraindication to the use of compresses or mild enemas. For treatment of obesity two suggestions are made … The vigorous massage of the body with pea flour counteracts phlegm diseases and obesity … The gullet hair compress and flesh of a wolf remedy [to treat] goiters, dropsy and obesity. [15]

1.1.4 Obesity after 1500 AD

Figure 1.1 presents a timeline for scientific and historical events related to obesity in the sixteenth century. Vesalius (1514–1564) laid the foundations of modern anatomy with his famous treatise *De humani corporis fabrica* (1543) [16], which was based on his own dissections. The first dissections of specifically obese individuals are attributed to Theophile Bonnet (Bonetus) (1620–1689) [17], which were followed in the eighteenth century by descriptions from Morgagni (1681–1771) [18] and Haller (1708–1777) [19] and in the early nineteenth century by the notable monograph *Comments on Corpulency, Lineaments of Leanness* of Wadd (1776–1829) [20]. Wadd presented 12 cases, 2 of whom had been examined postmortem and were found to have extensive accumulations of fat.

The adipocyte was recognized as a specific cell type when the first substantive textbooks of microscopic anatomy were published in the 1850s, and the growth and development of fat cells were described by Hassall (1817–1894) [21] and by Hoggan and Hoggan [22]. In his early observations on the development of the "fat vesicle" (adipocyte), Hassall suggested that certain types of obesity might result from an increased number of fat cells—the precursor of the concept of "hyperplastic" obesity that twentieth-century workers such as Bjurulf, Hirsh, and Björntorp would later elaborate. Much work was conducted on digestion during the seventeenth and eighteenth centuries, leading in the early twentieth century to the seminal and long-lasting theory that hunger resulted from gastric contractions; this was based on direct measurements of gastric motility and its association with hunger by Cannon and Washburn [23] and independently by Carlson [24].

Figure 1.2 provides another timeline showing scientific and historical events in the seventeenth century.

Observations made in antiquity by Roman and Indian physicians hinted at attempts to distinguish different types of obesity and diabetes. Many classifications of diseases have been proposed, with an early approach by the seventeenth-century English physician Thomas Sydenham (1624–1689) [25].

Perhaps the two best-known systematic classifications of diseases in the late eighteenth century were those of William Cullen (1710–1790) [26], a physician who became professor of medicine, physics, and chemistry in Edinburgh, and the French doctor Sauvages (1706–1767) [27]. Both referred to "polysarcia," from the Greek for "much flesh." In Cullen's work, polysarcia falls in the Order II (Intumescentiae, or swellings)

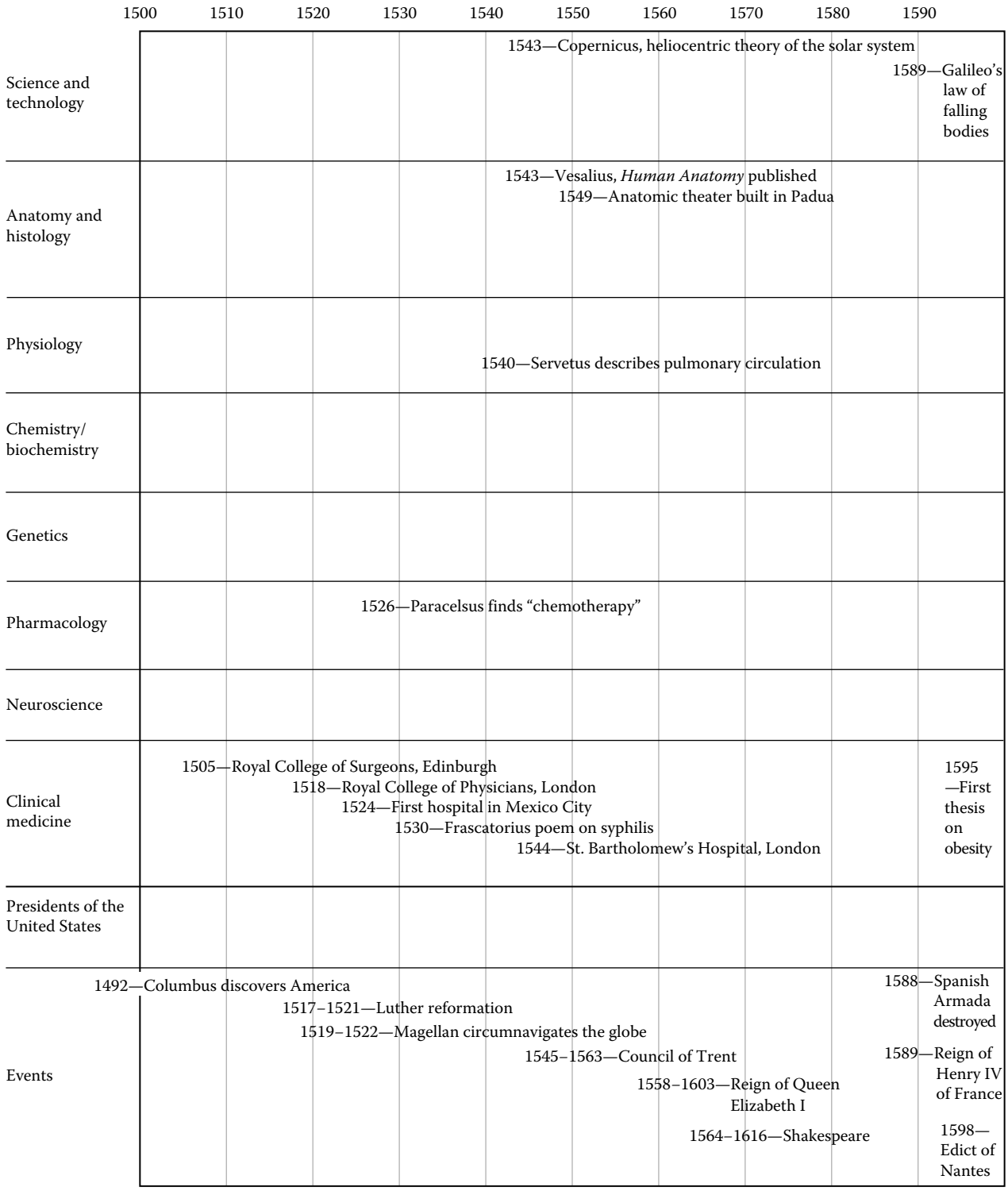

FIGURE 1.1 Timeline of events in the sixteenth century.

of Class III (Cachexiae), with the generic name of *Corporis pinguedinosa intumescentia molesta* ("harmful swelling of the body's fat"). During the nineteenth century, obesity (from the Latin *obesitas* meaning fatness) gradually came to replace polysarcia and other terms such as corpulence and embonpoint.

Figure 1.3 elaborates some of the scientific and medical events related to obesity in a timeline for the eighteenth century. The first monographs devoted to obesity appeared during the eighteenth century. In 1727, Thomas Short (1690 (?)–1772) [28] published the first English language monograph, and a few years later in 1760, Malcolm Flemyng (??–1764) [29] published the second monograph. Short's book opens with the statement: "I believe no age did ever afford more instances of corpulency than our own." He believed that the

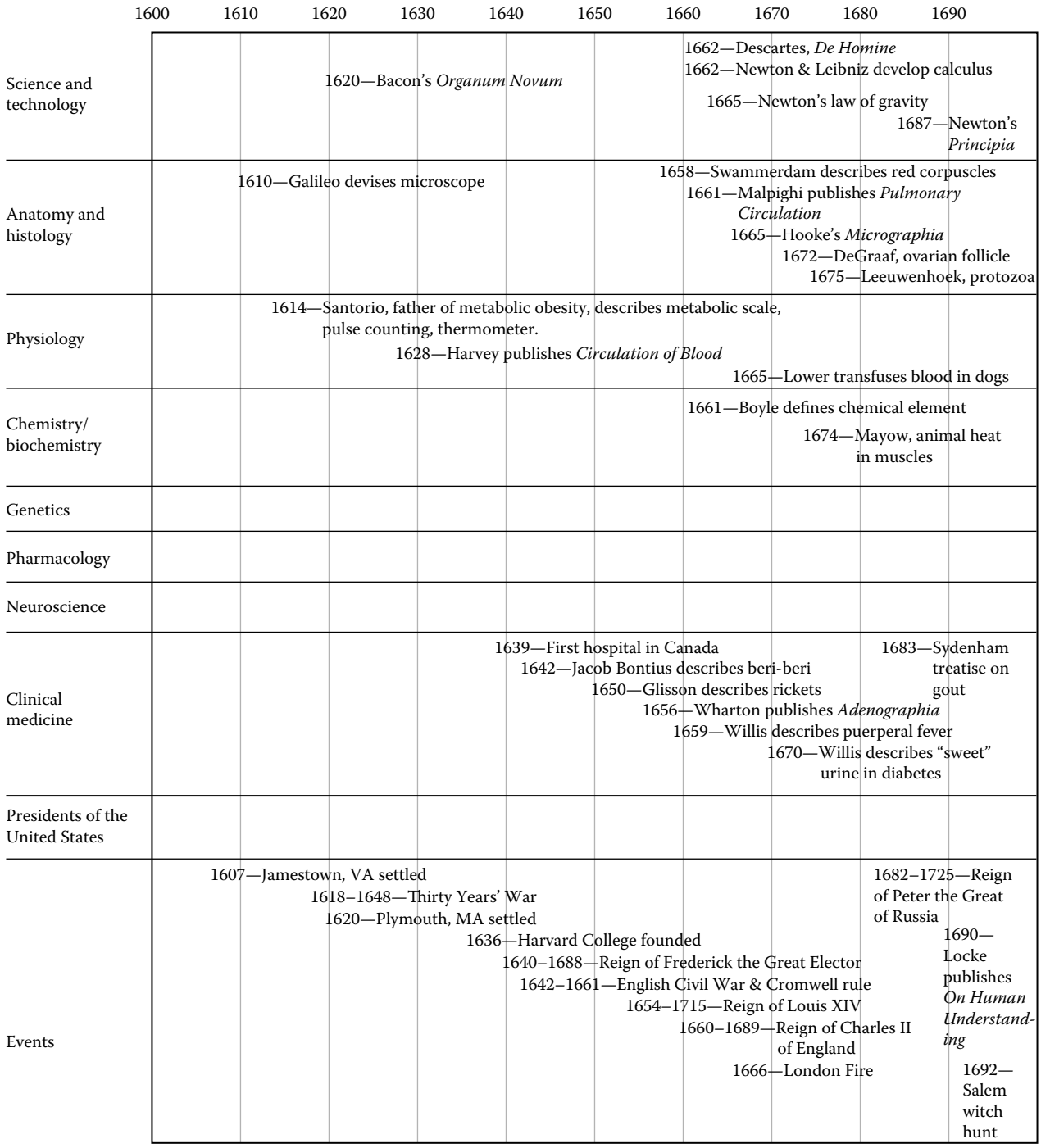

FIGURE 1.2 Timeline of events in the seventeenth century.

treatment of obesity required restoration of the body's natural balance and removal of secondary causes, ideally by living where the air was not too moist or soggy and avoiding flat, wet countries, cities, and woodlands. Short considered that exercise was important and that the diet should be "moderate, spare, and of the more detergent kind." Flemyng listed four causes of corpulency, beginning with "the taking in of too large a quantity of food, especially of the rich and oily kind"—but he did go on to note that not all obese people were big eaters. His second cause of obesity was "too lax a texture of the cellular or fatty membrane … whereby its cells or vesicles are liable to be too easily distended." The third cause was an abnormal state of the blood that facilitated the storage of fat in the vesicles. The fourth cause was "defective evacuation"; Flemyng believed that sweat, urine, and feces all contained oil and, therefore, that obesity could be treated by eliminating this oil through the administration of laxatives, diaphoretics, or diuretics.

There have been numerous attempts to quantify excess weight in ways that are appropriate to clinical practice,

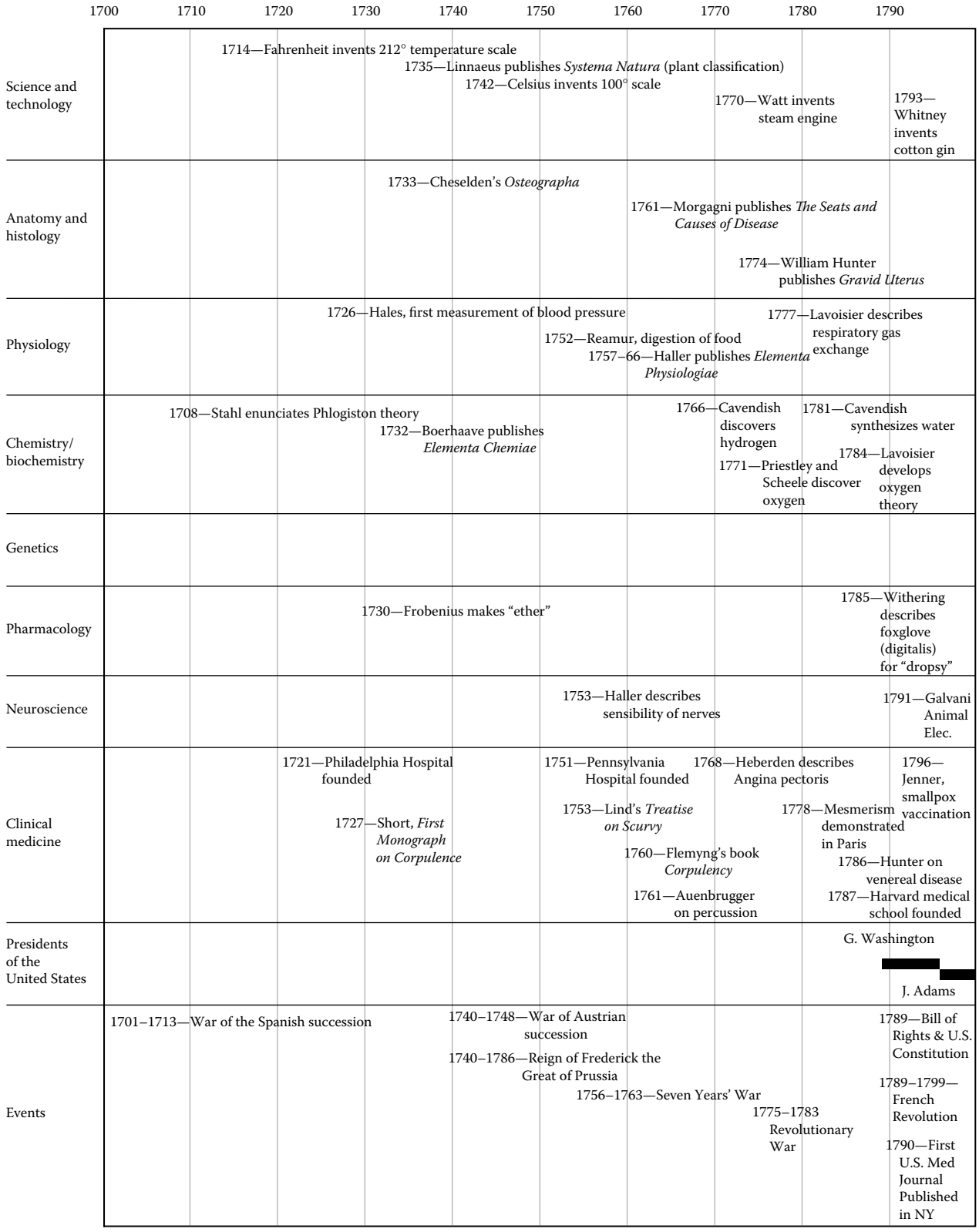

FIGURE 1.3 Timeline of events in the eighteenth century.

research, and epidemiology. Of particular interest has been the relationship between the severity of obesity and the various diseases to which it predisposes. The Belgian statistician and astronomer Adolphe Quetelet (1796–1874) [30] was one of the early leaders in developing and validating mathematical measures of obesity. Quetelet was responsible for the concept of the "average man" and suggested that the ratio of the subject's weight divided by the square of

the height (or stature) could be used as a measure of fatness that corrected for differences in height. This unit, the body mass index (BMI), is also known as the "Quetelet index" in some European countries; it correlates with body fat content and can predict risk for several of the comorbidities of obesity [30].

This and other events in the nineteenth century related to obesity and science are presented in a timeline in Figure 1.4.

The importance of oxygen in metabolism and life itself was first revealed by the work of Robert Boyle (1627–1691) [31], who established the concept of chemical elements. Crucially, Boyle demonstrated that when a lighted candle went out in a closed chamber, a mouse confined to the same chamber rapidly died. This theme was developed a century later by the French chemist Antoine Lavoisier (1743–1794) [32], whose research culminated in the "oxygen theory" that was to prove fundamental to the science of energy balance and obesity. Lavoisier, who was guillotined in 1794 during the French Revolution, recognized that oxidation and combustion both entailed combination with oxygen. He also conducted the first measurements of heat production (calorimetry)—calculated from the weight of ice melted by a guinea pig's respiration—and inferred that metabolism was analogous to slow combustion. In the nineteenth century, Hermann von Helmholtz (1821–1894) [33] and simultaneously Robert Mayer (1814–1878) [34] went on to develop the laws of conservation of mass and of energy. This work ultimately formed the basis for the law of surface area, which was formulated by the German Max Rubner (1854–1932) [35]. Rubner adapted bomb calorimetry, a method developed by Pettenkofer (1818–1901) and Voit (1831–1908) [36], to determine expired carbon dioxide and went on to measure energy expenditure in human subjects and experimental animals. He also observed a consistent linear relationship between energy expenditure and surface area among mammals of diverse species and sizes.

The twentieth century witnessed the application of a wide range of techniques to measure fatness with increasing sophistication and to define the content and distribution of fat throughout the body, as well as its impact on metabolism. These and the other significant events of the twentieth century related to the history and science of obesity are presented in a final timeline in Figure 1.5. Body density (and thus body fat content) was first calculated by applying Archimedes' principle to the difference in body weight when the subject was reweighed under water; the technique has been successfully adapted to the displacement of air rather than water, in the plethysmographic devices in use today. The widespread clinical use of ultrasound, computed tomography (CT) scanning, dual-energy x-ray absorptiometry (DXA), and magnetic resonance imaging (MRI) has shown that all these techniques are useful in measuring aspects of body composition, and the distribution and volume of specific fat depots. In addition, the metabolic impact of obesity, notably the insulin resistance that it induces (see later), has been clarified using a variety of techniques, including the insulin clamp invented by Ralph DeFronzo [37] during the 1970s, the minimal model intravenous glucose tolerance test devised by Richard Bergman [38], and the homeostatic modeling developed by David Matthews during the 1980s.

Interest in the law of conservation of energy, and whether it also applied to humans, stimulated Wilbur Olin Atwater (1847–1907) and Edward D. Rosa [39] to construct the first human calorimeter at Wesleyan College in Middletown, Connecticut, in 1896. By measuring the oxygen consumed by a subject in a sealed chamber, they proved that humans, like all other animals, obey the first law of thermodynamics, namely, the energy expenditure of an individual in steady state equals their energy intake. Their basic concept is perpetuated in the human calorimeters in use today, albeit with much more sophisticated measurements of oxygen consumption and carbon dioxide production that can yield detailed information about minute-by-minute energy expenditure and the utilization of specific macronutrients.

Other refinements the twentieth century has seen in the measurement of energy expenditure in humans have included portable hoods suitable for use at the bedside and the ingenious "doubly labeled water" technique [3]. The latter exploits differences in the ways that the hydrogen and oxygen atoms of the water molecule are metabolized in the body, and from the elimination rates of ^{2}H (deuterium) and ^{18}O after administration of a known dose of $^{2}H_{2}{}^{18}O$, energy expenditure can be calculated. Application of these techniques has helped to unravel the complicated physiology of human energy balance and has confirmed the fundamental principle that obese people in general expend more energy than lean ones and must therefore consume more energy to maintain their higher body weight [40]. Interestingly, it has also been demonstrated that overweight people underestimate their food intake to a greater degree than do lean people. This finding has challenged the validity of a large body of research based on conventional dietary records and has important implications for the practical management of obesity. The organs and tissues that are most metabolically active and responsible for energy expenditure have attracted interest, including as potential sites of defects in energy expenditure that could contribute or lead to obesity.

During the latter half of the twentieth century, much research focused on brown adipose tissue (BAT), or brown fat. This interesting tissue, first described in 1949 by Fawcett and Jones (1949) [41], is extremely rich in mitochondria and owes its brown color to mitochondrial cytochromes. BAT is metabolically highly active and, in lower mammals, is an important physiological defense against cold (and in waking animals from hibernation). Reductions in the thermogenic activity of BAT may contribute to obesity in certain genetic obesity syndromes, such as the *ob*/*ob* mouse and *fa*/*fa* rat. In humans, BAT is present in neonates and remains in lower amounts in adults. BAT oxidizes fatty acids to generate heat rather than adenosine triphosphate (ATP), a property finally explained in the early 1980s when Cannon and colleagues [42] discovered a protein that they named "thermogenin." Thermogenin was shown the following year by Daniel Ricquier et al. [43] in Paris to be a specific uncoupling protein, now termed UCP-1. UCP-1 was shown to "uncouple" fatty oxidation from ATP production

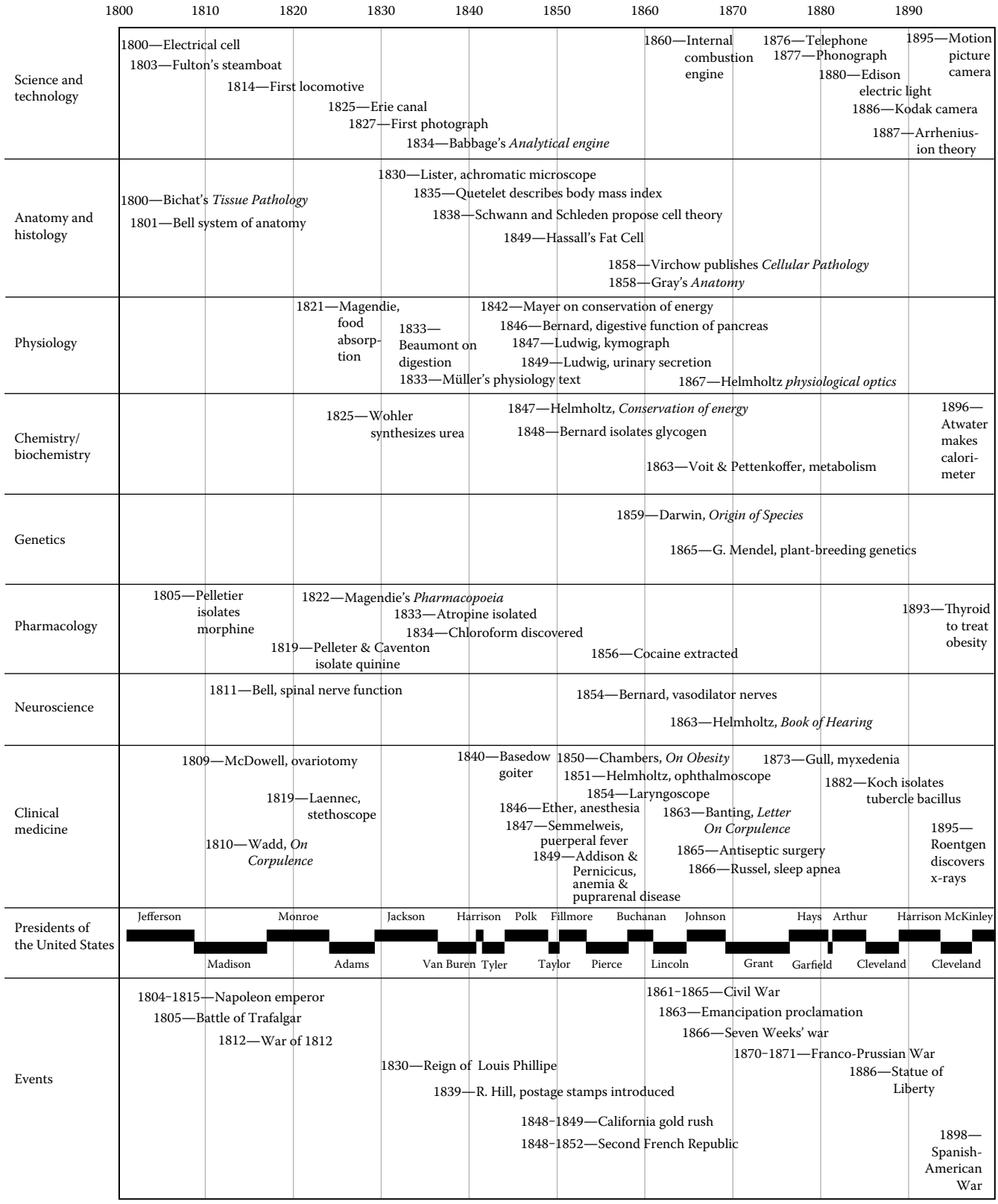

FIGURE 1.4 Timeline of events in the nineteenth century.

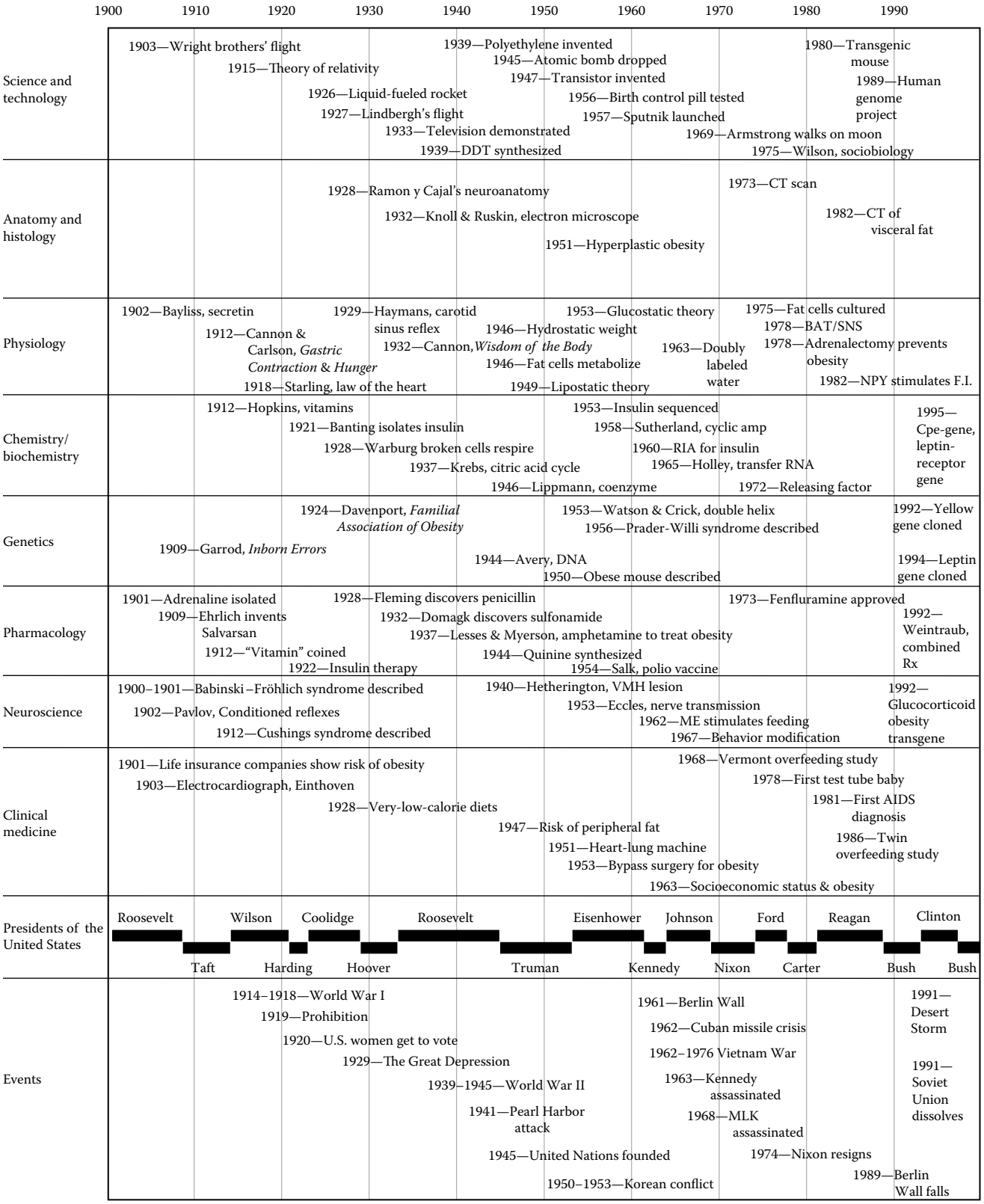

FIGURE 1.5 Timeline for the twentieth century.

by short-circuiting the proton electrochemical gradient across the inner mitochondrial membrane, thus producing heat.

During the nineteenth century, the prevailing concept was that only the macronutrients—carbohydrates, proteins, and fat—were needed to sustain human life. The discovery of vitamins in the early twentieth century overthrew this theory and gave birth to the broader discipline of nutrition [44]. Subsequently, the impact of macronutrients on human health and the development of obesity has returned to center stage through the recognition of the role of dietary fats and simple sugars as causes of obesity and contributors to cardiovascular and other obesity-related diseases.

Ancient clinical observations suggest that obesity was recognized in association with both diabetes and sudden death. The excess mortality in overweight and obese individuals was appreciated in the twentieth century, and the life insurance industry can claim credit for having drawn attention to the relationship between obesity and premature death. As early as 1901, actuarial data showed that excess weight, especially around the abdomen, was associated with a shortened life expectancy. This risk has been confirmed by large numbers of systematic studies in numerous populations, and these led to the World Health Organization classification of obesity, which stratifies increasing degrees of risk according to rising BMI [45]. It has subsequently been modified to make allowance for the increased susceptibility of Asian populations to the adverse effects of obesity.

Although a strong relationship between abdominal obesity and early death could be discerned from the early life insurance data, it was the thorough studies of Jean Vague (1911–2002) [46], working in Marseille, that clearly established the overriding importance of abdominal (central) obesity in conferring excess mortality. Vague's conclusions were clear, but the "adipo-muscular ratio" that he used to distinguish "android" obesity, the abdominal distribution of fat typical of males, from "gynoid" (gluteofemoral) adiposity, characteristic of women, was cumbersome. Simpler measures of abdominal obesity—the ratio of waist circumference to hip circumference, and even waist circumference alone—are now widely used in clinical practice and in research settings. Indeed, cutoff values of waist circumference that indicate increased cardiovascular risk and premature death have been proposed and these appear to be more powerfully predictive than BMI.

Obesity predisposes to type 2 (non-insulin-dependent) diabetes and is largely responsible for the current pandemic of diabetes, which is predicted to double the number of diabetics worldwide in just 30 years, from 150 million in 1995 to over 300 million in 2025. The association between obesity and type 2 diabetes was highlighted in classical studies of isolated ethnic groups that, after centuries of active and frugal existence, had suddenly become sedentary with easy access to food. Notable examples were the Pima Indians living near the Gila River in Arizona and the inhabitants of the Pacific Island of Nauru. Many of the metabolic consequences of obesity have been attributed to decreased sensitivity of various tissues and organs to insulin action ("insulin resistance").

The concept of insulin resistance can be traced back to the English diabetologist Harold Himsworth [47], who in 1936 classified diabetic patients as either insulin sensitive or insulin insensitive according to whether or not their blood glucose level fell after the coadministration of oral glucose and intravenous insulin. The American diabetologist Gerald Reaven [48] coined the phrase "insulin resistance syndrome" or "syndrome X" (now generally known as the "metabolic syndrome") in the late 1980s. However, this concept had been anticipated by Vague some 30 years earlier, who recognized that central obesity was associated with, and predisposed to, diabetes, atherosclerosis, and gout—all core features of the metabolic syndrome. Indeed, the Swedish physician Eskil Kylin (1889–1975) [49] had described the association between hypertension, diabetes, and gout even earlier during the 1920s.

Other comorbidities of obesity have been recognized since antiquity. Associated respiratory problems—possibly reminiscent of the obesity hypoventilation syndrome—were described long ago in the Greco-Roman era [50]. In his novel *The Pickwick Papers*, Charles Dickens describes a character called Joe, the fat boy who has all of the features of the hypoventilation syndrome, which led to the name "Pickwickian" syndrome that William Osler applied to the obesity hypoventilation syndrome. Fatty liver, long recognized as a consequence of overfeeding in geese (*foie gras*) and a feature of human obesity, is also a significant comorbidity that can lead to progressive liver damage.

The importance of overeating and inactivity as causes for the energy imbalance that leads to obesity was recognized by the ancients and has continued to be the underlying basis for this problem to the present day. Many diseases that cause obesity have been identified, and during the past two decades attention has shifted to the nature of the inherited predisposition to obesity and the specific genetic defects that underlie this susceptibility. Syndromes of genetic obesity in other species (especially rodents) have yielded valuable information about the normal regulation of energy homeostasis, and some of these "lessons of nature" have helped to clarify the etiology of certain subsets of human obesity [51].

The role of the brain in controlling body weight, initially highlighted by clinical cases, has been extensively explored. Obesity has been recognized for over 100 years in association with hypothalamic damage (mostly caused by tumors), notably in the "adiposogenital syndrome" (obesity with sexual infantilism) described in 1900 by Joseph Babinski (1857–1932) [52] in Paris and by A. Fröhlich (1871–1953) [53] in Vienna. The co-occurrence of truncal obesity with hypertension and other characteristic features in subjects with a basophil (adrenocorticotropic hormone [ACTH] secreting) tumor of the pituitary was described in 1912 by the American neurosurgeon Harvey Cushing (1869–1939) [54], and the syndrome of glucocorticoid excess now bears his name. These and other clinical observations stimulated interest in the central nervous system (CNS) and especially the hypothalamus, which in turn heralded the development of experimental techniques to produce localized brain damage in animals to identify the regions that control eating and body weight. Damage could

be induced by microinjection of toxins such as chromic oxide or by localized heating or electrolysis produced by special probes. Classical findings included the dramatic hyperphagia and obesity induced by bilateral lesions of the ventromedial hypothalamus, in striking contrast to the loss of appetite and wasting that followed destruction of the lateral hypothalamus. These observations led to Eliot Stellar (1919–1993) [55], in the early 1950s, to advance the "dual center" hypothesis. This proposed that feeding and weight were controlled by the balance between a ventromedial "satiety center" and a lateral hypothalamic "appetite center." This hypothesis shaped thinking about hunger and satiety for over two decades. It is now recognized to be oversimplistic and is referred to as the "old neurobiology" of obesity.

During the 1970s to 1980s, refinements in methods such as radioimmunoassay and immunocytochemistry and the tracing of neuroanatomical tracts helped to identify the neurotransmitters that control energy balance. These neurotransmitters include classical monoamines such as serotonin (whose potent appetite-suppressing action has been exploited in several antiobesity drugs), peptides including the potent orexigen (appetite-stimulator) neuropeptide Y and the anorectic melanocortin α-MSH, and the endocannabinoids that stimulate feeding. Landmark studies include the demonstration by James Gibbs, Young, and Smith [56] in 1973 that injection of cholecystokinin, the gut peptide named for its ability to stimulate gallbladder contraction, powerfully inhibited feeding in rats. This indicated that the gut could communicate through secreted peptides with the CNS to control feeding. Subsequent research has shown that the hypothalamus and other regulatory regions of the brain are surprisingly accessible to circulatory hormones that are now known to signal fat mass and energy needs such as insulin, leptin, and ghrelin.

The first of the animal obesity syndromes to be understood at a molecular genetic level was the yellow obese (Ay) mouse, whose striking coat color had been prized in ancient China. The cause, discovered in 1994 by Lu et al. [57], was "ectopic" overexpression of a peptide termed "agouti" in tissues where it does not normally occur. Agouti is an endogenous antagonist of α-MSH at its melanocortin receptors, leading to hyperphagia and obesity from inhibition of the appetite-suppressing effect of α-MSH in the hypothalamus and lightening of the fur because agouti also blocks the melanocortin-mediated production of melanin in the hair follicle. Interestingly, mutations of human melanocortin receptors have now been identified as a cause of obesity [51]. Other genetic obesity syndromes in rodents cast new light on the regulation of energy balance and opened up the new neurobiology of weight regulation. Notable were the *ob*/*ob* (obese) and *db*/*db* (diabetes) mice and the *fa*/*fa* (fatty) Zucker rat. These mutants had been identified during the 1950s and 1960s as autosomal recessive traits that conferred hyperphagia and obesity. At that time the causes were unknown, but meticulous cross-circulation "parabiosis" studies by Coleman [58] during the 1970s suggested that the *ob*/*ob* syndrome was due to deficiency of an appetite-suppressing hormone, whereas the *db* mutation apparently disabled the receptor that normally recognized this hormone. The hypothetical appetite-suppressing hormone would function as an "adipostat" whose existence had previously been postulated by Kennedy [59] to explain how eating and energy expenditure were modulated appropriately under conditions of under- or overnutrition so as to keep fat mass constant.

An important breakthrough in obesity research was the discovery by Jeffrey Friedman's team in 1994 of the *ob* gene by positional cloning and the characterization of its protein product [60]. This cytokine-like protein, which Friedman named leptin (from the Greek *leptos*, meaning "thin"), was secreted by adipocytes and circulated at concentrations proportional to total fat mass. Leptin was found to act in the hypothalamus to inhibit feeding and cause weight loss and therefore fulfilled the criteria for an adipostat by signaling adiposity to the brain and effecting appropriate responses to maintain a constant fat mass. Hyperphagia and obesity were explained in the *ob*/*ob* mouse by the *ob* mutation, which deleted bioactive leptin. The *db*/*db* and *fa*/*fa* syndromes were subsequently shown to be due to various mutations affecting the leptin receptor. Human obesity, due to absent leptin, although uncommon, can be due to mutations of leptin or its receptors, causing a striking phenotype of severe hyperphagia and massive obesity that develops in early childhood. Leptin-deficient individuals show a dramatic response to treatment with recombinant human leptin. However, the vast majority of obese people have raised leptin concentrations, roughly in proportion to their increased fat mass, suggesting that leptin is irrelevant to human energy balance as long as basal levels are present.

Research into the genetic susceptibility to "common" human obesity has also benefited from advances in molecular genetics. Earlier observational and epidemiological studies included those of Charles Davenport (1883–1969) [61] in 1923 on the inheritance of BMI in families and the works of Verscheuer (1896–1969) [62] in the 1920s, Newman et al. [63] in the 1930s, and Stunkard et al. [64] during the 1980s on identical twins raised together or separately, with the aim of determining the contribution of genetic versus environmental factors. Studies by Claude Bouchard and others have suggested that genetic susceptibility is determined by multiple genes that individually have only minor effects. A large and growing number of candidate genes have been explored and several have been shown to make a significant but limited contribution [65].

Restricting food intake and increasing physical activity have been the mainstays of managing obesity since antiquity. Many dietary regimes have been tried, ranging from total starvation to unlimited quantities of various foods. Numerous drugs have also been used in an attempt to treat obesity, mostly acting by reducing appetite. Vinegar has been tried on many occasions in the past 400 years. Various laxatives have been employed, sometimes together with hydrotherapy. In the 1890s, the newly discovered thyroid extract was first used and thyroid hormones were still being used in this context into the late twentieth century. The notion of stimulating an underactive endocrine system has been repeatedly invoked, ranging from various proprietary drugs and gonadal extracts to the more recent use of human growth hormone and human chorionic gonadotropin.

In the late nineteenth century, the synthetic organic chemical industry yielded various compounds with weight-reducing properties derived from aniline, which were used to make dyes for fabrics. One such product was dinitrophenol, which was found to induce marked weight loss in workers who handled the compound; much later, the mechanism was shown to be an uncoupling of oxidative phosphorylation to produce heat instead of ATP, mimicking the action of UCP-1 in brown fat. Dinitrophenol was used to treat obesity during the 1930s but was abandoned when it was shown to cause cataracts and peripheral neuropathy. This early therapeutic tragedy emphasizes the need for careful evaluation of the efficacy and safety of new drugs before their introduction into clinical practice [66].

Another early product of the organic chemical industry was D-amphetamine, synthesized in 1887. It was used during the 1930s as a stimulant to treat narcolepsy, when it was found to induce weight loss. Amphetamine was approved in the United States for the treatment of obesity in 1947 but was soon shown to be addictive, and its use declined markedly during the 1970s [67]. Phentermine and diethylpropion, structurally related to amphetamine, were introduced into clinical practice during the 1950s and were widely promoted. All these drugs are sympathomimetic agents that act like noradrenaline in the CNS and thus reduce appetite. Another structurally related compound, fenfluramine, which increases the release of the anorectic neurotransmitter serotonin, was also shown to reduce appetite and weight. Fenfluramine and its dextro isomer, D-fenfluramine, were prescribed widely during the 1980s and 1990s, the latter sometimes given together with phentermine. Fenfluramine was withdrawn in 1997 when it was shown that it caused cardiac valvular disease and primary pulmonary hypertension, which had previously been recognized as a rare complication of antiobesity drugs. Other drugs that have been used to treat obesity have included phenylpropanolamine and ephedrine (both sympathomimetic agents), the latter in combination with caffeine. Phenylpropanolamine was withdrawn because it was shown to cause stroke, and the safety and efficacy of ephedrine/caffeine remains uncertain. Various compounds designed to stimulate thermogenesis have been developed, but none are available clinically.

There was much interest in agonists at the β3-adrenoceptor, responsible for activating heat production in brown fat and other thermogenic tissues including skeletal muscle. These compounds proved highly effective and relatively selective in animals, but because of differences between the rodent and human β3-adrenoceptors these compounds proved to be ineffective or plagued by sympathetic side effects when tried in humans [43].

Bariatric (weight-reducing) surgery began in the mid-1950s with the Norwegian surgeon Hendrikson and the U.S. surgeon Kremen [68] who removed much of the small bowel to reduce nutrient absorption. This irreversible operation caused intractable losses of nutrients and electrolytes and was replaced in the 1950s by the jejunoileal bypass operation developed by Kremen and others. The jejunoileal bypass causes major side effects, notably the "blind loop" syndrome, and is now little performed. The gastric bypass operation was developed by Edward Mason [69] in the 1960s [69] along with various forms of gastroplasty. Recent innovations include sleeve gastrectomy, gastric banding using an inflatable implanted band whose tension can be varied by injecting saline into a subcutaneously buried port, and the adaptation of many bariatric techniques to be performed laparoscopically.

1.2 OBESITY COMES OF AGE

It was not until the 1960s that concerted attempts were made to bring together those interested in the science and clinical management of obesity. An early initiative, following the example of the long-established specialist societies in diabetes, endocrinology, and other disciplines, was the formation of national associations to promote research into obesity. The first such association was the Association for the Study of Obesity in the United Kingdom. It held its inaugural meeting in London in 1968. This was followed in 1973 by an American conference organized by the National Institutes of Health, in recognition of the important health problems posed by obesity, and in 1974 by the first International Congress on Obesity (ICO) in London. The North American Association for the Study of Obesity (NAASO), organized by George A. Bray, first met in 1982 at Poughkeepsie, New York. In 1986, the International Association for the Study of Obesity (IASO) was formed under the leadership of Barbara C. Hansen. Following the first ICO, it was clear that a specialist journal devoted to obesity was needed and the *International Journal of Obesity* began publication in 1976 under the joint editorship of Alan N. Howard and George A. Bray. In time, other journals have followed: *Obesity Surgery* in 1991; *Obesity Research* (now renamed *Obesity*), published by NAASO, in 1993; and a plethora of others [70].

In this chapter on the historical aspects of obesity, I hope I have whetted your appetite to go to some of the references to extend your knowledge. Several background references at the end can provide this introduction. A list of additional readings in the history of obesity is also appended.

In summary, what have we learned?

In this chapter on the history of obesity, we have learned that obesity is an ancient problem that has occurred before the development of agriculture and in all cultures. It has afflicted women more often than men and seems to be abundant in times of abundance and among the wealthy. The anatomical developments of the sixteenth century mirrored in the dissection of obesity in human beings. As new techniques were developed in biology, chemistry, and physics, they were in due course applied to the study of obesity.

The nineteenth century solidified the oxygen theory and the idea of energy balance, which underlies obesity. This also saw the introduction of BMI to relate height and weight.

In the twentieth century, the understanding of obesity continued to expand. Its hazards, initially initiated by the

insurance industry, are now widely recognized. More recently, it has been clearly documented that weight loss prolongs life. The concept that there are many causes and types of obesity was furthered by the identification of hypothalamic injury as a cause of obesity and recognizing that adrenal or pituitary hyperfunction can cause obesity in Cushing's syndrome. The identification of leptin in fat whose absence is associated with massive obesity was a major breakthrough. Some, but not all, studies have suggested that the abundance of food drives the obesity epidemic. Aniline dyes, which were developed for the clothing industry, proved invaluable as the starting materials for drugs to treat obesity—often with unintended consequences. The use of both surgery and behavioral strategies to treat obesity were products of the late twentieth century.

Where do we go in the twenty-first century? Both genetics and epigenetic studies will contribute to the growth of new knowledge about obesity. To understand why some people never get obese while others do, we need to identify long-term signals and understand how they can help overcome the hedonic value of food for some people, but not others. The fact that obesity can be transmitted over social networks offers a new behavioral challenge in how to put this into practice to reverse the epidemic. We are all price sensitive, and there is no doubt that food is often purchased based on price and taste as well as nutrition. The idea that obesity can be "conquered" in the same way as dental caries by adding a nutrient, such as fluoride in the case of dental caries, to food or water is an intriguing one. Similarly, the idea that "cheap oil" and "farm subsidies" to grow all you can are fueling the epidemic needs serious consideration.

1.3 SUMMARY

Artifacts with obesity existed more than 30,000 years ago in the Paleolithic period, showing that obesity has a long history. The agriculture revolution that began 10,000 years ago introduced new dietary patterns, although obesity developed on any food plan and in every culture, indicating that there is no essential dietary composition needed for its appearance. Obese patients and their treatment have been described in all medical traditions. Diet and exercise were the mainstays of treatment even before the Greeks, 2500 years ago. The sixteenth century was a century of discovery, and for obesity this included initial dissections of obese human bodies. The seventeenth century might be called a century of physics. During this period, blood cells were discovered using microscopes and scales were used to weigh food intake by human beings eating on a balance beam in real time. In the eighteenth century, oxygen was discovered and metabolism was shown to be like burning a candle. The nineteenth century saw formulation of the laws of thermodynamics and their application to human beings, the introduction of BMI, and the publishing of the first popular diet book.

The twentieth century differentiated types of obesity, unraveled feeding control systems in the brain, saw behavioral therapy emerge as a pillar of treatment programs, witnessed the introduction of rational pharmacological and surgical therapy, and passed from the old to the new neurology of obesity with the discovery of leptin.

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2 Measurement of Total Adiposity, Regional Fat Depots, and Ectopic Fat

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CONTENTS

2.1 INTRODUCTION

Quantifying the amount and distribution of adipose tissue and its related components is integral to the study and treatment of human obesity. Body composition research is a field devoted specifically to the development and extension of methods for in vivo quantification of adipose tissue and other biochemical and anatomical components of the body. This chapter focuses on methods of estimating the components of body composition in the context of evaluating human obesity and its associated risks.

The chapter first describes the organization of human body composition with an emphasis on body adiposity. The human body can be organized into five levels of increasing complexity—atomic, molecular, cellular, tissue organ, and whole body. Obesity-related components are recognized at each of the five body composition levels.

Two main groups of methods are reviewed: those that are useful mainly in research laboratories as reference methods, including whole-body ^{40}K counting, in vivo neutron activation analysis (IVNAA), hydrometry, underwater weighing (UWW), air displacement plethysmography (ADP), three-dimensional photonic scanning (3DPS), dual-energy x-ray absorptiometry (DXA), quantitative magnetic resonance (QMR) (EchoMRI™ [Echo Medical Systems, Houston, TX]), multicomponent models, and imaging methods such as computerized tomography (CT) and magnetic resonance imaging (MRI) and spectroscopy (MRS); and those that are applicable in field settings including anthropometry and bioimpedance analysis (BIA). Some methods such as ADP and DXA are now applicable in both research and field settings. An overview of method errors is included in Section 2.5.

2.2 ADIPOSITY COMPONENTS

2.2.1 Atomic Level

The human body is composed of 11 elements that account for >99.5% of body weight.[1] Three of these elements, carbon, hydrogen, and oxygen, are found in storage triglycerides or "fat." The average proportions of triglyceride as carbon, hydrogen, and oxygen are considered stable at ~76.7%, 12.0%, and 11.3%, respectively. These stable elemental proportions allow the development of methods for deducing total body fat from total body carbon and other elements.

Carbon is the characteristic component of adiposity at the atomic level. "Reference Man," for example, contains 16 kg carbon, and 60% or 9.6 kg of carbon exits in adipose tissue.[2]

2.2.2 Molecular Level

Major molecular-level body composition components include water, lipids, proteins, minerals, and glycogen.[3] Each of the nonaqueous components represents many different but closely related chemical compounds.

Lipid is the main molecular-level component of interest in the study of human obesity. The term "lipid" refers to all chemical compounds that are insoluble or weakly soluble in water, but are soluble in organic solvents such as chloroform and diethyl ether.[4] Lipids isolated from human tissues include triglycerides, sphingomyelin, phospholipids, steroids, fatty acids, and terpenes. Triglycerides, commonly referred to as "fats," are the primary storage lipids in humans, and comprise the largest fraction of the total lipid component. The Reference Man has 13.5 kg of total lipid, of which 12.0 kg, or 89%, is fat.[2] The term "ectopic fat" refers to the lipids frequently associated with metabolic derangements that are found within cells of the liver, pancreas, heart, and organs or tissues other than adipose tissue.[5]

The "stable" relationships between the various components form the basis of many widely used molecular-level body composition methods. The most important of these are the hydration of fat-free mass (FFM) (i.e., mean total body water [TBW]/FFM = ~0.73), which estimates fat mass (FM) from the difference between body mass and FFM, and the densities of FM (0.9007 g/cm^3) and FFM (1.100 g/cm^3). FM can be calculated as FM = body mass − TBW/0.73 and FM = $(4.95/D_b - 4.50) \times$ body mass, where D_b is body density measured by UWW or ADP.[6–9]

Since the assumption of a constant FFM density of 1.100 g/cm^3 causes some model error, three-, four-, and five-component models were developed for measuring total body fat with improved accuracy.[10–12]

2.2.3 Cellular Level

The cellular level includes three main components: cell mass, extracellular fluid, and extracellular solids. Adipocytes or fat cells serve as the primary storage site for triglycerides. All cell mass can be separated into two components: one metabolically active "body cell mass" and the other triglycerides, or "fat."[13]

2.2.4 Tissue-Organ Level

The main components at this level are adipose tissue, skeletal muscle, bone, and visceral organs (e.g., brain, liver, kidneys, heart).

Human adipose tissue is often assumed to have an average composition consisting of 80% lipid, 14% water, 5% protein, and <1% mineral, and a density of 0.92 g/cm^3 at body temperature.[2] Since level of adiposity, age, gender, and heredity all play an important role in determining fat content of adipose tissue, this average belies the large variation observed in adipose tissue composition. For example, for every 10% increase in relative adiposity, there is a corresponding increase in lipid fraction of 0.124.[14] A notable feature of adipose tissue is the large extracellular fluid compartment relative to cell mass. Of the 14% of average adipose tissue samples as water, 11% is extracellular water.

An important aspect of obesity research is examination of regional adipose tissue biology (subcutaneous and internal).[2,15] Adipose tissue occurs in abundance in subcutaneous sites as well as in and around female breasts. Subcutaneous adipose tissue (SAT) can be partitioned into superficial and deep SAT by fascial planes.[16]

The most important internal adipose tissue component in the obesity field is found in the visceral compartment (i.e., thoracic, abdominal, and pelvic visceral adipose tissue [VAT]). The word *viscera* is Latin for "organs in the cavities of the body." However, the medical literature varies widely in defining VAT based on imaging methods.[17] This topic is reviewed in Section 2.3.8.

TABLE 2.1
Selected Adipose Tissue Compartments and Their Measurement Methods

Compartment	Measurement Method	Reference
Subcutaneous	CT, MRI	1
Superficial	CT, MRI	16
Deep	CT, MRI	16
Visceral	CT, MRI, DXA, US	18–28
Intraperitoneal (Mesenteric and Omental)	MRI	29–31
Extraperitoneal	MRI	29–31
Pericardial/epicardial	CT, MRI, US	32–34
Intermuscular	CT, MRI	35
Bone marrow	CT, MRI, MRS	36
Brown	PET, CT, MRI	37–39

CT, computed tomography; DXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; US, ultrasound.

Of the nonvisceral internal adipose tissue, interstitial adipose tissue is interspersed within tissue (e.g., skeletal muscle) so tightly that it may be included with the tissue/organ at dissection. Adipose tissue is almost absent in some anatomic sites such as the penis, scrotum, labia minora, nipple, nose, ear, eyelids, and brain. Some triglyceride exists within skeletal muscle, liver, and other nonadipose tissue cells and this component is classified as intracellular lipid. Each anatomic adipose tissue component has specific metabolic and functional characteristics. The adipose tissue depots of clinical research interest and their main measurement methods are summarized in Table 2.1.

2.2.5 Whole-Body Level

Skinfolds, circumferences, lengths, linear dimensions, body surface area (BSA), and body volume are all measurements at the whole-body level. These measurements are often used with prediction equations to estimate components at the other four body composition levels.

2.3 COMPONENT REFERENCE METHODS

2.3.1 Whole-Body ^{40}K Counting

The natural abundance of ^{40}K in the human body is constant at 0.0118% of total body potassium (TBK). ^{40}K emits a characteristic 1.46 MeV γ-ray that can be counted by whole-body counter detection systems and the calculated TBK can be applied to estimate FFM by assuming a constant relationship between TBK and FFM.[13] FM is calculated as the difference between body weight and FFM. Many early obesity studies used ^{40}K counting as the reference method for estimating FM and FFM. However, today there are several lower cost methods that are used to quantify FM and FFM. TBK estimates provide a useful measure of body cell mass, a compartment that is often considered a measure of metabolically active tissue.[13,40] Recent studies also support the use of TBK in skeletal muscle mass measurement.[41]

2.3.2 In Vivo Neutron Activation Analysis

IVNAA methods quantify the main elements at the atomic body composition level in vivo including H, C, N, O, P, Ca, CI, K, and Na.[42] When subjects are exposed to a neutron source, elements can be quantified by delayed-gamma neutron activation, prompt-gamma neutron activation, or inelastic neutron scattering. These elements can be used to calculate, using simultaneous equations, the main molecular-level components such as fat, protein, water, and minerals.[43] The between-measurement coefficient of variation (CV) for total body C, N, and Ca are 3.0%, 2.7%, and 0.8%, respectively. The propagated error in the total body carbon method of measuring FM is 3.4–4.0%.[44] Radiation exposure is the main disadvantage of the total body carbon method, and this approach is therefore not widely used in the study of body composition.

2.3.3 Hydrometry

Dilution methods, or "hydrometry," quantify body fluid compartments based on a labeled tracer. TBW is the most important dilution method in the obesity field. A known dose of labeled water (i.e., deuterium $^{2}H_2O$, tritium $^{3}H_2O$ and $H_2{}^{18}O$) is administered to the subject and TBW (corrected by isotope exchange fraction) is calculated from sample analysis (i.e., blood sample) by assuming that labeled water homogeneously distributes within TBW.[45] As noted earlier, TBW can be used to estimate FFM and FM with errors caused by variation of the assumed FFM hydration (0.73) with age, gender, race, obesity, disease, early-stage weight loss, or other factors.[7,46] Hydrometry is a reasonable approach for estimating adiposity in morbidly obese patients for whom other methods may not be suitable. The use of deuterium and ^{18}O-labeled water-stable isotopes is safe for children and pregnant women.

2.3.4 Body Volume-Based Body Composition Measurement

Body volume combined with body mass allows derivation of body density. Body volume measurement techniques assume that the body has two main components, FM and FFM, with further partition of FFM into TBW, protein, and minerals, all with known densities. Percent fat (%fat) is calculated from body density in the simple two-component model that assumes stable densities for FM and FFM.[9,47,48] Volume measurements should be corrected for lung volume and intestinal air.[49] Body volume estimates are also used in multicomponent body composition methods and these are discussed in Section 2.3.7.

2.3.4.1 Hydrodensitometry

Hydrodensitometry, often referred to as UWW, is one of the oldest methods of analyzing human body composition based on the Archimedean principle (i.e., applying measured body density to partition FM and FFM based on their assumed respective densities).[50] The technical and biological errors from all sources for %fat estimates by UWW are about ±2.5%.[51] A limitation of UWW is that it requires substantial subject cooperation during the procedure. UWW is not feasible in very young children, frail elderly, or those with serious cardiovascular or pulmonary diseases. However, UWW can be used in very obese subjects who cannot be evaluated by other methods.

2.3.4.2 Air Displacement Plethysmography

ADP is a technique that quantifies body volume by measuring air displaced by a body's introduction into a controlled environment.[52] The subject, wearing a form-fitting bathing suit and swim cap, is weighed on a scale and then seated in the calibrated BOD POD unit (BOD POD Body Composition System, Cosmed, Rome, Italy) for body volume measurement. The reproducibility of %fat measurement is high (CV, 1.7 ± 1.1%).[53] Agreement of BOD POD %fat estimates with those by hydrodensitometry is good, although some studies report small but statistically significant differences.[54] BOD POD requires minimal instruction for subjects and technicians. The process takes only a few minutes and the chamber is relatively accessible for young children, elderly, disabled, and obese. The ADP system has a weight limit of 200 kg. The PEA POD is a specially designed ADP instrument for children below 8 kg. The system has good accuracy (i.e., mean difference: 0.6 ± 3.7% body fat; $p = 0.62$) and precision (reproducibility of %fat: 0.4 ± 1.3%).[55]

2.3.4.3 Three-Dimensional Photonic Scanner

The 3DPS and similar counterparts is a body volume measurement technique that has been recently used to evaluate body adiposity. Compared to UWW and ADP, 3DPS has the advantage of obtaining information on regional volume and body dimensions such as shape, circumferences, lengths, and BSA.[56]

The 3DPS system uses a high-speed camera to record the point or line projected by a laser source on the subject's body surface at diverse angles. Subjects have to stand with legs separated and arms bent away from the trunk in a prespecified place and hold their breath for ~10 seconds for each body dimension (i.e., front and side). The scanner then reconstructs the 3D image of the body shape.

Volume measured by 3DPS is highly correlated with volume measured by UWW ($r^2 = 0.999$).[49,57] 3DPS measured chest, waist, and hip circumferences are also highly correlated with those measured by a cloth tape ($r = 0.960–0.999$).[49,57] No significant difference was detected on %fat measurements between 3DPS and UWW, although the correlation between the two method is lower than that for volume (i.e., $r^2 = 0.654$ vs. 0.999).[49] The 3DPS technique has a high reproducibility with intraclass correlations for circumferences and volumes larger than 0.97.

Unlike UWW, 3DPS requires minimal cooperation from the subject. The method can be used in elderly, children, and extremely obese subjects. The method is also useful in subjects with diseases who cannot hold their breath under water. In contrast to ADP's weight limit, the 3DPS system has no upper limitation on weight. The 3DPS method has been used in the National Sizing Survey to identify population body shape[57,58] and is likely to be widely used for shape and body fat measurement in both clinical and research settings.

2.3.5 Dual-Energy X-Ray Absorptiometry

DXA technology uses a filtered x-ray source or a pulsating voltage source that produces two main energy peaks.[59] The difference in attenuation between the two energy peaks has a characteristic signature for fat, lean, and bone mineral. Although DXA was primarily designed for bone mineral measurement, the capacity for quantifying the fat and lean soft tissue compartments evolved into DXA's central role. Most studies show that DXA estimates of body composition are highly reproducible (CV, 0.5%–4% for %fat, 1%–1.7% for FM, and 0.7%–1.0% for FFM).[60,61] The arms, legs, and trunk body composition measurements are somewhat less precise and accurate than those for the whole body.[59] The minimal radiation exposure of DXA (<1 mrem) allows DXA to be used longitudinally in children and adults, but not in pregnant women. Because of the size of the scan field, older DXA systems do not recommend scanning individuals >100 kg. Newer DXA system (iDXA, GE Healthcare Lunar, Madison, WI) can scan subjects up to 204 kg, 197.5 cm in length, and 66 cm wide. When a subject is wider than the width limit, "mirror image" software is used to double the one half of the body that was scanned. Note that few studies were specifically designed to test the accuracy of DXA body composition estimates in moderately or severely obese subjects.

2.3.5.1 Fat Distribution Measurement by DXA (Gynoid/Android Fat)

Since men tend to deposit fat in the upper body and abdomen and women tend to deposit fat in the lower body and hip, DXA can characterize fat distribution by measuring android fat (upper body or central region fat) and gynoid fat

(lower body or peripheral region fat). Android fat is considered to be closely related to cardiovascular risk while gynoid fat distribution appears to play a protective role.[62]

With DXA scanning, the android region is approximately defined as the region between the rib cage and the iliac crest or region from the top of the iliac crest to 20% of distance from chin to iliac crest.[63,64,18] The gynoid region is usually defined as a standardized measurement in the hip region or occasionally as a region in the lower limb region.[63,64,65]

The CV for android and gynoid fat measurement by DXA is reported as 2.32% and 0.96%, respectively.[66] In addition, the android-to-gynoid fat ratio is also used as a measurement of fat distribution and has been found to be related to insulin resistance.[65]

2.3.5.2 Visceral Adipose Tissue Measurement by DXA

VAT has a closer relationship with obesity-related diseases such as diabetes compared to SAT, and in this context, a new DXA VAT measurement technique has been developed.[67–69]

The standard whole body DXA method cannot separate abdominal VAT and SAT. The DXA VAT measurement approach estimates SAT on the right and left sides of the body and uses this information to derive the total SAT around the abdominal cavity by using a geometric model based on anatomical relationships. VAT can then be obtained by subtracting SAT from total abdominal fat.[19] DXA VAT measurements do not include the whole abdomen. The iDXA (GE Healthcare Lunar, Madison, WI) system defines VAT region as from the top of the iliac crest to 20% of the distance from chin to iliac crest; on the Discovery system (Hologic Discovery W, Bedford, MA), VAT is measured in a 5 cm-wide region at about the fourth lumbar vertebrae.[19,20]

DXA VAT measurements are highly correlated with CT measured VAT on both iDXA and Discovery systems (r = 0.93−0.98), Bland–Altman bias is +56 cm^3 with 95% limit of agreement from −355 to +468 cm^3 for iDXA, and the SEE is 16 cm^2 (cm^3) for the Discovery system.[19,20]

Although abdominal CT and MRI are the only methods that directly measure VAT, DXA VAT measurements have the advantage of including minimal radiation exposure and short scan time as part of the whole body DXA scan. DXA may be used to measure VAT in the clinical setting and in research studies, but further evaluation of the relationship of DXA VAT measurements to obesity-related health risk factors, morbidity and mortality in large samples is needed.

2.3.5.3 Body Volume Measurement by DXA

A recent report describes a DXA approach for estimating body volume.[70] Tissue volume is first calculated for each pixel that only contains soft tissue. Total body volume is then calculated by adding together tissue volume of each pixel with interpolation of volumes of pixels that contains bone tissue. DXA measured total body volume is highly correlated with ADP measured total body volume (r^2 = 0.99). DXA body volume measurement has the advantage of eliminating errors introduced by inaccurate estimates of residual lung volume as are needed with hydrodensitometry and ADP methods. In four-compartment (4C) body composition models, a measurement of body volume and DXA can potentially replace hydrodensitometry or ADP as is now required and discussed in Section 2.3.7.

2.3.6 Quantitative Magnetic Resonance/ EchoMRI™ Methods

QMR, also called EchoMRI™ is a static, low-intensity magnetic field (0.0065 T) body composition measurement instrument. The QMR system uses radio pulses to stimulate hydrogen atoms in different tissues of the subject who rests recumbent on the instrument bed. Unlike a conventional MRI scanner, QMR does not generate anatomical images. The QMR system records nuclear magnetic resonance responses from the hydrogen nuclei in different tissue compartments and then calculates tissue mass as FM, lean tissue, free water, and TBW through established models.[71,72]

Although QMR-measured FM was significantly smaller than FM measured by the reference 4C model method (difference, males: −4.66 kg, 13.7%, p = 0.0001; females: −0.68 kg, 1.9%, p = 0.0222), the correlation between these two methods is high (r = 0.967 for males, r = 0.993 for females, and r = 0.956 for all subjects, $p < 0.001$) and no bias was detected with increasing FM.[73] The CV for repeated FM measures by QMR in this study was 0.437%, which is lower than the FM CV measured by DXA (3.1%) or ADP (2.9%). QMR can detect a change in FM of as little as 250 g with 80% power.[73] A simulated change in FM created by adding oil next to human subjects was accurately detected.[71] However, in the study by Myint et al., FM loss measured by QMR was less than that measured by the reference 4C model method (p = 0.0008) in 22 subjects who lost weight.[74] Future studies with larger samples are needed to test the accuracy of QMR in detecting FM change.

QMR has been validated for pediatric evaluation by carcass analysis in piglets and by the 4C model method in human infants and children.[75–77] The precision of QMR is high in piglets (1.3% for FM, 0.9% for FFM) and pediatric subjects (1.42% for FM).[75,76] QMR estimates of FM were highly correlated with QMR FM estimates in infants and children older than 6 years of age ($r \geq 0.95$, $p < 0.001$). However, FM was overestimated by QMR by 2% to 4.7% in piglets and by 10% in children older than 6 years. Moreover, FM was overestimated in infants less than 8 kg by 96.8%.[75–77] Corrective equations were developed to recalibrate QMR FM estimates to those obtained by 4C.[75]

The high precision of FM measurements by QMR makes this a potentially promising new method for FM measurement, especially in detecting small FM changes in short-term weight-loss clinical trials. If the accuracy of QMR is further improved in both pediatric and adult populations, the use of this method can be expanded. An important need thus exists to conduct further validation studies, particularly over the short term. The possibility exists for additional QMR system calibration with feedback from these kinds of studies.

2.3.7 Multicomponent Models

A supplementary approach to the two-compartment hydrodensitometry or ADP methods is to use multicomponent (i.e., three or more components) model methods that include measures of TBW, bone mineral mass, and soft tissue mineral mass in addition to body density, assuming fixed densities for each component.[78–80] Multicomponent models reduce the number of applied model assumptions and are often applied as the criterion against with other methods are compared.[81]

In certain groups in which two-compartment model assumptions may be unreliable, such as children, the elderly, African-Americans, or sick patients, multicomponent models may provide more accurate estimates of FM. Precise measures of TBW, bone mineral mass, and soft tissue mineral mass are required, however, to avoid swamping the gain in accuracy with increased propagated errors of the additional measurements.[82] In addition, the benefit in terms of improved accuracy should always be evaluated in relation to the increased cost associated with obtaining the additional measurements of TBW, bone mineral mass, and soft tissue mineral.[81,83] These costs may be justified when the goal is to estimate changes in FM over the long term, as in clinical weight-loss studies, and in evaluating the accuracy of other potential reference methods.

2.3.8 Imaging Methods

CT and MRI are the main methods for estimating organ and tissue volumes, and to a lesser extent, ultrasound also serves in this capacity.[32] Positron emission tomography is used to estimate brown adipose tissue.[37] Both CT and MRI are also capable of quantifying tissue and cell lipid content, particularly ectopic fat that is present mainly in the form of triglycerides.[5] Ectopic fat deposition is associated with insulin resistance and disruption of multiple metabolic processes.[5] Fat present in liver, pancreatic, heart, and skeletal muscle cells is generally considered "ectopic fat." Liver fat can be measured by CT, chemical-shift water-fat "Dixon" imaging, MRS, and semiquantitatively by ultrasound.[84–87] Pancreatic fat can be measured by both chemical-shift water-fat "Dixon" imaging and MRS.[85,88,89] On the other hand, fat in skeletal and heart muscles can be measured only by MRS.[85,88,90–93]

2.3.8.1 Computed Tomography

The basic CT system consists of an x-ray tube and receiver that rotate in a perpendicular plane to the subject. Gray scale cross-sectional images of the human body are reconstructed by mathematical techniques with signal intensity in each pixel reflecting x-ray attenuation. Tissue physical density is the main determinant of x-ray attenuation, which is expressed as Hounsfield Unit (HU) with air and water defined as –1000 and 0 HU, respectively.[94] The pixel HU value is used to differentiate adipose tissue, skeletal muscle, bone, visceral organs, and brain (i.e., –190 to –30 HU for adipose tissue).[21] Because of the radiation exposure involved with CT, most studies use a single image slice for fat measurement.

Heymsfield et al. were among the first to explore the use of CT in body composition research.[95] The authors initially used CT to quantify the cross-sectional area of arm muscle in 1979[96]; subsequent reports described methods of estimating visceral organ volumes and VAT.[95] CT measurement of tissue area and volume showed high reproducibility (CV for repeated SAT and VAT measurement are both ~2%).[97–99]

In recent years, CT has been employed to evaluate the lipid content of skeletal muscle. Muscle cross-sectional area is subdivided into normal-density muscle (31−100 HU) and low-density muscle (0−30 HU). Low-density muscle has a high lipid content, which includes both fat within muscle fibers and small adipose tissue depots that infiltrate the muscle. The CV of mean attenuation values obtained from two repeated CT scans for the mid-thigh is 0.51% and 0.85% for the mid-calf.[100] In a manner similar to that used to determine skeletal muscle density, CT has also been employed to determine liver fat with spleen as the "0" fat reference.[101]

2.3.8.2 Magnetic Resonance Imaging

As the prevalence of obesity continues to rise, the need to quantify adipose tissue depots and fat in organs and skeletal muscles has become increasingly important. Noninvasive 3D assessment of whole-body and regional fat distribution by MRI can provide useful biomarkers to stratify risks and evaluate therapy efficacy. Over the past two decades, a significant increase in the utilization of MRI for body fat assessment[102–108] has been reported in the literature. MRI does not involve ionizing radiation, can be safely repeated in longitudinal studies, and is applicable to nearly all cohorts and ages. Next, a description of T_1-weighted imaging, single-voxel proton MRS, frequency-selective MRI, and state-of-the-art chemical-shift water-fat "Dixon" imaging methods is provided. The principles with which each technique generates signal contrast between lean and fatty tissues are emphasized (Figure 2.1).

2.3.8.2.1 Signal Formation in MRI

The MRI signal arises primarily from hydrogen protons in free water and fat (triglyceride) molecules. While other protons exist in macromolecules, they are usually invisible in conventional MRI. When an object is placed inside a magnetic field, a longitudinal magnetization from the proton ensemble is created. The magnetization establishes resonance at a specific Larmor frequency proportional to the magnetic field strength. During a scan, a train of radiofrequency (RF) pulses is applied every repetition time to gather data via a pulse sequence. The pulses are tuned to the Larmor frequency to repeatedly excite the longitudinal magnetization into the transverse plane. After each excitation, an echo of the transverse magnetization is acquired by receivers at a time specified by echo time (TE). After each successive RF excitation, two processes occur. First, the perturbed longitudinal magnetization recovers toward its original state prior to RF excitation. This rate of exponential recovery is called T_1

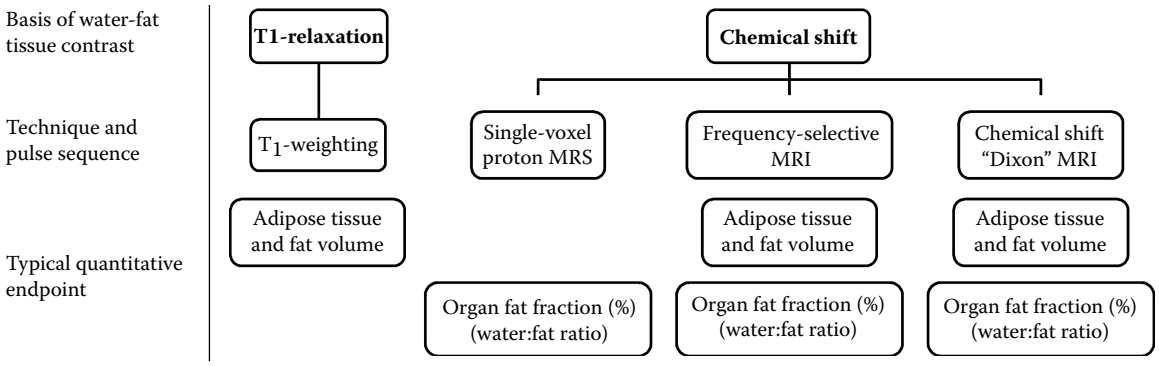


FIGURE 2.1 Magnetic resonance imaging and spectroscopy techniques available for fat quantification.

relaxation. Second, the transverse magnetization loses signal coherence and decays at an exponential rate called T_2 relaxation. T_1 and T_2 values are intrinsic tissue properties and vary with magnetic field strength.

2.3.8 2.2 T_1-Weighted Methods

MRI signal intensities are influenced by many factors, including tissue-specific T_1 and parameter settings of the pulse sequence. The T_1 of fat is one of the shortest in vivo, which indicates a rapid recovery of longitudinal magnetization between RF excitations. By using a T_1-weighted sequence, strong tissue contrast can be achieved between short-T_1 fat and muscles and organs with longer T_1 values. Fat is consequently brighter on the resultant image and can be identified and delineated from other structures with intermediate and darker gray levels. T_1-weighted sequences have been used by many investigators as the standard workhorse tool for assessing subcutaneous and VAT distributions and can be acquired very rapidly and efficiently for whole-body analysis.[103–107]

2.3.8.2.3 Magnetic Resonance Spectroscopy

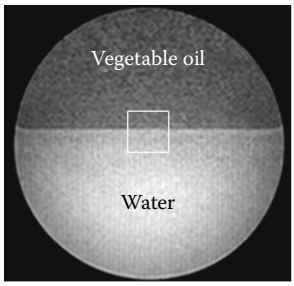
Single-voxel proton spectroscopy has long been considered the noninvasive reference for organ fat quantification and has been widely used in assessing liver, heart, pancreas, and skeletal muscle fat content.[85–87,89–92] MRS remains the only method that can differentiate intra- and extra-myocellular lipids in cardiac and skeletal muscle tissue.[5,93] Localized single-voxel MRS does not provide anatomical information in the form of an image. Instead, MRS yields a detailed frequency spectrum, which provides an intuitive visualization of the presence and quantity of proton moieties (e.g., relative area under each spectral peak) within the interrogated voxel. MRS relies on chemical shift, which refers to differences in the Larmor frequencies of water and fat (triglyceride) protons (Figure 2.2). Water protons from hydroxyl (–OH) groups are uniquely characterized by a spectral peak at 4.7 ppm (parts per million). The predominant protons of triglycerides are from the methylene $(–CH_2)_n$ groups, which have a slightly lower resonance frequency at 1.3 ppm. Note that while water is a symmetrical molecule with a single proton resonance, triglycerides have additional minor fat resonances. Selection of MRS voxels requires operator expertise so that the voxel does not contain any undesired tissues. Typically, the voxel size is on the order of 1–10 cm^3. Subject motion, respiration, cardiac motion, and peristalsis can lead to spatial misalignments and erroneous measurements.

2.3.8.2.4 Frequency-Selective Methods

The chemical shift phenomenon has also been translated to imaging methods. Since data acquisition by MRI involves frequency-tuned RF pulses, techniques have been described that exploit the frequency shift between water and fat to quantify adipose tissue and highlight the presence of organ and skeletal muscle fat.[109–111] There are two variants, depending on whether water (fat) is chosen for signal suppression (excitation). One approach is to selectively target methylene fat protons by tuning the RF pulse specifically to that resonance. Consequently, only fat protons are excited into the transverse magnetization plane and detected by receivers. The encoded data thus exhibit only signals from methylene fat and the image appearance resembles T_1-weighting where fat appear recognizably bright, in contrast to darker muscles and water-dominant tissues whose protons were not excited. In lieu of selective-fat excitation, one can employ a water-suppression RF pulse sequence to achieve similar outcomes. Alternatively, selective water excitation or fat suppression can also be used to isolate water signals. Protocol tuning is typically needed with frequency-selective pulse sequences to optimize performance, especially at higher magnetic field strengths.

2.3.8.2.5 Chemical-Shift Water-Fat "Dixon" Imaging

Chemical-shift water-fat "Dixon" imaging robustly integrates sensitive water-fat spectral detection from single-voxel proton MRS with the benefits of 2D and 3D MRI.[112–115] In contrast to frequency-selective methods, these strategies do not generally employ frequency-tuned RF pulses for targeted signal excitation or suppression of water or fat. Rather, water and fat signals are both acquired by receivers and sophisticated yet elegant mathematical algorithms are used to solve for the individual components. Dixon demonstrated in 1984 that by controlling the TE when data were acquired after RF excitation, the net detected MRI signal can be uniquely comprised of either water and methylene fat signals approximately in-phase (IP = W + F, parallel) or approximately out-of-phase (OP = W − F, anti-parallel).[116] Dixon recognized that by using this



Peak	Assignment
1	-**H**C = C**H**- -C**H**-O-CO-
Water	$\mathbf{H_2O}$
2	-CH = CH-C$\mathbf{H_2}$-CH = CH-
3	-CO-C$\mathbf{H_2}$-CH_2- -CH_2-CH = CH-CH_2-
4	-CO-CH_2-C$\mathbf{H_2}$- -(C$\mathbf{H_2}$)$_n$-
5	-$(CH_2)_n$-C$\mathbf{H_3}$

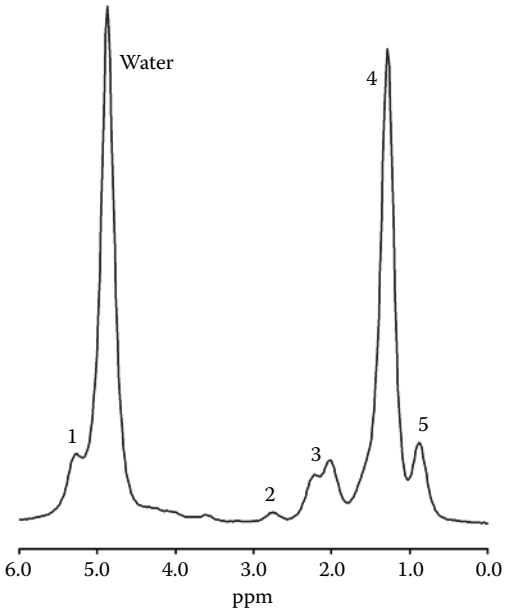


FIGURE 2.2 Example of a spectrum from single-voxel MRS containing water and fat, acquired at the interface of a bottle laid horizontally containing water and vegetable oil. The water resonance is at 4.7 ppm. The dominant methylene peak (#4) of fat is shifted 3.4 ppm downfield, at 1.3 ppm. While water (H–O–H) is a symmetrical molecule and has a true single peak, fat exhibits additional minor resonances from other moieties, some of which, especially the olefinic group (#1), is in close proximity to the water peak. The area under each peak represents the amount of each species present in the voxel, such that water to fat ratio (e.g., a fat fraction) can be computed. (Data courtesy of Gavin Hamilton, PhD, University of California, San Diego.)

two-point (IP/OP) approach, separated water and fat images could then be obtained. Intuitively, one can realize that for a voxel (tissue) containing only water or fat, its net signal on IP and OP acquisitions will be similar, as one component's signal will be zero. In contrast, a voxel containing both water and fat will have different signals on the IP/OP pair (Figure 2.3).

Methodological developments in chemical-shift-based water-fat imaging have greatly advanced the two-point approach to arbitrary TEs and more robust algorithms in recent years.[117,118] Variants such as three- and six-point Dixon techniques have overcome magnetic field inhomogeneity issues that cause erroneous water–fat decomposition.[119–121] With robust separation and identification of water and fat components, a subsequent fat fraction map can be computed to facilitate meaningful quantitative measurements of fat content on a voxel-by-voxel basis. Other methodological advances have addressed the ambiguity in determining whether water or fat as the dominant species, thus facilitating voxel-wise fat fractions to be computed on a full 0%–100% rather than an aliased 0%–50% scale. Finally, quantitative accuracy in estimating fat fraction has been improved by strategies that employ multipeak spectral models of triglycerides[122] and account for systematic confounding factors.[123] The former is a critical advancement since early works have only considered the single-peak spectral model with the methylene resonance. Many studies have validated chemical-shift water-fat MRI in the liver.[124–127] Chemical-shift "Dixon" pulse sequences have also been demonstrated in the heart[33] skeletal muscles,[128] and abdomen.[106] Figure 2.4 illustrates representative examples used in body composition research.

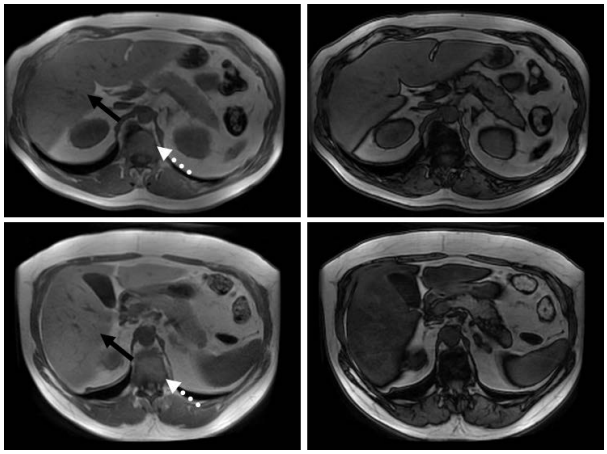


FIGURE 2.3 The two-point Dixon technique. In-phase on the left (IP: W + F) and opposed-phase on the right (OP, W − F) images from two subjects are shown. In the first subject (top row), the signal intensities within the liver (black arrow) between IP and OP images are similar, with the latter being just slightly darker. This signifies a small presence of hepatic fat. In the second subject (bottom row), the liver signal intensity is significantly lower in the OP image. This indicates a much greater presence of hepatic fat. The hepatic fat fractions of the subjects were 9% and 24%, respectively, as determined by MRS. Note that IP and OP signal variations are not observed in the subcutaneous and visceral adipose tissue (fat dominant) and muscles (water dominant). For comparison, note that in both subjects the change in signal intensity between IP and OP images in the vertebral bone marrow, which contains near equal amounts of water and fat (dotted white arrows). This leads to a near cancellation of signals in the OP images. The two-point Dixon technique only considers the dominant methylene resonance of fat.

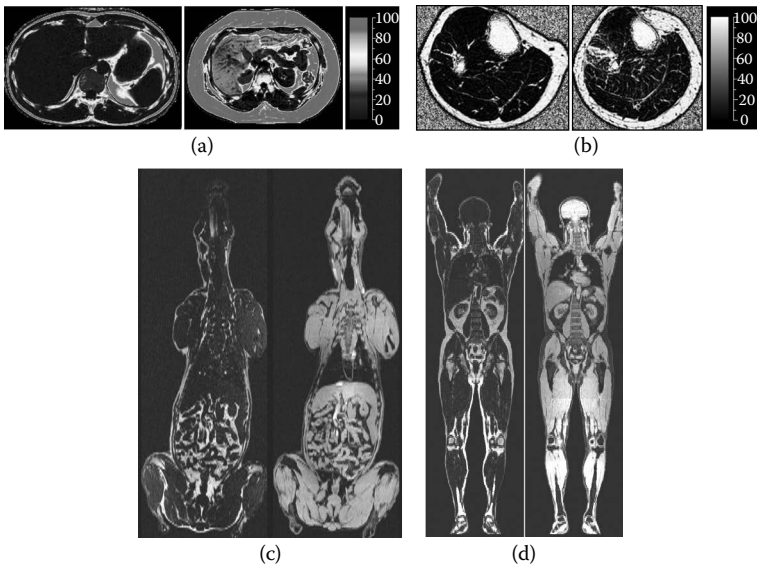


FIGURE 2.4 Examples of results from three-point and six-point Dixon water-fat MRI. Note color bars representing 0%–100% fat fraction range. (a) Two axial images from a lean (left) and an overweight (right) individual showing significant differences in liver fat content and subcutaneous adipose tissue (red). (b) Similar images from two other individuals showing skeletal muscles in the legs and highlighting noticeable differences in intermuscular fat accumulation. Coronal whole-body examples illustrated in (c) a dog and (d) a human. Each image pair reflects reconstructed fat-only and water-only images. (Dog data courtesy of E. Brian Welch, PhD, Vanderbilt University; whole-body human data courtesy of Joel Kullberg, PhD, Uppsala University, Sweden.)

2.3.8.3 Image Protocol Selection and Standardization

2.3.8.3.1 Acquisition-Related Image Protocol Selection and Standardization

- Adipose tissue components standardization: With the fast growth of MRI and CT, imaging methods have been widely applied in adipose tissue measurements. However, a review in the literature revealed inconsistencies in the use of specific definitions, especially for the compartment termed "visceral" adipose tissue.[129] In an effort to standardize the use of adipose tissue components, an imaging-based classification of total body adipose tissue and VAT has been proposed and tables of classification can be found in the reference.[129] Major adipose tissue components include SAT, VAT, and perimuscular adipose tissue (also called intermuscular adipose tissue). It is believed that the intraperitoneal adipose tissue, including mesenteric and omental adipose tissue, is most closely related to obesity-related health risks, because these two depots drain through portal vein. It is important to adopt standard anatomical classification of adipose tissue to facilitate comparison among different studies.[129]
- Single-slice versus multislice protocol: Because of the relatively high cost of acquiring and analyzing whole body images, single cross-sectional imaging has been used as a compromise between cost and accuracy. Traditionally, single-slice imaging was acquired at the L4–L5 intervertebral disk level. However, recent large-scale studies have found that an image slice higher in the abdomen (i.e., the L2–L3 level or 5–10 cm above the L4–L5 level) estimates abdominal VAT better than an L4–L5 slice.[22–24] A single-slice image in the upper abdomen may correlate with health risks better than the L4–L5 slice.[25] On the other hand, SAT is less influenced by single-slice location and slices at different anatomical locations.[24]

2.3.8.3.2 Postprocessing Image Protocol Selection and Standardization

- Volume reconstruction model: Once tissue areas have been quantified from MRI images, volumes are then calculated using geometric models based on the measured areas and the distances between adjacent slices. Equations based on the parallel trapezium and the two-column models (Equations 2.1 and 2.2) are more accurate in estimating tissue volumes than the corresponding equation for truncated pyramid and truncated cone models.[17]

$$V_i = \frac{h(A_i + A_{i+1})}{2} \tag{2.1}$$

$$V = (t + h)\sum_{i=1}^{N} A_i \tag{2.2}$$

where V_i is the estimated volume between two adjacent slices and V is the total volume of a tissue component, A_i and A_{i+1} are the areas of two adjacent scans, h is the interval between adjacent sampled

slices, t is the thickness of each slice, and N is the total number of slices.

- Automatic segmentation versus semiautomatic segmentation: Currently, there is a lack of standardization of the segmentation protocol of adipose tissue. Several groups have recognized the time-consuming and labor-intensive work involved with image segmentation. Efficient semiautomated and automated algorithms have been developed and there has been substantial progress in refining automated software in the past 10 years and development is ongoing.[107,26,27,28,130] Although automatic segmentation works well on high-quality images in small-scale studies, some whole body adipose tissue segmentation requires the total imaging matrix (TIM) technique.[107,130] In addition, it is unknown whether automatic segmentation procedures work well in large-scale studies including subjects with a small amount of adipose tissue or when artifacts are present. In addition, future automatic segmentation procedures may need to be developed for measurement of intermuscular adipose tissue as well as automatic segmentation of lean tissue subcomponents such as organs and skeletal muscle. At present, semiautomatic segmentation performed by experienced analysts should still be considered as the reference method for regional adipose tissue analysis.
- Reproducibility and accuracy: MRI-measured adipose tissue components have been validated by cadaver analysis.[131,132] The CV for repeated SAT measurements by CT and MRI are similar and in the range of ~2%.[97–99] Early studies reported that CT has better reproducibility than MRI for VAT measurement, but this difference is diminishing with advanced MRI techniques. It should be noted that automatic segmentation usually has better reproducibility than semiautomatic segmentation, because a fully automatic process theoretically would generate identical results on the same image on repeated processing. However, this does not necessarily mean that automatic segmentation is more accurate than semiautomatic segmentation, because the same mistakes can exist with repeated automatic segmentation while manual segmentations carried out by experienced analysts are less likely to include mistakes.

2.3.8.4 Imaging Summary and Outlook

While CT is still a broadly accepted body composition method, MRI has been increasingly used in the past decade. The increasing popularity of MRI can be attributed to a combination of the increased availability of MRI scanners, the lack of radiation concerns, the decreased scanning time with technology advances, and the more flexible tissue signal contrast for quantifying fat and lean tissue compared to CT.

MRI remains a relatively untapped resource in body composition and obesity research and has not yet reached full potential. Opportunities abound for future investigation, particularly in lipid metabolism and noninvasive adipocyte characterization. New techniques to assess water diffusion within adipose tissue[133] and an extension of Dixon methods to quantify triglyceride chain lengths and unsaturation have strong potential.[134,135]

The development of efficient semiautomated and automated algorithms for adipose tissue segmentation is an ongoing effort. In conclusion, MRI is emerging as a powerful and comprehensive imaging tool for body fat quantification. The modality provides investigators with unparalleled flexibility in exploring fat biomarkers and associations in obesity. Future directions include developing fully quantitative MRI methods for total lipid content, as well as fully automatic segmentation for regional adipose tissue depots. Reliable quantification methods should also be developed across the life span including infancy, childhood, and adulthood.

2.4 COMPONENT FIELD METHODS

2.4.1 Anthropometry

2.4.1.1 Body Weight and Stature

Body weight is typically measured to the nearest ±0.1 kg using a high-quality calibrated beam-balance or electronic scale, and stature is measured to the nearest ±1 cm using a wall-mounted stadiometer.[136] Self-reported weight and stature are used in very large epidemiological surveys and retrospective studies, but it is associated with recall bias and social desirability bias. Body mass index (BMI, weight/stature^2) is a measure of "relative weight" independent of stature. Body weight, stature, BMI, age, and sex can be used in equations to estimate %fat.[137]

2.4.1.2 Skinfolds

Skinfold methods estimate SAT by pinching and elevating a skinfold and measuring the thickness of the fold with specially designed calipers. Because SAT occupies ~70%–90% of total adipose tissue and SAT thickness varies among anatomical locations, skinfold thicknesses in standard sites (i.e., the triceps and subscapular sites) can be used to grade or predict FM and describe "fat patterning."[138] Skinfolds are also used in equations to predict body density, FM, %fat with an error of 3.5%–5%, and whole-body skeletal muscle mass.[51,139,140] A disadvantage is that body composition prediction equations based on skinfold thicknesses are "population specific." In addition, the reliability of the measurements may decrease in very obese subjects.[141]

2.4.1.3 Ultrasound

Ultrasound measurement of SAT thickness does not compress tissue and therefore theoretically has greater validity and greater thickness measurement capacity than calipers.[142] Reliable ultrasonic measurements require highly trained technicians using B-mode imaging that provides a real-time 2D image of SAT. SAT thickness can be measured using a ruler or digitizer.[143] Ultrasound has also been explored as

a method of predicting %fat (e.g., correlation with DXA, $r = 0.98$) with fat thickness measured at mid-thigh level and umbilical level. Ultrasound measurements to predict body composition are also population specific.

Intra-abdominal adipose tissues can be estimated by applying equations including measurements of fat layer thickness of the posterior right renal wall, the distance from the internal surface of the abdominal muscle to the splenic vein, and the distance from the internal surface of the abdominal muscle to the posterior wall of the aorta on the umbilicus and has a correlation with corresponding CT estimates of $r = 0.86$.[142–146] Ultrasound measurements to predict body composition are also population specific. Ultrasound, particularly in the form of echocardiography, has gained some interest among clinical researchers for estimation of pericardial and epicardial adipose tissue.[32] Abdominal ultrasound is also used by some investigators as a means of evaluating hepatic steatosis that is more practical and less costly than CT and MRI approaches.[84]

2.4.1.4 Circumferences

Body circumferences are useful in that, unlike skinfold thicknesses, they can always be measured, even in extremely obese subjects. Circumferences reflect internal adipose tissue as well as SAT, but are also influenced by variation in muscle and bone. As a result, the interpretation of circumference measurements, and especially circumference ratios, is often not straightforward. As for all anthropometric variables, body circumferences should be measured with close attention to standardized procedures.[136] Flexible, inelastic tapes are recommended.

The most useful circumferences for grading or predicting body fat and for describing adipose tissue distribution are upper arm, chest, waist or abdomen, hip or buttocks, proximal or mid-thigh, and calf.[136,147] Several investigators have emphasized that waist circumference (WC) is a better index of variation in VAT than the waist-to-hip ratio (WHR), which was used early in the study of fat distribution.[148,149] Changes in visceral obesity are clearly associated with changes in WC, but this circumference cannot accurately predict small changes in VAT. There are four commonly used WC measurement sites (i.e., smallest circumference on the torso below the sternum, umbilicus, lower margin of the ribs, and iliac crests) and this variation makes it difficult to compare results across studies.[150,151]

2.4.1.5 Adipose Tissue Distributions

Skinfold thicknesses have been used to describe the distribution of SAT. This aspect of adipose tissue distribution has been called "fat patterning," to distinguish it from the more general form that includes the amounts and distribution of VAT.[152] WC and WHR describe fat distribution including VAT, which represents the obesity phenotype that conveys the largest risk for major chronic diseases and mortality.[153,154] Recent efforts have been focused on developing equations for predicting the amount of VAT, but the errors associated with these equations tend to be large, in the range of 25% to 40%.[148,149,155,156] Several studies have suggested that sagittal trunk thickness (or sagittal diameter) correlates with VAT volume better than other anthropometric measurements.[149,157] Anthropometric estimates of VAT may be appropriate for populations studies but not for small sample studies or individual subjects.

2.4.2 Bioimpedance Analysis

BIA is a method for predicting body composition based on the electrical conductive properties of the human body. The ability of the body to conduct an electric current is due to the presence of free ions, or electrolytes, in the body water. Measures of bioelectric conductivity are therefore proportional to TBW and to body composition components with high water concentrations such as the FFM and skeletal muscle masses. FM is derived as the difference between body weight and predicted FFM.[158]

Since many factors such as body proportions or "geometry" influence measurements of electrical conductivity, the exact functional relationships between measurements of bioelectric conductivity and TBW or FFM cannot be derived from either physicochemical models or experimentally. Statistical calibration against criterion measures (e.g., estimates of TBW from hydrometry) in a sample of subjects is necessary. It is recommended that any externally developed BIA equation should be cross validated in a random subsample against estimates from an accepted reference method before general extension to an entire study population. The relatively low cost, portability, ability to track long-term body composition changes, operation simplicity, and lack of radiation exposure make appropriately developed BIA methods a good choice for field applications.

2.5 ERRORS OF ESTIMATION

Measurement error can be caused by instrument error and observer error. Model error is intrinsic to the developed equation in estimating certain body components. For example, a population-specific prediction equation may have errors when applied to a different population. Another example is that calculation of FFM from the assumed hydration of 0.73 is based on average population values and this causes error in estimating individual subject hydration. If assessed by calculation from several direct measurements, the propagation error can be used to calculate the error of this estimation. For example, if an estimation Q equals to the sum of two direct measurements X and Y (i.e., $Q = X + Y$), the error for Q can be calculated as $\sigma_Q = (\sigma_X^2 + \sigma_Y^2)^{1/2}$.[159]

Body composition method errors can be evaluated by measuring accuracy and reproducibility of the measurement. Accuracy is the level of agreement between the measured value and the "true" dimension, and it is usually established by comparison to a reference method. Precision, as distinct from accuracy, is the degree to which a measurement is replicable using the same instrument. It can be quantified as the variability among repeated measurements

TABLE 2.2
Main Qualitative Features of Available Body Composition Methods Used to Evaluate Adiposity-Related Components

	^{40}K	IVNA	TBW[a]	UWW	ADP	DXA	MCM	MRI[b]	CT[c]	ANTH	BIA
Accurate?	•••	••••	•••	•••	•••	•••	••••	••••	••••	•	••
Reproducible?	••	••	••	••	••	••••	•••	•••	•••	•	••••
Cost to purchase?	••••	••••	•	••	•••	•••	•••	••••	••••	•	•
Cost to operate?	•••	•••	••	••	••	••	••	•••	•••	•	•
Technician training?	••	••	••	••	••	••	••	•••	•••	••	•
Radiation exposure?	•	••••	•	•	•	••	••	•	••••	•	•
Requires subject participation?	•	•	•	•••	••	•	•••	•	•	•	•
Transportable?	•	•	••••	•	••	••	•	•	•	••••	••••
Regional estimates?	√	√	X	X	X	√	X	√	√	√	√
Appropriate for											
Very obese adults?	√	√	√	√	√	X	X	X	X	X	√
Children?	√	X	√	√	√	√	√	√	X	√	√
Elderly?	√	√	√	√	√	√	√	√	√	√	√

ANTH, anthropometry; ADP, air displacement plethysmography; BIA, bioimpedance analysis; CT, computerized axial tomography; DXA, dual-energy x-ray absorptiometry; IVNA, in vivo neutron activation analysis; K, potassium; MCM, multicomponent models; MRI, magnetic resonance imaging; TBW, total body water; UWW, underwater weighing; √, yes; X, no·

Scale: • (least or none) •••• (most).

[a] Assumes TBW measured by stable isotope dilution.

[b] Assumes four or more components and stable isotope for TBW.

[c] Radiation exposure varies with number of slides.

over a short time period in the same subject. Precision-related errors include both technical error of measurement and physiological variation (i.e., fluid status variation).[160] Reproducibility of a method can be expressed as standard deviation or CV. Other statistical tools for evaluating reproducibility include Bland-Altman method and intraclass correlation.[161]

2.6 SUMMARY AND CONCLUSIONS

The remarkable technological advances over the past decade provide investigators with the tools needed to evaluate components at all five body composition levels. The applications for body composition analysis abound and dictate the selected method requirements. While our method organization was separated into two categories, reference and field, each method has an array of definable characteristics that ultimately determine research and clinical utility. Most methods are capable of providing estimates of more than one adiposity-related component so that the investigator can choose among them depending on instrument availability and specific method features. Some of the qualitative characteristics of the methods reviewed in this chapter are summarized in Table 2.2. These "gradings" are subjective but should give the reader some idea of how to select a method among those available with consideration for the evaluated subject population. The present overview should be supplemented by the interested reader with in-depth body composition reviews and the available texts published since 1985 are presented in the Appendix.

APPENDIX: MONOGRAPHS ON BODY COMPOSITION RESEARCH PUBLISHED SINCE 1985

1985—Norgan NG, ed. Human body composition and fat distribution. EUR-NUT Report 8.

1985—Roche AF, ed. *Body-Composition Assessments in Youth and Adults*. Columbus, OH: Ross Laboratory.

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3 Anthropometric Indicators in Relation to the Gold Standards

Peter T. Katzmarzyk

CONTENTS

3.1 INTRODUCTION

This chapter outlines the associations among common anthropometric measurements and more precise measurements of body fat obtained from "gold standard" methods. Anthropometry (anthropos = human, metron = measure) refers to a set of standard measurements of the dimensions of the human body.[1] To ensure reliable assessments, anthropometry requires standardized equipment and protocols, and technicians need to be trained to be proficient. Anthropometric measurements are commonly used for the clinical assessment of obesity as well as for population health surveillance and in other cases where the use of more direct measures of adiposity may be prohibitive because of cost, time, or other logistical constraints. The use of gold standard measures of body fatness has been generally limited to laboratory studies of obesity, in addition to the clinical assessment of obesity in cases where imaging protocols are indicated.

3.2 COMMON ANTHROPOMETRIC MEASUREMENTS RELATED TO OBESITY

The list of anthropometric measurements that can be obtained on a subject is almost limitless, but several measures and indices have emerged as common markers of body fatness (Table 3.1). Protocols for the measurement of anthropometric dimensions have evolved over time, and the most common protocols are described in this section.

3.2.1 Height and Weight

Standard protocols for the measurement of standing height and weight are described by Lohman et al.[2] Height is measured as the distance from the floor to the apex of the skull using a fixed or portable stadiometer, with the subject standing erect with weight evenly distributed on both feet (without shoes). The subject is asked to inhale deeply and maintain the erect posture as the measurement is obtained. Body weight has traditionally been measured using a beam balance scale, with the subject in light clothing, although it is becoming more common in both clinical and research settings to use a calibrated electronic scale. Given that body weight exhibits diurnal variation, it is preferable to measure subjects at the same time of the day, preferably in the morning.[1,2]

3.2.2 Waist Circumference

Several protocols exist for the measurement of waist circumference.[3] Common elements of waist circumference protocols include (1) using a nonelastic anthropometric tape,

TABLE 3.1
Common Anthropometric Measurements and Indices Related to Body Fatness

Measurements	Subcutaneous skinfolds
Weight	Indices
Waist circumference	Body mass index
Hip circumference	Waist-to-hip ratio
Abdominal sagittal diameter	Waist-to-height ratio

(2) ensuring that the tape remains horizontal to the floor and perpendicular to the long axis of the body, and (3) wrapping the tape snugly around the body without compressing the skin. The main difference in waist circumference protocols is the anatomic site of measurement. Common protocols include measurement at the (1) midpoint between the lower margin of the last palpable rib and the top of the iliac crest, (2) top of the iliac crest, (3) umbilicus, and (4) minimal waist.[3,4] The correlation among values measured at different anatomic sites is typically high ($r > 0.93$)[5,6]; however, there are significant differences in the absolute value of waist circumference across the different measurement sites.[5–9] Thus, it is important to clearly specify the measurement protocol for waist circumference when reporting the results of scientific studies and when comparing across different studies and surveys.

3.2.3 Hip Circumference

Hip circumference is typically measured at the level of the widest portion of the buttocks using a nonelastic anthropometric tape.[3] As with the protocol for waist circumference, care must be taken to ensure that the tape remains horizontal to the floor and perpendicular to the long axis of the body, and the tape should fit snugly around the body without compressing the skin.

3.2.4 Skinfolds

The measurement of subcutaneous skinfolds in the field of nutritional assessment has a long history.[10] The use of standard protocols and the rigorous training of technicians are critical to ensure the reproducibility of skinfold measurement within and between technicians. Standard protocols for the measurement of skinfolds involve the elevation of a double fold of skin and subcutaneous adipose tissue between the thumb and index finger, which is measured with calibrated calipers.[2] The fold is raised perpendicular to the surface of the body, aligned with specific anatomic landmarks. Common measurement sites for skinfolds include the triceps, biceps, medial calf, subscapular, suprailiac, and abdominal sites. Skinfold measurements are often summed to provide a single measure of subcutaneous adiposity, or they may be expressed as ratios to provide an index of relative fat distribution. Skinfolds have also traditionally been used in prediction equations for the estimation of body fat percentage,[11–13] with reported errors of approximately 3%–5%.[2]

3.3 COMMON ANTHROPOMETRIC INDICES RELATED TO OBESITY

Anthropometric measurements are often combined to produce indices that may better predict overall body fatness or adiposity in specific fat depots (abdominal visceral, subcutaneous, intramuscular, intraorgan, etc.). The most common index of obesity is the body mass index (BMI = weight [kg]/height [m^2]). BMI is currently recommended as the primary clinical tool for the assessment of obesity, and ranges of BMI are used to classify individuals into body weight categories.[14,15] Among American and European adults, BMI < 18.5 kg/m^2 signifies underweight, BMI 18.5–24.9 kg/m^2 is normal weight, BMI 25–29.9 kg/m^2 is overweight, and BMI ≥ 30 kg/m^2 indicates obesity.[14–17] Furthermore, the obesity category is often subdivided into Class I (BMI 30–34.9 kg/m^2), Class II (BMI 35–39.9 kg/m^2), and Class III (BMI ≥ 40 kg/m^2) obesity to identify increased health risks.[14] Given differential associations between BMI and health outcomes, lower BMI thresholds have been proposed for Asian populations[18]; however, more research is required to support definitive Asian-specific thresholds.

Among children and youth, age- and sex-specific reference data have been developed to account for expected differences due to normal growth and maturation. The Centers for Disease Control and Prevention in the United States developed reference data by combining several national surveys, and children ≥85th but <95th percentile are considered overweight while those ≥95th percentile are considered obese.[19,20] To facilitate international comparisons of obesity prevalence, the International Obesity Task Force (IOTF) developed pediatric reference data for BMI using large international samples of children.[21] In these cross-national samples, the adult BMI cutoff points for overweight and obesity at age 18 years were regressed back through the growth curve, providing age-specific (6-month intervals) and sex-specific overweight and obesity cutoff points for children. More recently, the World Health Organization (WHO) produced BMI growth standards for children from birth to 5 years of age based on data from the WHO Multicentre Growth Reference Study.[22] The WHO

growth standards are beginning to be adopted in some clinical settings, but to date, they are not in widespread use.

The waist-to-hip circumference ratio (WHR) is another commonly reported anthropometric index. WHR is an index of relative fat distribution (i.e., trunk vs. extremity), and epidemiological studies have reported that it is related to risk of cardiovascular disease (CVD) and premature mortality.[23,24] However, WHR has lower correlations with measures of body fat than do measures of overall adiposity such as BMI or waist circumference.[25] In addition to WHR, there is interest in the waist-to-height ratio (WHtR), an anthropometric index related to CVD risk and premature mortality.[24,26] WHtR may have particular clinical relevance as a predictor of obesity-related risk in children and adolescents, as the inclusion of height in the denominator may negate the need for age- and sex-specific reference data.[27,28] A value of 0.5 for WHtR has been proposed as a clinical threshold denoting an increased obesity-related health risk in children and adults.[28,29]

3.4 OTHER ANTHROPOMETRIC MEASUREMENTS AND INDICES OF OBESITY

In addition to the common measurements and indices just described, several other anthropometric markers have been proposed over the years to assess adiposity. Examples of these less common indicators include the somatotype, the conicity index, abdominal sagittal diameter, and the body adiposity index (BAI). The somatotype has a long history in the field of human biology, and the concept evolved particularly during the first half of the twentieth century. Sheldon et al.[30] used a series of reference photographs plus height and weight (a so-called anthroposcopic method) to somatotype individuals along three dimensions labeled ectomorphy, mesomorphy, and endomorphy. A modification of this approach that relied entirely on anthropometric measurements was reported by Heath and Carter, and it has remained the predominant method over the past 40 years or so.[31] Over time, the endomorphic component of physique (body fatness) has dominated the discussion regarding health risks, and interest in overall physique and somatotype has declined.

The conicity index was developed as an indicator of abdominal obesity, and it expresses an individual's waist circumference relative to the circumference of a cylinder generated from the subject's height and weight, assuming a constant for body density.[32,33] The conicity index has not been widely adopted, in part because simpler indices have been developed that are not as computationally complex. Abdominal sagittal diameter can be defined as the diameter of the abdomen in the sagittal plane, typically measured from images of the abdomen (magnetic resonance imaging [MRI] and computed tomography [CT]) or anthropometrically with large sliding calipers with the subject in a supine position.[34,35] Several studies have suggested that abdominal sagittal diameter is related to visceral adiposity[36,37] and CVD risk factors[38,39]; however, it has not been widely adopted as a clinical or research tool. The most recently reported anthropometric index related to obesity is the BAI ((hip circumference/(height)$^{1.5}$) – 18).[40] Limited information regarding the utility of BAI exists, yet there is some evidence that it is similar to, but not better than, BMI in its relationship with total body fat.[41]

3.5 GOLD STANDARD MEASUREMENTS OF BODY FAT

In most fields, so-called gold standard measurements change over time. This is particularly true in the field of obesity, as recent technological advances have allowed for the more precise measurement of total adiposity as well as body fat stored in specific body depots. As described in Chapter 2, there are numerous laboratory methods for the assessment of adiposity. The major methods include densitometry (both water and air), measurement of total body water, whole-body counting and neutron activation analysis, dual-energy x-ray absorptiometry (DXA), bioimpedance analysis, and imaging techniques such as MRI and CT. For the purposes of this chapter, which focuses on the relationship between anthropometry and gold standard methods, the discussion is limited to the most widely used current gold standard methods: DXA, MRI, and CT.

3.6 ANTHROPOMETRIC PREDICTORS OF TOTAL BODY FAT MASS AND PERCENTAGE BODY FAT

The prediction of body fat from anthropometric measurements has a long history in the fields of nutrition, sports science, and human biology. Earlier studies focused on developing prediction equations that use various skinfold measurements, while more recent work has focused on the utility of BMI and body circumferences in predicting body fat. Many studies have examined the associations between anthropometry and gold standard measures of body fat. This discussion focuses on key studies that have examined these issues using comprehensive samples and approaches.

3.6.1 Adults

Several studies of body fat associations with BMI, waist circumference, and other circumferences have been published. Two important studies of the relationship between BMI and body fat were published by Deurenberg et al.[42,43] The first study assessed the relationship between BMI and densitometrically determined percentage body fat in a sample of 1229 adults and children. Among adults, a prediction model that included age, BMI, and sex, accounted for 79% of the variance in body fat percentage, with a standard error of estimate (SEE) of 4.1%.[42] The second study was a meta-analysis of existing studies with the purpose of determining whether the relationship between BMI and percentage body fat differed among ethnic groups.[43] The results indicated that for a given level of BMI, African-Americans and Polynesians had lower percentage body fat than whites, and BMI in Chinese,

Ethiopians, Indonesians, and Thais was lower than in whites. Given these intriguing results, Gallagher et al.[44] examined the relationship between BMI and body fatness (DXA) using a large sample ($n = 1626$) of adults from three ethnic groups (white, African-American, and Asian). There was a high correlation between BMI and body fat in each sex-by-ethnicity group. Regression models were developed for predicting percentage body fat from BMI, and the prediction formulas were then used to develop sex- and ethnic-specific thresholds for percentage body fat that corresponded to BMI thresholds of 18.5, 25, and 30 kg/m^2. For every level of BMI, females were about 12% fatter; Asians were found to have higher percentage body fat; and the percentage body fat corresponding to a given level of BMI increased with age (see Figure 3.1).[44]

A recent study provided some insights into the comparative strength of the associations among several anthropometric indicators and total body fat (kg) from DXA in a large sample ($n = 2037$) of white and African-American adults.[25] Figure 3.2 presents the correlations separately in the four sex-by-race groups from that study. It is evident that there was great homogeneity in the strength of the correlations across indicators, with the exception of height and WHR, which exhibited significantly lower correlations with total body fat than the other indicators, especially among women.[25] With these exceptions, the correlations were generally above ~0.70 across all sex-by-race groups. These results reinforce the notion that WHR is not as strongly associated with total body fat as other anthropometric measures.

Skinfolds are useful measures on their own as an index of subcutaneous adiposity, and many studies have published data on individual skinfolds (triceps, subscapular, etc.), while others have created indices based on the sum of several skinfolds or the ratio of trunk to extremity skinfolds. Given that the subcutaneous adiposity compartment represents a substantial proportion of the total body fat mass, skinfolds tend to be highly correlated with total body fat. Early work focused on assessing the relationship between skinfolds and body fat, and several predictive equations were developed.[11–13,45] The most commonly used equations are those produced by Jackson and Pollock,[11,13] as well as those by Durnin and Womersley, which relied on underwater weighing as the gold standard for body fat at the time.[12] More recently, efforts have been made to cross-validate these equations in ethnically diverse samples of men and women.[46,47] When the Jackson and Pollock estimates were compared against the current gold standard measure of percentage body fat (from DXA), there was a high correlation between predicted and actual percentage body fat ($r = 0.85$ in women and 0.93 in men).[46] However, the original equations, which were developed using a sample of white men and women, systematically underestimated the percentage body fat of Hispanic men and women and systematically overestimated percentage body fat in African-American men. Similarly, when the Durnin and Womersley estimates were compared against DXA-derived percentage body fat in white, African-American, Hispanic, and Asian-Americans, the mean differences were significantly different in four of the eight sex-by-race groups,

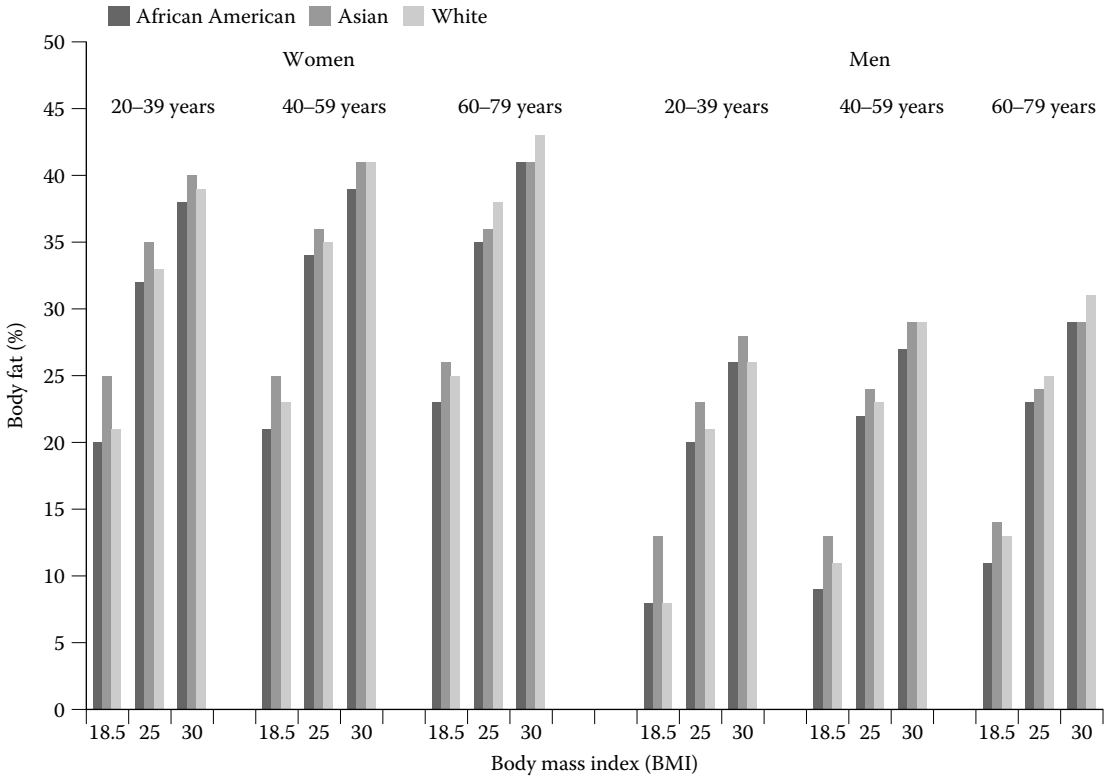

FIGURE 3.1 Percentage body fat at BMI thresholds of 18.5, 25, and 30 kg/m^2 in African-American, Asian, and white men and women. (Data from Gallagher D et al., *Am. J. Med.*, 72, 694–701, 2000.)

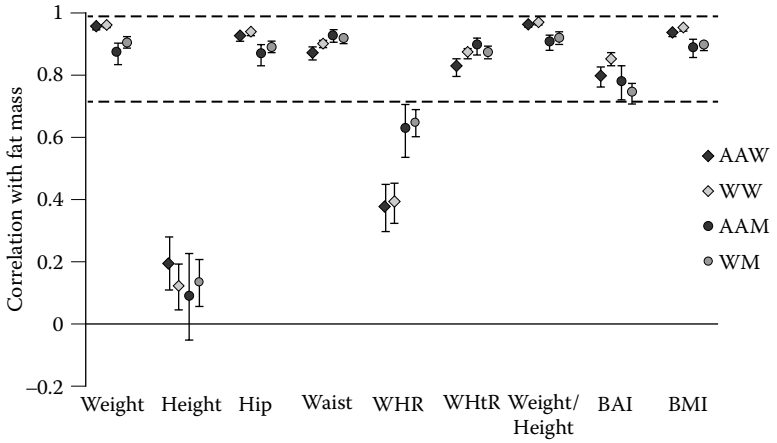

FIGURE 3.2 Correlations between anthropometric measures and total body fat mass in a large sample ($n = 2037$) of white and African-American adults. Error bars indicate 95% confidence intervals. AAM, African-American men; AAW, African-American women; BAI, body adiposity index; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WM, white men; WW, white women. (Adapted from Barreira TV et al., *Mayo Clin. Proc.*, 87, 452–60, 2012.)

especially among Asian women and African-American men.[47] The results of these two studies suggest that care should be taken when using these popular body fat equations in modern populations. Given the increasing availability of DXA, the reliance on skinfolds to estimate body fatness should be discouraged in most research and clinical settings.

3.6.2 Children

The relationships among anthropometric variables and gold standard measures of body fat are more complex in children than in adults. Issues related to normal growth and maturation make the study of these associations more difficult in growing children. Nevertheless, there is great interest in identifying clinical markers of childhood obesity that are valid and reliable. As described in Section 3.3, BMI is recommended for screening for obesity among children and adolescents, and reference data have been developed in several countries. The study by Deurenberg et al.[42] developed a regression equation for children ages 7–15 years, in which age, sex, and BMI accounted for 38% of the variance in percentage body fat, with a SEE of 4.4%. Given that BMI is a measure of height and weight, it cannot distinguish between lean and fat tissue. Work from Freedman et al.[48] showed that among children with a high BMI (≥85th percentile), there was a strong relationship between BMI and fat mass, yet at lower levels of BMI, BMI was more highly correlated with fat-free mass than with fat mass. These results suggest that BMI should be used cautiously in clinical settings. Data from 7-year-old children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC) ($n = 3948$) were used to test the clinical utility of BMI in the identification of obesity.[49] The "true" measure of obesity was defined as the top 5% of body fat (from bioimpedance). The results indicated that the 95th percentile of BMI (U.K. reference) had relatively high sensitivity (88%) and specificity (92%) at identifying the obese children, whereas the IOTF obesity cutoff[21] had very high specificity (99%) but significantly lower sensitivity (59%).[49]

In addition to using BMI, there is a long-standing interest in using skinfolds to predict body fatness in children.[50–52] The most well-known equations are those published by Slaughter et al.,[50] which were developed using a sample of white and African-American children and youth and used underwater weighing as the gold standard. These authors recommended the use of two skinfolds, either the triceps and calf or the triceps and subscapular, for the prediction of body fat in children.[50] A more recent study compared several published equations in their ability to predict percentage body fat from DXA in a sample of 238 white children ages 13–17 years.[53] Most of the equations did not show good agreement; however, the authors recommended the use of the Slaughter et al.[50] equations for both sexes and the Brook[51] equation for girls, as these equations had limits of agreement that were narrower than the other equations and they did not show any bias that was dependent on level of body fat.[53]

A study from the Pennington Biomedical Research Center demonstrated that the prediction of body fat from skinfolds was better in the upper half of the body fat distribution compared to the lower half of the distribution, suggesting that skinfolds may not have the same predictive ability across the entire range of body fatness.[54]

Although several studies have examined the associations among different anthropometric measurements and CVD risk factors in children, there are surprisingly few studies of anthropometry (other than BMI and skinfolds) and total body fat in children. One recent study examined the ability of WHtR to predict DXA-derived total body fat in children ages 5–18 years.[55] The areas under the curves for the prediction of total body fat (>85th percentile) from WHtR were 0.89 in men and 0.91 in women. These values were not improved by using sex- and age-specific exponents for WHtR, suggesting that a single threshold may be suitable for all ages.

3.7 ANTHROPOMETRIC PREDICTORS OF ABDOMINAL VISCERAL FAT

3.7.1 Adults

Interest in the relationship between anthropometry and imaging-derived measures of abdominal visceral adipose tissue (VAT) began in the 1980s,[56,57] and many studies have subsequently investigated these relationships in adults. The sample sizes vary considerably among studies, and there has been a steady increase in published reports over the past decade as imaging technologies become more available in clinical and research settings. This section reviews a few key studies that have contributed to our understanding of the relationship between common anthropometric measures and VAT.

Data from the Atherosclerosis Risk in Communities Study provided good evidence of a relationship between anthropometry and MRI-measured VAT in a sample of 60 women and 97 men.[58] Quadratic functions of BMI, waist circumference, and subscapular skinfold were the best predictors in men, explaining 32.2%, 35.2%, and 20.2% of the variance in VAT, respectively. Linear functions of BMI, waist circumference, and subscapular skinfold were the best predictors in women, explaining 45.8%, 45.8%, and 33.8% of the variance in VAT, respectively. The association with WHR was best explained by a linear function in both men and women, explaining 32.9% and 33% of the variance, respectively.[58] Age-adjusted correlations between anthropometry and VAT were investigated in another sample of 71 men and 34 women from the Netherlands.[59] Among men, BMI ($r = 0.81$), waist circumference ($r = 0.85$), and WHtR ($r = 0.87$) had the highest correlations with VAT, whereas WHR had a somewhat lower correlation ($r = 0.78$). Similar results were found for women: correlations were highest for BMI ($r = 0.77$), waist circumference ($r = 0.72$), and WHtR ($r = 0.71$), while they were lower for WHR ($r = 0.40$). The correlations between subcutaneous skinfolds and VAT were also moderate in this sample ($r = 0.72$ in men and 0.65 in women).[59] Similar results were obtained using a sample of 76 white adults (ages 20–80 years); the correlations with VAT were highest for waist circumference and abdominal sagittal diameter ($r = 0.84$–0.93) and were lower for WHR ($r = 0.64$–0.75).[60]

The results of several studies have provided evidence of the clinical utility of anthropometric measurements in identifying high levels of VAT. Pouliot et al.[36] demonstrated that waist circumference and abdominal sagittal diameter were better correlates of VAT than WHR in a sample of 70 women and 81 men. Rankinen et al.[61] used receiver operating characteristic curve analyses in a large sample of 458 women and 331 men to examine the clinical utility of anthropometry at identifying those with elevated levels of VAT. The results indicated that waist circumference was the best overall predictor (compared to BMI, percentage body fat, and WHR), whereas WHR was a poor indicator (especially in women). This work was confirmed in a sample of 690 Chinese adults, in which waist circumference, BMI, and WHR were all associated with VAT levels; however, waist circumference exhibited the highest sensitivity and specificity at identifying those with high VAT.[62]

A recent study of 900 white and African-American adults compared correlations between several anthropometric indicators and levels of abdominal VAT.[25] Figure 3.3 presents the correlations from that study, and it is evident that the correlations with VAT are lower than those with total body fat in Figure 3.2. With the exception of height, the correlations ranged from about 0.40 to 0.80, and there was not one marker of obesity that stood out as superior to the others.[25]

The question of whether BMI or waist circumference is the better predictor of VAT was addressed in a study of 341 white men and women.[63] In that study, the authors used regression analysis to determine the independent effects of BMI and waist circumference on MRI-derived VAT. The results indicated that waist circumference was the strongest correlate of VAT ($R^2 = 0.76$ in women and 0.55 in men), and that adding BMI to the model did not add significantly to the variance explained.[63]

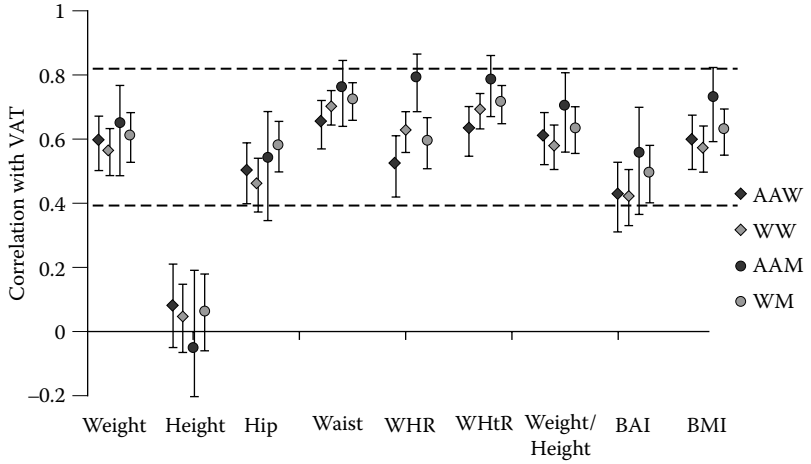

FIGURE 3.3 Correlations between anthropometric measures and VAT in a large sample ($n = 900$) of white and African-American adults. Error bars indicate 95% confidence intervals. AAM, African-American men; AAW, African-American women; BAI, body adiposity index; BMI, body mass index; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WM, white men; WW, white women. (Adapted from Barreira TV et al., *Mayo Clin. Proc.*, 87, 452–60, 2012.)

In a more recent study, researchers pooled data from several research sites in Canada and Finland to investigate the relative contributions of BMI and waist circumference to VAT.[64] Waist circumference explained 51% of the variance in VAT, and the addition of BMI to the model added an additional 1%.[64] The results of this study, as well as the others described in this section, suggest that waist circumference is the best anthropometric predictor of VAT; however, waist circumference explains only about half of the variance. Further work is required to determine the best approach for using waist circumference as a clinical marker of abdominal VAT.

3.7.2 Children

VAT is present in humans at birth, and it increases throughout childhood into adulthood.[65,66] But on average, children have low levels of VAT compared to adults, which sometimes makes measurement challenging. Several studies have examined the associations among anthropometric measurements and VAT in children and adolescents.

Goran et al.[67] investigated the associations among anthropometric measurements and VAT (quantified by CT) in a small sample of 16 young children (ages 4–8 years). The highest correlations were observed for skinfolds on the trunk (abdominal, suprailiac, and axillary; $r = 0.72$–0.78), whereas the correlations with waist and hip circumferences were not significant. This was followed by a larger study that included 113 white and African-American children ages 4–10 years.[68] The highest correlations with VAT (quantified by CT) were observed for trunk skinfolds (abdominal, suprailiac, and subscapular, $r = 0.85$–0.88), and the correlations with waist circumference ($r = 0.84$), hip circumference ($r = 0.81$), and BMI ($r = 0.81$) were of a similar magnitude. The correlations with sagittal diameter ($r = 0.40$) and WHR ($r = 0.32$) were somewhat lower.[68] A study published around the same time by Owens et al.[69] in 76 overweight and obese white and African-American children ages 7–16 years measured VAT using MRI at the L4-L5 lumbar vertebrae landmark of the spine. The highest correlations with VAT in this sample were observed for sagittal diameter ($r = 0.63$) and waist circumference ($r = 0.62$), followed by BMI ($r = 0.55$) and WHR ($r = 0.52$). A study of 42 boys and girls ages 11–13 years found that trunk skinfolds were most highly correlated with VAT measured by MRI at L4-L5 in boys (abdominal, suprailiac, and subscapular; $r = 0.62$–0.70), followed by BMI ($r = 0.58$), waist circumference ($r = 0.48$), and hip circumference ($r = 0.40$); the correlation with WHR was lower ($r = 0.24$).[70] A similar pattern was observed in girls, with the highest correlations for trunk skinfolds (abdominal, suprailiac, and subscapular; $r = 0.54$–0.64), followed by BMI ($r = 0.52$), waist circumference ($r = 0.42$), and hip circumference ($r = 0.40$); the correlation with WHR was lower ($r = 0.16$).[70]

A study of 196 overweight Latino youth ages 8–13 years used MRI to assess VAT at the level of the umbilicus.[71] The highest correlation with VAT was observed for waist circumference ($r = 0.65$) followed by trunk skinfolds (abdominal, suprailiac, and subscapular; $r = 0.47$–0.54) and hip circumference ($r = 0.44$). A later study of 96 boys and 74 girls from the ALSPAC study from the United Kingdom found high correlations between MRI-derived VAT volumes and both BMI and waist circumference in boys ($r = 0.83$ and 0.84) and in girls ($r = 0.77$ and 0.80), respectively.[72] Brambilla et al.[73] pooled data from several laboratories to analyze the association between anthropometry and MRI-measured VAT (L4 level) in 407 white and Hispanic children ages 7–16 years. Univariate regression analysis revealed that waist circumference (64.8% of the variance) and BMI (56.3% of the variance) were the best anthropometric predictors of VAT. A more recent study among 6- and 7-year-old boys and girls ($n = 31$) reported that the highest correlations with CT-derived VAT were observed for the abdominal skinfold ($r = 0.72$), waist circumference ($r = 0.70$), BMI ($r = 0.69$), and hip circumference ($r = 0.65$), whereas the correlation with WHR was much lower ($r = 0.11$).[74]

Taken together, the evidence suggests that VAT is moderately correlated with anthropometric measurements in children and adolescents. The highest correlations are with trunk skinfolds, waist circumference, and BMI. Few studies included abdominal sagittal diameter, and those that did demonstrated correlations comparable to those with BMI and waist circumference. The correlations between VAT and WHR were consistently lower than those for other anthropometric markers, further emphasizing that WHR is a marker of *relative* fat distribution (trunk vs. extremity) and may not be a good predictor of body fat stored in the visceral compartment in children.

Although waist circumference is often reported to be the best anthropometric marker of VAT, the weighted average variance in VAT explained by waist circumference in the seven studies in children just described (that reported a correlation) was 52.7%. Thus, approximately half of the total variance in VAT is explained by waist circumference in these studies. Further research is required to identify ways in which anthropometric measurements can be combined with other simple clinical measures to improve the prediction of VAT.

3.8 ANTHROPOMETRIC PREDICTORS OF ECTOPIC FAT

Ectopic fat can be defined as body fat stored in locations and organs not normally associated with adipose tissue storage.[17,75] There is surging interest in the metabolic health consequences of ectopic fat accumulation, particularly of fat stored in the liver, heart, muscle, and pancreas.[75–77] Ectopic fat can be measured using imaging methods such as ultrasound, multidetector CT, MRI, and magnetic resonance spectroscopy methods.[75] The degree to which anthropometry can be used to assess ectopic fat is potentially of interest, but it has been explored in only a few studies to date. For example, results from the Framingham Heart Study indicated modest correlations between pericardial fat and BMI ($r = 0.46$ for men and 0.41 for women) and waist circumference ($r = 0.49$ for men and 0.43 for women).[78] Similarly, pericardial fat was modestly correlated with BMI ($r = 0.35$)

and waist circumference ($r = 0.48$) in men and women from the Multi-Ethnic Study of Atherosclerosis.[79] Data from the Framingham Heart Study also demonstrated low to moderate correlations between the liver-to-spleen fat ratio and BMI ($r = 0.27$) and waist circumference ($r = 0.27$) in the combined sample of men and women.[80] Another study of interest examined associations among anthropometry and both intrahepatic and intramuscular lipid stores in a sample of 477 men and women.[81] Both BMI ($r = 0.63$ in men and 0.62 in women) and waist circumference ($r = 0.71$ in men and 0.62 in women) were correlated with intrahepatic fat. Furthermore, both BMI ($r = 0.38$ in men and 0.45 in women) and waist circumference ($r = 0.50$ in men and 0.44 in women) were correlated with intramuscular fat in the soleus. Similar results were observed for intramuscular fat in the tibialis anterior, with correlations of 0.34 in men and 0.27 in women for BMI and 0.39 in men and 0.28 in women for waist circumference.[81]

Given the weak association between anthropometry and ectopic fat observed to date, it is unlikely that precise anthropometric methods will be developed to estimate ectopic fat distribution in specific organs. Most of this association is likely explained by the joint relationships between total adiposity, adipose tissue metabolism, and ectopic body fat accumulation.

3.9 CONCLUSIONS

This chapter has explored the associations among anthropometric markers of obesity and gold standard measures. Overall, there are significant associations among anthropometric measurements and the more direct measures of total and regional body fat. Equations that rely on skinfolds to predict body fat percentage have been used for many years, but recent studies have shown that these equations may not work well in modern populations. There is a need to develop sex- and ethnic-specific equations using diverse population samples. BMI is currently recommended for screening for obesity in children and adults; nevertheless, care should be used when interpreting BMI in clinical settings. A wide range of anthropometric indicators (BMI, waist circumference, etc.) are associated with body fat levels, and in large samples, these indicators have been shown to have similar correlations with percentage fat and total fat mass.

In both adults and children, waist circumference is a consistent, significant predictor of VAT and is typically a stronger predictor than other anthropometric measures. However, waist circumference explains only approximately 50% of the variance in VAT and is more highly correlated with total fatness than with VAT.[82] Care should be taken when using waist circumference to make inferences about the amount of abdominal VAT. The assessment of ectopic fat accumulation is currently a topic of great interest. Anthropometric measures are only modestly correlated with fat stored in ectopic depots, and it is unlikely that they will prove to be an efficient means of quantifying ectopic fat.

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4 Worldwide Prevalence of Obesity in Adults

Jacob C. Seidell

CONTENTS

4.1 INTRODUCTION

Over the last two to three decades, overnutrition and obesity have been transformed from relatively minor public health issues that primarily affect the most affluent societies to a major threat to public health that is being increasingly seen throughout the world. The plight of the most affected populations, like those in North America, Australia, and Europe, has been well publicized. However, increases in population obesity elsewhere in the world have been less well recognized.

The Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group analyzed data from 199 countries and 9.1 million adults with respect to the prevalence of overweight and obesity between 1980 and 2008 [1]. During this 28-year period, the prevalence of obesity doubled in every region of the world. In 2008, about 1.5 billion people were estimated to have a body mass index (BMI) of 25 kg/m^2 or more. Of these, 500 million were considered obese.

In 2008, the highest rates of obesity in women were observed, in the descending order of magnitude in southern Africa, North Africa and the Middle East, central Latin America, North America (high income), and southern Latin America. In men, the top five regions were North America (high income), southern Latin America, Australasia, Central Europe, and central Latin America. Note that many of these regions comprise countries undergoing economic transition.

About 25 years ago, obesity in developing countries was considered to be a condition of the socioeconomic elite. Monteiro and others [2], however, show that obesity is a low socioeconomic status problem particularly in women in lower middle income countries. In this chapter, we take a closer look at the levels and trends of obesity across regions in the world.

4.2 CLASSIFICATION OF OBESITY AND FAT DISTRIBUTION

The epidemiology of obesity was for many years difficult to study because many countries had their own specific criteria for the classification of different degrees of overweight. Gradually, during the 1990s, however, BMI (weight/height^2) became a universally accepted measure of the degree of overweight, and now identical cutoff points are recommended. This most recent classification of overweight in adults by the World Health Organization (WHO) [3] is given in Table 4.1. In many community studies in affluent societies, this scheme has been simplified and cutoff points of 25 and 30 kg/m^2 are used for descriptive purposes. The prevalence of both very low BMI (<18.5 kg/m^2) and very high BMI (40 kg/m^2 or higher) is usually low, on the order of 1% to 2% or less.

A WHO expert consultation [4] addressed the debate about interpretation of recommended BMI cutoff points for determining overweight and obesity in Asian populations and considered whether population-specific cutoff points for BMI are necessary. They reviewed scientific evidence that suggests that Asian populations have different associations between BMI, percentage of body fat, and health risks than do European populations. The consultation concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs

TABLE 4.1
Classification of Overweight in Adults by the WHO

Classification	BMI (kg/m^2)	Associated Health Risks
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5–24.9	Average
Overweight	25.0 or higher	
Preobese	25.0–29.9	Increased
Obese class I	30.0–34.9	Moderately increased
Obese class II	35.0–39.9	Severely increased
Obese class III	40 or higher	Very severely increased

Source: World Health Organization, *Obesity: Preventing and managing the global epidemic*, WHO Technical Report Series, No. 894, WHO, Geneva, 2000.

lower than the existing WHO cutoff point for overweight (≥25 kg/m^2). However, available data do not necessarily indicate a clear BMI cutoff point for all Asians for overweight or obesity. The cutoff point for observed risk varies from 22 to 25 kg/m^2 in different Asian populations; for high risk, it varies from 26 to 31 kg/m^2. No attempt has been made, therefore, to redefine cutoff points for each population separately.

Much research over the last decade has suggested that for an accurate classification of overweight and obesity with respect to the health risks, one needs to factor in abdominal fat distribution. Traditionally, this has been indicated by a relatively high waist-to-hip circumference ratio. It has been proposed that waist circumference alone may be a better and simpler measure of the health risks associated with abdominal fatness [5]. In 1998, the U.S. National Institutes of Health (National Heart, Lung, and Blood Institute) adopted the BMI classification and combined this with waist cutoff points [6]. In this classification, the combination of overweight (BMI between 25 and 30 kg/m^2) and moderate obesity (BMI between 30 and 35 kg/m^2) with a large waist circumference (≥102 cm in men and ≥88 cm in women) is proposed to carry additional risk [6].

4.3 OBESITY PREVALENCE AND TRENDS IN ADULTS

4.3.1 North America

In the United States, there are two important sources of data on the prevalence of obesity. One is the Behavioral Risk Factor Surveillance System, which is based on an annual survey by telephone in random representative samples of the population in the United States [7]. The other set of data comes from the National Health and Nutrition Examination Survey (NHANES), which is also based on random representative samples of the U.S. population but weights and heights are measured in people attending a health examination [8]. Although the slopes of time trends are similar in both studies, this illustrates how difficult it is to assess the true prevalence of obesity. Because of likely underreporting of weight with increasing obesity, and the lower nonresponse rate in NHANES, it can be assumed that the data of NHANES give a more valid estimate of the true prevalence compared to those based on the self-reported weights and heights in the telephone survey. However, there also may be other methodological differences that account, at least partly, for the large differences in the estimates of the prevalence of obesity. These methodological issues are related to sampling design; response rate, including selective response; and selection based on telephone ownership, since many people may have unlisted numbers, cell phones, or no phones and this may lead to bias.

Flegal et al. [8] published the most recent estimates of the prevalence of overweight, obesity, and severe obesity in the United States in men and women (2009–2010). The data show that over 74% of American men and 65% of American women are now overweight or obese. Over 35% of men and women were obese in 2009–2010. In women, obesity is more common than overweight, demonstrating a marked skewness in the distribution of BMI. There are marked ethnic differences in the prevalence of obesity. For instance, the prevalence of severe obesity (BMI > 40 kg/m^2) overall in women was 8.2% and in men 4.4%. Severe obesity was observed in about 6% in non-Hispanic whites, over 13% in non-Hispanic blacks, and about 5% in Mexican Americans. Although overall rates of overweight and obesity showed some leveling off between 2003 and 2010, the prevalence of severe obesity continued to climb during this period.

The prevalence of obesity in Canada used to be much lower than that in the neighboring United States. However, Canada has also experienced an increase in the prevalence of overweight and obesity, particularly in men. One publication documented the increase in the prevalence between 1970 and 1992 [9]. A more recent study described an increase in the prevalence of obesity from 9% in 1981 to 14% in 1996 in men [10]. In women, the corresponding figures were 8% in 1981 and 12% in 1996. In 2007–2009, the Canadian Health Measures Survey, however, found that 26% of adult men and 23% of adult women were obese [11]. They also documented considerable bias in prevalences based on self-report (based on self-report, the prevalence of obesity was 19% in men and 16% in women). The prevalence of obesity varied between different population groups. In the United States, the highest prevalence is observed in indigenous populations [12].

These groups are also among the least privileged and often live under economically disadvantaged conditions.

The prevalence of obesity in Mexico is approaching that of the United States with about 30% of the adults being obese according to the national survey in 2006 [13].

4.3.2 Europe

Doak et al. [14] recently documented the prevalence of overweight and obesity in Europe. This study shows the importance of age standardization when comparing countries and also the difficulty of working with measured and self-reported data. Surveys were included if they were conducted on adults 25–64 years old between 1985 and 2005 in the 53 countries of the WHO European Region. Overweight/obesity prevalences were adjusted to the European standard population aged 25–64 years with separate analyses for older (25–49 years) and younger (50–64) adults (Tables 4.2 and 4.3).

The older 50- to 64-year-olds had consistently higher overweight/obesity compared to 25- to 49-year-olds. While age comparisons showed evidence of the influence of older age on overweight/obesity, age-adjusted prevalences remained high for all countries. In surveys with measured data conducted between 2001 and 2005, the lowest adjusted prevalences in males were 63.2% for overweight and 15.9% for obesity (Bosnia and Herzegovina). In females, the lowest adjusted prevalences (measured data) were 50.9% for overweight (Croatia) and 17.0% for obesity (Portugal). In the United Kingdom, Scotland had the highest adjusted prevalences with 71.0% overweight in males and 60.6% in females and 24.9% obesity in males and 25.7% in females. Trend data showed increases even after adjusting for age (Table 4.4).

The highest prevalences in Europe are seen in the United Kingdom, in Eastern European countries, and in the Mediterranean area. Howel [15] showed that in 2006 adult obesity in the United Kingdom was approaching 30%. Between 1991 and 2006, the prevalence of obesity had risen by 8.2% in women and 6.0% in men.

Webber et al. [16] showed exceptionally high prevalences in some Eastern European countries. For instance, the expected prevalence in 2050 of overweight and obesity (BMI > 25 kg/m^2) is 80% or higher in adult women in Bulgaria, Croatia, and the

TABLE 4.2
Age-Adjusted Prevalence Data for Overweight and Obesity Based on Measured Height and Weight in Males

		Percentage Overweight > 25 BMI			Percentage Obesity > 30 BMI		
Country	**Year of Survey**	**25–49 years**	**50–64 years**	**25–64 years**	**25–49 years**	**50–64 years**	**25–64 years**
Belgium	1979–1984				9.4	14.7	**11.2**
Bosnia and Herzegovina	2002	59.3	70.9	**63.2**	13.7	20.2	**15.9**
Croatia	1999	49.6	68.5	**56.0**	9.7	15.5	**11.6**
	2003	60.2	75.6	**65.4**	18.4	27.6	**21.5**
Estonia	1997	41.7	52.7	**45.4**	9.8	12.9	**10.8**
Finland	2000–2001				25.9		
Germany	1997–1999				16.4	25.6	**19.5**
Hungary	1985–1988	52.6	63.9	**56.4**	10.7	15.4	**12.3**
Ireland[a]	1990	62.2	73.2	**65.9**	8.7	10.7	**9.4**
	1997–1999	65.8	75.0	**68.9**	20.0	24.4	**21.4**
Israel	1999–2001	60.9	75.6	**65.8**	17.8	24.0	**19.9**
Kyrgyzstan	1993	39.4	42.2	**40.3**	6.3	7.5	**6.7**
Latvia	1997	46.3	61.8	**51.5**	7.6	14.2	**9.8**
Lithuania	1997	50.8	64.3	**55.3**	9.9	16.7	**12.2**
Poland	2000	53.9	70.5	**59.5**	13.5	23.6	**16.9**
Portugal	2003–2005	61.1	72.1	**64.8**	15.4	20.0	**16.9**
Serbia	2000	55.6	66.2	**59.2**	13.5	18.4	**15.2**
United Kingdom[b]							
England	1991–1995	58.6	70.0	**62.4**	13.9	18.9	**15.6**
	1995–2000	63.7	74.3	**67.2**	18.2	23.5	**20.0**
	2001–2005	68.3	76.4	**70.9**	22.5	28.0	**24.4**
Scotland	1995	60.1	72.7	**64.3**	17.7	21.4	**18.9**
	1998–1999	65.2	75.7	**68.7**	19.9	25.3	**21.7**
	2003–2004	67.1	78.9	**71.0**	21.7	31.0	**24.9**
Uzbekistan	2002	42.3			7.0		

Source: Doak CM et al., *Obes. Rev.*, 3, 174–191, 2012.

Note: Prevalence estimates are age standardized to the European standard population [14].

[a] Includes Northern Ireland.

[b] United Kingdom of Great Britain and Northern Ireland.

TABLE 4.3
Age-Adjusted Prevalence Data for Overweight and Obesity Based on Measured Height and Weight in Females

		Percentage Overweight > 25 BMI			Percentage Obesity > 30 BMI		
Country	**Year of Survey**	**25–49 years**	**50–64 years**	**25–64 years**	**25–49 years**	**50–64 years**	**25–64 years**
Armenia	2000	51.7			19.0		
	2005	53.9			20.5		
Belgium	1979–1984				10.5	24.9	**15.4**
Bosnia and Herzegovina	2002	49.2	77.1	**58.6**	16.3	37.1	**23.4**
Croatia	1999	30.8	60.7	**40.9**	7.8	20.0	**12.0**
	2003	44.5	71.6	**50.9**	12.7	30.2	**18.6**
Estonia	1997	26.9	62.5	**39.0**	4.8	15.6	**8.4**
Finland	2000–2001				29.4		
Germany	1997–1999				15.8	28.7	**20.2**
Hungary	1985–1988	42.2	59.0	**47.8**	13.5	22.1	**16.3**
Ireland[a]	1990	36.4	71.6	**48.3**	8.4	31.1	**16.1**
	1997–1979	45.1	66.4	**52.2**	12.6	29.6	**18.4**
Israel	1999–2001	51.0	76.3	**59.6**	20.7	37.2	**26.3**
Kazakhstan	1995				22.8		
	1999	43.3			18.2		
Kyrgyzstan	1993	41.6	54.5	**45.9**	13.4	20.4	**15.7**
Latvia	1997	34.9	75.9	**48.7**	9.1	30.3	**16.3**
Lithuania	1997	41.0	74.2	**52.2**	11.8	32.5	**18.8**
Poland	2000	37.9	66.7	**47.6**	12.2	31.1	**18.6**
Portugal	2003–2005	50.8	70.6	**57.5**	13.3	24.2	**17.0**
Republic of Maldovia	2005	55.2			25.2		
Romania	1997				15.1	30.3	**20.2**
Serbia	2000	38.4	70.7	**49.3**	12.8	30.2	**18.7**
Turkey	1998	64.8			30.0		
	2003	70.2			38.9		
Turkmenistan	2000				16.7		
Ukraine	2002	50.3			21.0		
United Kingdom[b]							
England	1991–1995	44.5	60.9	**50.0**	15.6	22.4	**17.9**
	1995–2000	49.0	65.0	**54.3**	18.3	26.6	**21.1**
	2000–2005	53.2	65.2	**57.2**	22.2	28.4	**24.3**
Scotland	1995	45.2	63.3	**51.3**	16.4	24.8	**19.2**
	1998–1999	51.4	68.3	**57.1**	21.0	29.4	**23.8**
	2003–2004	56.0	69.8	**60.6**	23.7	29.8	**25.7**
Uzbekistan	1996				9.0		
	2002	39.6			11.8		

Source: Doak CM et al., *Obes. Rev.*, 13, 174–91, 2012.
Note: Prevalence estimates are age standardized to the European standard population [14].
[a] Includes Northern Ireland.
[b] United Kingdom of Great Britain and Northern Ireland.

Czech Republic. In men, extremely high prevalences (>90%) are expected in Latvia, Estonia, Romania, and Serbia.

Papandreou et al. [17] divided the Mediterranean region into an "Asian" part (Turkey, Syria, Cyprus, Lebanon, and Israel) and a "European" part (Spain, France, Italy, Slovenia, Croatia, Bosnia and Herzegovina, Albania, Montenegro, and Greece). The average prevalences of obesity in the Asian part were about 26% in men and 35% in women. In the European part, the prevalences were lower: about 20% in men and 24% in women (Table 4.5).

Self-reported data showed lower levels of overweight and obesity for men and women with the lowest prevalences in Switzerland (49.3% overweight and 8.6% obesity for men, and 21.9% overweight and 5.0% obesity for women).

4.3.3 Middle East

Generally, there is a lack of good representative data (e.g., national surveys) from this region. Table 4.6 shows the prevalence of overweight and obesity in northern Africa and the

TABLE 4.4
Time Trends in Age-Adjusted Prevalence Data for Overweight and Obesity Based on Measured Height and Weight in Males

				Percentage Point Change Per Year Overweight > 25 BMI			Percentage Point Change Per Year Obesity > 30 BMI		
Country	First Survey Year	Last Survey Year	Years Elapsed	25–49 years	50–64 years	25–64 years	25–49 years	50–64 years	25–64 years
Croatia	Pooled 1996–2000	Pooled 2001–2005	5	+2.1	+1.4	**+1.9**	+1.7	+2.4	**+2.0**
Ireland[a]	1990	1997–1999	8	+0.5	+0.2	**+0.4**	+1.4	+1.7	**+1.5**
United Kingdom[b]									
England	Pooled 1991–1995	Pooled 2001–2005	10	+1.0	+0.6	**+0.9**	+0.9	+0.9	**+0.9**
Scotland	1995	2004	9	+0.8	+0.7	**+0.7**	+0.4	+1.1	**+0.7**

Source: Doak CM et al., *Obes. Rev.*, 13, 174–91, 2012.
[a] Includes Northern Ireland.
[b] United Kingdom of Great Britain and Northern Ireland.

TABLE 4.5
Time Trends in Age-Adjusted Prevalence Data for Overweight and Obesity Based on Measured Height and Weight in Females

				Overweight > 25 BMI			Obesity > 30 BMI		
Country	First Survey Year	Last Survey Year	Years Elapsed	25–49 years	50–64 years	25–64 years	25–49 years	50–64 years	25–64 years
Armenia	2000	2005	5	+0.4			+0.3		
Croatia	1996–2000	2001–2005	5	+2.7	+2.2	**+2.0**	+1.0	+2.0	**+1.3**
Ireland[a]	1990	1997–1999	8	+3.7	+0.4	**+2.6**	+0.5	–0.2	**+0.3**
Kazakhstan	1995	1999	4				–1.2		
Turkey	1998	2003	5	+1.1			+1.8		
United Kingdom[b]									
England	1991–1995	2000–2005	10	+0.8	+0.4	**+0.7**	+0.7	0.6	**0.6**
Scotland	1995	2003–2004	9	+1.2	+0.7	**+1.0**	+0.8	+0.6	**+0.7**

Source: Doak CM et al., *Obes. Rev.*, 13, 174–91, 2012.
[a] Includes Northern Ireland.
[b] United Kingdom of Great Britain and Northern Ireland.

TABLE 4.6
Overweight (BMI of 25–29.9 kg/m^2) and Obesity (BMI ≥ 30 kg/m^2) Levels in Women Aged 15–49 Years in North Africa and the Middle East

			Percentage Overweight		Percentage Obese	
Country	Year of Survey	Sample Size	Men	Women	Men	Women
Bahrain	1991–1992	290	16.0	31.3	26.3	29.4
Kuwait	1993–1994	3,435	35.2	32.3	32.3	40.6
Saudi Arabia	1996	13,177	29.0	27.0	16.0	24.0
Jordan	1994–1996	2,836	—	—	32.7	59.8
Morocco	1984–1985	41,921	18.7[a]		5.2[a]	
	1992	2,850	—	22.3	—	10.5
	1998–1999	17,320	28.0	33.0	5.7	18.3
Tunisia	1997	2,760	23.3	28.2	6.7	22.7
Egypt	1995–1996	6,769	—	31.7	—	20.1
Turkey	1993	2,401	—	31.7	—	18.6

Source: Ng SW et al., *Obes. Rev.*, 12, 1–13, 2011.
[a] Men and women combined.

Middle East [18]. The available data show that the prevalence of obesity is higher in women than in men (particularly in the Middle East and the Gulf States).

More recent data of the last decade [19] show extremely high levels of obesity in women from the Gulf States: Oman (27%), Bahrain (34%), United Arab Emirates (40%), Saudi Arabia (44%), Qatar (45%), and Kuwait (47%). Male obesity rates were lower in most countries: Oman (32%), Bahrain (23%), United Arab Emirates (26%), Saudi Arabia (28%), Qatar (35%), and Kuwait (36%).

4.3.4 Australia, New Zealand, and Oceania

Trend data on the prevalence of overweight and obesity are available for Australia [20]. The AusDiab study showed that the prevalence of obesity in 1999–2000 was 19.3% in men and 22.2% in women. This was 2.5 times higher than the values in 1980. The prevalence in young adult men aged 25–34 years is particularly high (17.4%). In New Zealand, obesity prevalence was 11% in 1989; in 1997, this had risen to 17% (14.7% in men and 19.3% in women) [21].

There are data that indicate some of the Pacific island populations have extremely high rates of obesity. The prevalence of obesity in Nauru in 1987, for example, was reported to be around 65% in men and 70% in women [22]. Similar high rates have been observed in urban areas of Papua New Guinea (36% in men and 54% in women), whereas the prevalence in the highlands was not higher than about 5% in men and women. In 1991, urban Samoans had a prevalence of 58% in men and 77% in women and in rural areas also obesity prevalence was high (42% in men and 59% in women).

4.3.5 Asia

In Japan, the prevalence of obesity over the past 20 years has increased in men from 0.8% in 1976–1980 to 2.0% in 1991–1995. In women, there has been no change over this period [23]. In the National Nutrition Survey in Japan in 2000, the prevalence of overweight (BMI of 25–30 kg/m^2) in men was 24.5% and of obesity (BMI > 30 kg/m^2) 2.3%; in women, the figures were 17.8% and 3.4% for overweight and obesity, respectively. In (South) Korea, the prevalence of overweight (BMI between 25–30 kg/m^2) was 27% and of obesity (BMI > 30 kg/m^2) 3% in 2001. These figures are very similar to those in China in 2002 [24]. The highest rates of obesity (BMI > 30 kg/m^2) in Asia were found in Mongolia (13.8% in men and 24.6% in women), Singapore (6.4% in men and 7.3% in women), and Thailand (4.3% in men and 10.8% in women) [24].

However, the International Diabetes Institute has proposed that the international classification of obesity should be adapted for Asian countries [24]. They indicated that overweight should be classified as a BMI above 23 kg/m^2 and obesity as a BMI of 25 kg/m^2 or higher. If such a classification was applied, then the prevalence of obesity (BMI ≥ 25 kg/m^2) in Japan would be substantially higher (20% rather than 2%) [25].

Xi et al. [26] defined obesity in China as a BMI > 27.5 kg/m^2. They analyzed data from the China Health and Nutrition Survey, which was conducted from 1993 to 2009. The prevalence of obesity increased from about 3% to 11% in men and from 5% to 10% in women. Similar trends were seen in all age groups and regions.

In India, high prevalences of obesity (BMI > 25 kg/m^2) are seen in urban women. The National Family Health Survey in 2005–2006 in women aged 15–49 years showed that 24% of women in urban areas and 7% in rural areas were obese [27]. In urban areas, also the prevalence of obesity among women in slum areas was surprisingly high. For instance, Yadav and Krishnan [28] reported high prevalences of obesity (BMI > 30 kg/m^2) in urban women in Haryana (13%) and also in urban slums (7%) compared to women living in rural areas (4%).

Other Asian countries also show a high prevalence of overweight and obesity. In Malaysia, for instance, the best estimate of overweight (BMI between 25 and 30 kg/m^2) is 29% and obesity (BMI > 30 kg/m^2) is 14% [29]. This is similar to the prevalence in many European countries such as the Netherlands and France. In Sri Lanka, researchers observed 17% overweight (BMI between 25 and 30 kg/m^2) and 4% obesity (BMI > 30 kg/m^2). When they used Asian cutoff points for obesity (BMI > 27.5 kg/m^2), the prevalence of obesity was 9% [30].

4.3.6 Africa

Good representative data from Africa are usually scarce. Abubakari et al. [31] reviewed data from countries in West Africa (Cameroon, Gambia, Ghana, Nigeria, and others). They estimated that the pooled prevalence of obesity (BMI > 30 kg/m^2) was 10% for West Africa in the period 2000–2004. Rates were usually doubled in urban compared to rural areas.

A study from Dakar [32], the capital of Senegal in West Africa, illustrates the double burden of undernutrition and overnutrition: 30% of the population is overweight (of which 8% is obese) and over 12% is underweight (BMI < 18.5 kg/m^2).

In Mozambique in East Africa, the prevalence of obesity (BMI > 30 kg/m^2) was 7% in women and 9% in men with higher rates in urban areas compared to rural areas [33].

As mentioned earlier in this chapter, prevalence is notably higher in northern African countries bordering the Mediterranean Sea. For instance, in Tunisia national representative data showed that the prevalence of obesity (BMI > 30 kg/m^2) was 23% in women [34]. There were marked differences by degree of urbanization: 30% in big cities, 26% in smaller cities, 19% in rural clustered areas, and 10% in rural dispersed areas.

Particularly high are the rates of obesity in black urban areas in South Africa with many studies observing prevalences between 40% and 50% [35].

4.3.7 Latin America

Monteiro et al. [36] showed that the prevalence of obesity (BMI > 30 kg/m^2) increased from 3% in 1975 to 9% in 2003. In women, it increased from 7% to 13%. More recent estimates showed a prevalence of 11%–12% in men and women in 2006. In Brazil [37], there was not a clear relationship between

TABLE 4.7
Prevalence of Obesity in Seven Latin American Countries

Country	City	Prevalence in Men (%)	Prevalence in Women (%)
Venezuela	Barquisimeto	24	26
Colombia	Bogota	13	22
Argentina	Buenos Aires	23	17
Peru	Lima	21	23
Mexico	Mexico City	32	30
Ecuador	Quito	10	22
Chile	Santiago	24	29

Source: Schargrodsky H et al., *Am J Med*., 121, 58–65, 2008.

educational level and obesity in men, but in women the prevalence was highest in those with low education: 19% in women with 0–4 years of education versus less than 8% in women with 12 years or more of education. In young adult women (20–45 years of age), the prevalence of overweight (BMI between 25 and 30 kg/m^2) was 30% and of obesity (BMI > 30 kg/m^2) was 15%. Obesity was more common among women from urban areas compared to those from rural areas. The largest study in this area is the CARMELA study conducted in 11,550 adults aged 25–64 years in seven studies across Latin America [38]. The results shown in Table 4.7 illustrate high prevalences across the region, especially in women. There is a wide variation in prevalences, with those in men ranging from 10% in Ecuador to 32% in Mexico and in women from 17% in Argentina to 30% in Mexico.

4.4 CONCLUSIONS

The prevalence of obesity is increasing at an alarming rate in many parts of the world. About 1.5 billion people are overweight and a third of them obese. In populations living in the west and north of Europe, Australia, Canada, and the United States, the prevalence of obesity is high in men and women, as well as in children. Based on the existing prevalence and trend data, and the epidemiological evidence linking obesity with a range of physical and psychosocial health conditions, it is reasonable to describe obesity as a public health crisis that severely impairs the health and quality of life of people and adds considerably to national health-care budgets. Intersectoral action is urgently required to reverse current trends.

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5 Prevalence and Consequences of Pediatric Obesity

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CONTENTS

5.1 INTRODUCTION

Childhood obesity is a serious, worldwide issue that is one of the major challenges for health in the twenty-first century. In this chapter, we consider available classification schemes for pediatric overweight and obesity, examine the epidemiology of overweight and obesity in the United States and other countries using body mass index (BMI)-based cut points, and review the medical complications of obesity during childhood and adolescence.

5.2 CLASSIFICATION OF OVERWEIGHT AND OBESITY IN CHILDREN

Obesity is defined as the accumulation and storage of excess body fat, and overweight is weight in excess of a weight reference standard.[1] Because there are no consensus criteria defining childhood obesity on the basis of excessive body adipose tissue, weight-based classification has been routinely used for both epidemiological and clinical purposes.

5.2.1 Pediatric Standards Based on the Body Mass Index

BMI is calculated as weight in kilograms divided by height in meters squared. It is considered the least expensive and most practical metric available.[2] BMI typically decreases from ages 2 to 5–7 years with corresponding decreases in percentage body fat[3] and then starts to increase for the reminder of childhood up to adult levels. Because the distribution of BMI changes dramatically with age and differs by sex in children, age- and sex-specific BMI percentiles rather than raw BMI values are used (Figure 5.1).[4] The reference standards most commonly used in the United States for evaluating children's BMI are the 2000 Centers for Disease Control and Prevention (CDC 2000) growth charts that provide age- and sex-specific standards for ages 2–18 years.[5,6] These charts supply smoothed percentiles for BMI that were constructed from data obtained in five nationally representative U.S. surveys conducted between 1963 and 1980.[6] More recent data were not included in this revision of the 1977

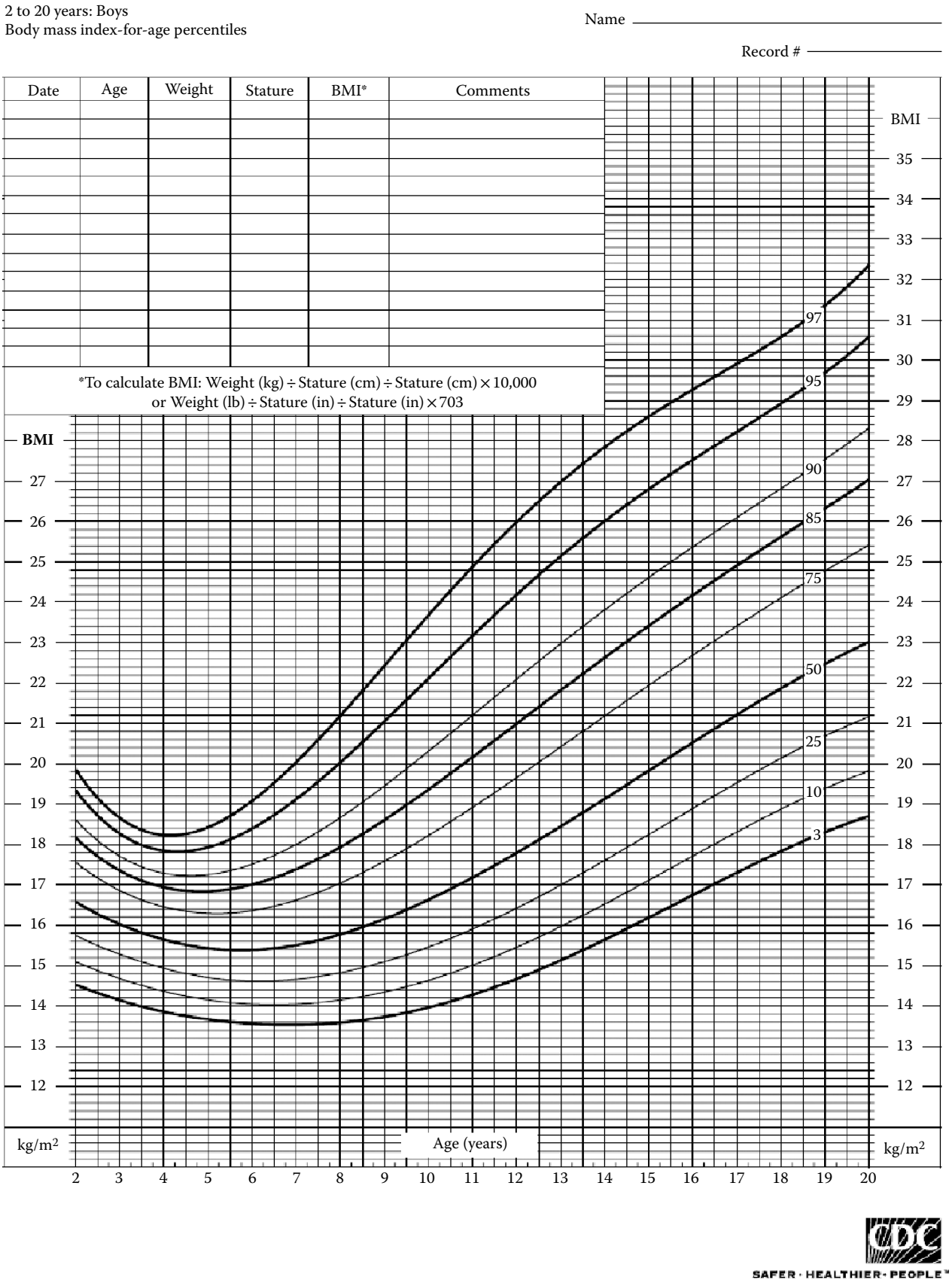

FIGURE 5.1 BMI percentiles for boys and girls ages 2–20 years. (Data obtained from the U.S. Centers for Disease Control and Prevention, http://www.cdc.gov/growthcharts.)

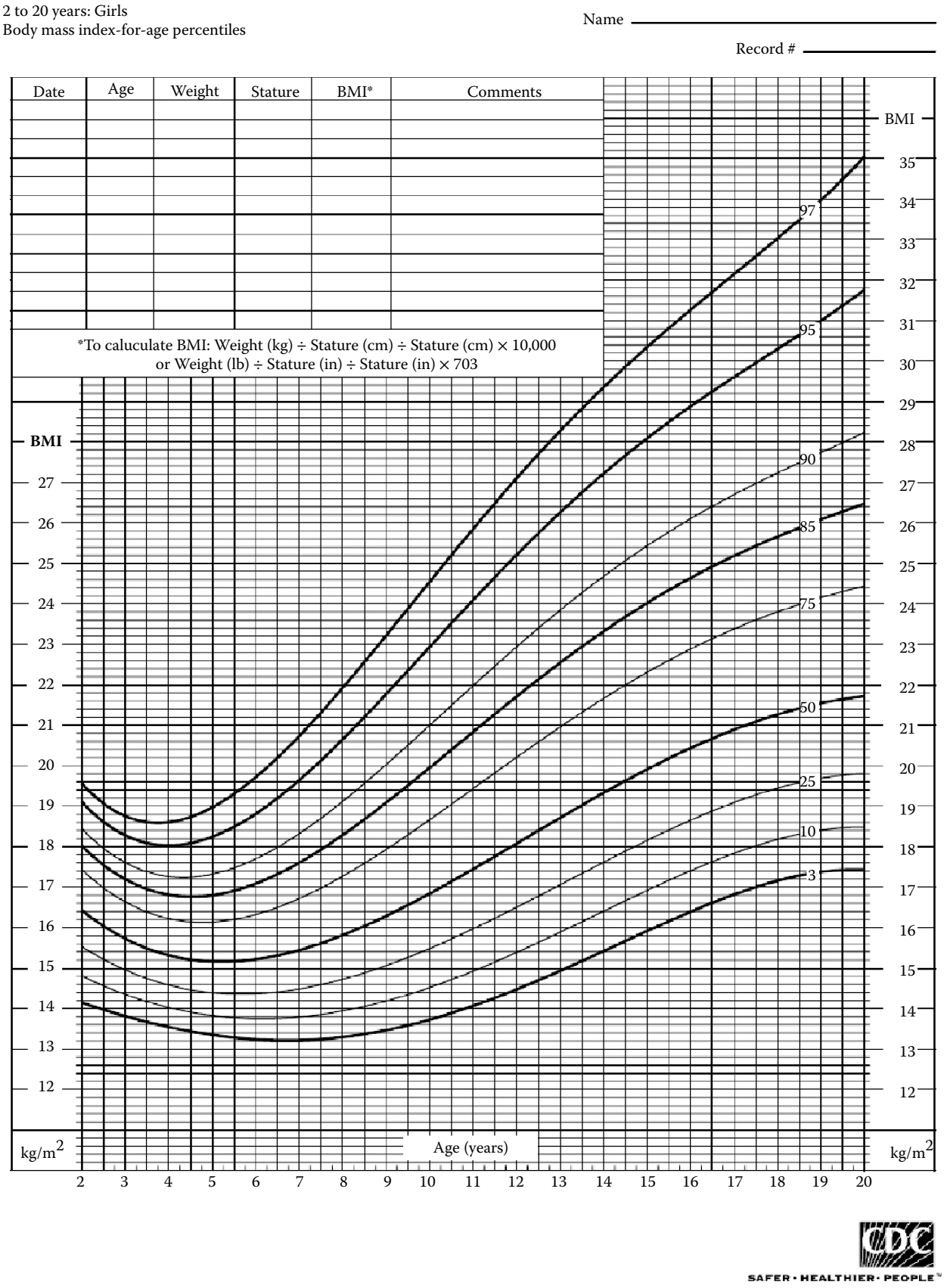

FIGURE 5.1 (*Continued*) BMI percentiles for boys and girls ages 2–20 years. (Data obtained from the U.S. Centers for Disease Control and Prevention, http://www.cdc.gov/growthcharts.)

U.S. National Center for Health Statistics standards because of the marked increases in BMI that have been observed in subsequent U.S. surveys.[7,8] Because of the paucity of data for children at the greatest BMIs in the data sets used, the top percentile defined by the CDC 2000 growth charts is the 97th percentile. To compute the standardized scores assigned to all intermediate percentiles of BMI, the smoothed curves were approximated using a modified lambda, mu, and sigma (LMS) estimation procedure to provide the transformation parameters lambda, mu, and sigma.[5] The mu and sigma values correspond to the median and coefficient of variation for BMI at each age, whereas the lambda curve allows adjustment for age-dependent skewness in the BMI distribution. *Z*-scores for age and sex are calculated using the Box–Cox transformation by the formula: $Z = [(\mathrm{BMI}/M)^L - 1]/(L \times S)$.

Before 2010, CDC 2000 growth charts for ages 2–18 years demarcated the 85–94.99th percentiles for BMI as "at risk for overweight" and ≥95th BMI percentile as "overweight" based on the recommendation of an expert panel convened by federal agencies.[9] These cut points were subsequently renamed to be "overweight" for the 85–94.99th BMI percentiles and "obese" for ≥95th BMI percentile to be consistent with recommendations by multiple U.S. and non-U.S. groups.[1,9–16] This approach was based on the notion that most children with high BMI are also likely to have excess adiposity and that relatively few children with low BMI have excess adiposity, an issue discussed in more detail in Sections 5.2.2 and 5.2.3 of this chapter. Overweight among infants and toddlers below age 2 years is defined as weight-for-recumbent length ≥95th percentile. Expert committees have recommended against using the term "obese" in this age category.[11]

An expert committee convened by the American Medical Association proposed recognition of the 99th BMI percentile as a cut point to classify children with severe obesity who are likely to be at increased risk for cardiovascular risk factors.[12] However, the 97th percentile is the highest level shown on the CDC 2000 growth charts, and estimates of the cut points for the 99th percentile for age and sex are considered unstable. Extreme percentiles extrapolated from the CDC-supplied LMS parameters do not match well to the empirical data for the 99th percentile. A statistically defensible cut point for severe obesity based on available U.S. data is 120% of the smoothed 95th percentile.[17]

In an effort to create an internationally acceptable definition for childhood obesity, and recognizing the essentially arbitrary nature of defining overweight and obesity by the 85th and 95th percentiles of BMI for U.S. children, the International Obesity Taskforce (IOTF) in 2000 also developed standard cut points based on children's BMI.[18] The IOTF used data from six countries with nationally representative cross-sectional surveys (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States) from birth to age 25 years; forced the percentile curves at age 18 years to pass through the accepted adult BMI cut points of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity[18] and then applied the percentiles derived from the pediatric data at age 18 years to younger children to establish comparable cut points at younger ages. Because the curves for overweight and obesity based on the adult cut points appeared quite similar among most of the countries, a single set of curves for boys and girls was generated.[18] The IOTF charts provided cutoff values only for overweight and obesity and did not provide data for other percentile levels; hence they were not particularly helpful for monitoring the progress of BMI and were not recommended for routine clinical use.[11] The generalizability of the IOTF standards was also considered to be somewhat limited because they did not include data from developing countries.

Some have argued that because of differences in body composition across ethnic and racial groups, universal cut points for overweight and obesity may not be reasonable. For example, it has been suggested that among Asian Indian children, the use of the IOTF cut points may underestimate overweight and obesity prevalence[19]; many other investigators have found evidence for racial and ethnic differences in the relationship between BMI and body fatness, suggesting the need for additional BMI-based growth charts.[20–23] Another potential source of error in assessment with a universal reference is the timing of puberty. At puberty, female BMI curves are generally higher and more concave than the male curves, reflecting earlier puberty-related gains in adiposity in females. In countries where puberty is appreciably delayed, the cut points may be affected.[18] Some countries have developed their own BMI population reference data and percentile charts. Where these exist and are based on a nationally representative sample,[9] particularly when the data were collected before pediatric obesity became commonplace,[2] it is recommended that they should be used to assess weight status.[9] In the absence of such national data, then either the CDC or the IOTF charts are recommended for use.[6,18] Another, perhaps less preferred, alternative is to employ charts constructed by the World Health Organization (WHO). In 2006, new child growth standards intended to reflect normal growth among breast-fed infants were developed from the WHO Multicentre Growth Reference Study. The data for ages 0–2 years were constructed from an international longitudinal data set of 882 children supplemented by cross-sectional data from 6669 "healthy breastfed infants and young children raised in environments that do not constrain growth."[24] BMI curves were produced from ages 0 to 5 years by using length for ages 0–2 years and using height thereafter; thus, there are discontinuities in the BMI curves at age 2 years.

The prescriptive WHO approach (limiting data to healthy breast-fed infants) leads to differences in percentiles when children are transitioned to other purely descriptive growth charts. To address this, WHO growth standards for children ages 5–19 years were produced from a reanalysis of the original data used for the U.S. National Center for Health Statistics 1977 reference curves (nonobese children with good height growth), supplemented with data from the preschool WHO child growth standards.[25] WHO recommends both sets of charts for both clinical and epidemiological use.[2] On the BMI-for-age curves for children ages 0–5 years, those above +1 standard deviation (SD) are described conservatively as being

at risk of overweight, above +2 SD as overweight, and above +3 SD as obese. For children ages 5–19 years, those above +1 SD are described as being overweight and above +2 SD as obese. At age 19 years, the BMI-for-age curves match the cut points for adult overweight (BMI ≥ 25) at +1 SD and adult obesity (BMI ≥ 30) at +2 SD. These curves also use the LMS method to assign percentiles.

Each set of BMI standards produces different estimates for the prevalence of overweight and obesity among children. For example, when applied to National Health and Nutrition Examination Survey (NHANES) data from 2003 and 2004,[26] the IOTF standards produced somewhat lower prevalence data for overweight in boys and markedly lower prevalence for obesity in both boys and girls compared to either CDC 2000 or WHO standards. Compared to the CDC 2000 standards, the WHO standards identified more children as overweight but roughly the same percentage as obese.

5.2.2 Limitations of the Body Mass Index for Children

BMI-based standards used to define obesity have limitations[9–12,23] because excess body fatness cannot be measured directly from weight and height.[9] In 1995, a WHO expert committee suggested using the term "obesity" to describe high weight-for-height for population-wide description but recommended against using such metrics for individual classification of weight status.[13] Similarly, the expert committee convened by the American Medical Association that proposed the term "obesity" for BMI ≥ 95th percentile[11] also suggested that more neutral terms be used when discussing weight issues with families.

BMI reflects body mass rather than body fatness.[9] BMI-based standards make the assumption that increasing weight at a given height is associated with increasing adiposity. However, a high BMI may be due to a large lean body mass and not excess body fat. Because BMI cannot discriminate between lean and fat mass, it is an imperfect measure of adiposity.[27] However, there is a high correlation between BMI and fat mass among children,[28,29] and a majority of children with BMI ≥ 95th percentile have high adiposity. Overall, transformations of BMI do reasonably well in correctly identifying children at the highest body fat percentage levels.[30] Nevertheless, it should be noted that only about 75% of U.S. children with BMI ≥ 95th percentile appear to have particularly high amounts of body fat[23]; thus BMI is a first screening tool to identify children who may be overfat even when BMI reaches the cut point for obesity. Indeed, those who are particularly muscular should not be classified as obese even when BMI exceeds the threshold. When higher levels of BMI are used as cut points, the sensitivity decreases and the specificity increases for identifying overfatness; on the other hand, some children with BMI < 95th percentile may have excess body fat,[23] although less than one-half of U.S. children with BMI between the 85th and 95th percentiles have high adiposity and even fewer at lower percentiles.[23]

Finally, BMI-based criteria may systematically misclassify individuals belonging to particular racial or ethnic groups. For example, non-Hispanic black children have been shown to have lower body fat percentage compared to their Mexican and non-Hispanic white counterparts at the same BMI level.[23] Caution needs to be applied when using the BMI cut points for clinical diagnostic criteria. To prevent misclassification, additional clinical information should be used before determining whether an intervention is warranted.[12]

5.2.3 Adiposity-Based Approaches

The ideal measure of obesity should be based on measurement of body fat; however, other than in a limited capacity for research, this is not practical for epidemiological or clinical purposes. Dual-energy x-ray absorptiometry (DXA) scan, air displacement plethysmography, and bioelectric impedance analysis (BIA) are some of the methods that have been used to measure body fat. However, there are no widely accepted standard values to define adiposity cut points in children.[13] Percentile body fat curves for a select sample of British schoolchildren ages 5–18 years and the average body fat percentage data for U.S. children over age 12 years assessed from BIA[31,32] and DXA[33] have been published.

For clinical purposes, it has been suggested that additional screening and assessment criteria, such as waist circumference or body fat estimation based on skinfold thickness, may be used to complement BMI assessment.[11] Waist circumference has been shown in some studies to have better correlation with visceral adiposity and metabolic variables than BMI, but currently there are no readily available waist circumference cut points to identify children with high visceral adiposity.[11] In addition, lack of accepted reference data and potential measurement errors limit the utility of skinfold thickness measurements. For these reasons, expert committees do not recommended skinfold thickness or waist circumference measurements for routine clinical use.[11]

There is some evidence to suggest that BMI provides an as good if not better assessment of metabolic risk as skinfold thickness among children and adolescents.[34] A cross-sectional study comparing BMI and subscapular and triceps skinfold thickness found that BMI was as strongly correlated to levels of lipids, fasting insulin, and blood pressure as skinfold thickness.[34] It is also not apparent that body fatness is a stronger predictor of obesity-related comorbidities than BMI.[34] This is likely because of high correlation between body fat measures and high BMI.

5.3 GLOBAL PEDIATRIC OBESITY TRENDS

Over the past 50 years, global trends in the prevalence of overweight and obesity among children (using BMI-based criteria) have paralleled those of adult populations, and childhood obesity has increased significantly.[35,36] Since the 1960s, prevalence rates have quadrupled in many countries.[37] The problem is most severe in developed, industrial countries

where, according to 2011 estimates from the Organization for Economic Cooperation and Development (OECD), 21.4% of girls and 22.9% of boys ages 5–17 years in OECD countries are now overweight or obese, ranging from 10% to 16% in Korea and Turkey to more than 40% in Greece (Figure 5.2). The unweighted average percentage of overweight or obesity among 5–17-year-olds in the top 10 OECD countries is near 30%.[38]

In low- and middle-income countries, childhood overweight and obesity prevalence is generally lower but has been rising. A lack of consistent cross-country/time series data hampers the analysis (see the last paragraph of Section 5.3 of this chapter), but the evidence is nevertheless robust. A 2006 literature review by Wang and Lobstein[36] compiled survey results from 60 of the 191 WHO member countries, representing around half the world's population. With only a few exceptions—Russia and to a lesser extent Poland after the dissolution of the Soviet Union—childhood overweight and obesity had increased in every country evaluated. Generally, prevalence rates in developing countries were below those in industrial countries, with a few exceptions such as Brazil, Chile, Egypt, and Mexico, which had levels comparable to those in fully industrialized countries. In broad terms, prevalence rates were lower in Southeast Asia and sub-Saharan Africa and were higher in South and Central America, Northern Africa, and the Middle East.

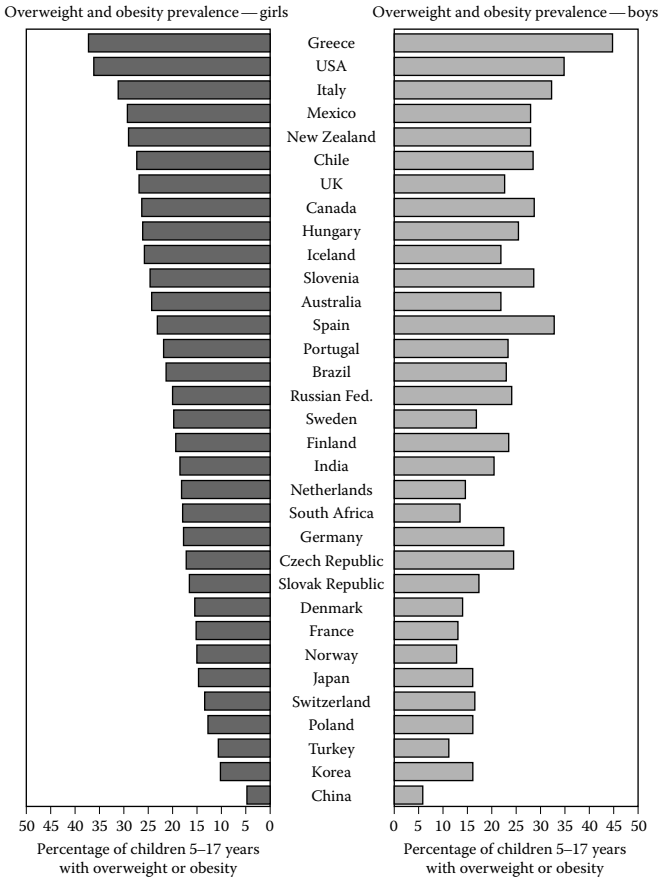

FIGURE 5.2 Prevalence (%) of overweight and obesity in boys and girls ages 5–17 years for select developed and developing countries. (Adapted from Organization for Economic Cooperation and Development [OECD], *Health at a Glance 2011: OECD Indicators*, OECD Publishing, http://www.oecd.org/dataoecd/6/28/49105858.pdf.)

Using a very different approach, de Onis, Blössner, and Borghi[39] drew similar conclusions for preschool children. By pooling data from the WHO Global Database on Childhood Growth and Malnutrition, they were able to calculate trends in regional average prevalence rates of overweight and obesity. The 2010 estimates for children ages 0–5 years ranged from 4.9% in Asia to 6.9% in Latin America and the Caribbean, 7.6% in Southern Africa, and 17% in Northern Africa (Figure 5.3). Overall, they estimated average global prevalence at 6.7%, with rates of 11.7% in developed countries and 6.1% in developing countries. An upward trend was apparent in all regions except for Latin America and the Caribbean, with particularly steep increases in North Africa. Overweight and obesity in developing countries exhibited a positive correlation with income and socioeconomic status, whereas in developed countries, the opposite was the case. The evidence further suggested a higher overall incidence in countries with less equal income distribution.

Given the state of knowledge, it would be premature to draw conclusions about future trends. Nevertheless, there is at least a glimmer of hope that the increase in prevalence may be abating in some high-prevalence countries. A 2010 OECD study noted a moderation in the pace of increase in four countries, the United States, England, France, and Korea.[40] For the United States, NHANES data published in 2012[41] indicated a marked slowdown among girls during the 2000s (Figure 5.4). However, these data also suggested that the prevalence of obesity continues to rise in U.S. boys.

Despite its serious direct and indirect consequences, childhood obesity has received, until recently, little attention from policymakers, and a lack of data and ad hoc methodologies continue to hamper careful monitoring. Different measures have been used, such as percentiles of BMI and weight-for-height or

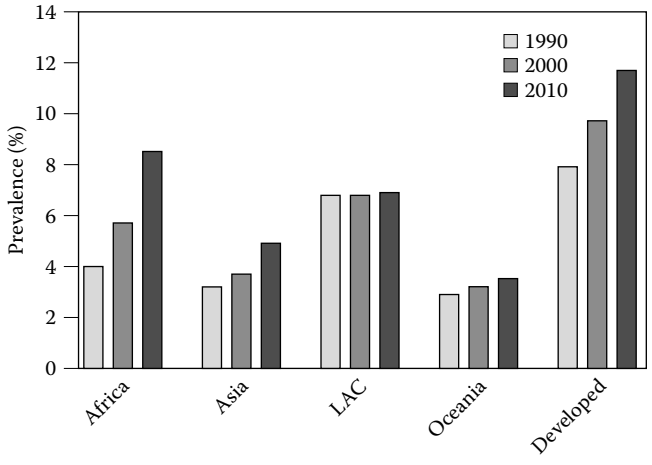

FIGURE 5.3 Prevalence (%) of overweight and obesity in preschool boys and girls from 1990 to 2010. LAC, Latin America and Caribbean countries. Asia excluding Japan. Oceania excluding Australia. Developed countries including Europe, North America, New Zealand, Japan, and Australia. (From de Onis, M et al., *Am. J. Clin. Nutr.*, 92, 1257–64, 2010.)

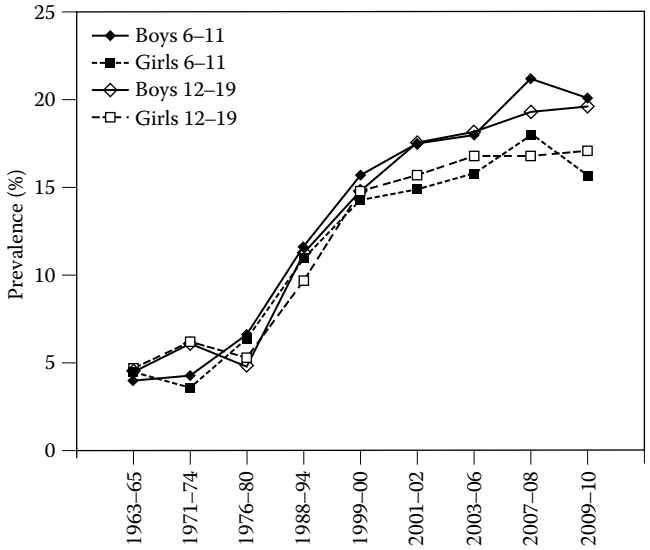

FIGURE 5.4 U.S. prevalence (%) of obesity (BMI ≥ 95% percentile) by age (6–11 years and 12–19 years) and sex from 1963 to 2010. (Data from the U.S. Centers for Disease Control and Prevention. *Health, United States, 2003 with Chartbook on Trends in the Health of Americans,* 2003, http://www.cdc.gov/nchs/data/hus/hus03.pdf; Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM, *JAMA,* 291, 23, 2847–2850, 2004; Ogden CL, Flegal KM, Carroll MD, Johnson CL, *JAMA,* 288, 14, 1728–1732, 2002; Ogden CL, Carroll MD, Kit BK, Flegal KM, *JAMA,* 307, 483–490, 2012.)

percent above ideal weight-for-height. No perfect measure is available that satisfies criteria such as accuracy, precision, simplicity, acceptability, and low cost.[42] Few countries outside the OECD conduct regular surveys. Of 144 countries with national survey data in the WHO Global Database on Childhood Growth and Malnutrition, 33 were represented by only 1 survey, and 38 were represented by 2—the minimum number needed to infer a trend.[39] Moreover, even where multiple successive data points exist, they are often based on different age ranges and cut points; methodologies (self-reported vs. measured); and sample frames (national, regional, urban only, school-based, or focusing on specific vulnerable groups). Fortunately, the situation is improving: 70 surveys were conducted before 1990, 171 between 1991 and 1999, and 209 subsequently.[39]

5.4 OBESITY COMORBIDITIES IN CHILDREN AND ADOLESCENTS

Pediatric overweight and obesity are of concern because of both immediate and later onset health consequences.[43] Pediatric obesity is associated with myriad medical and psychosocial complications that are reviewed in this section. Children at the highest levels of BMI are usually at the greatest risk of obesity-associated adverse health outcomes.[14] Obesity in childhood is more likely to lead to adult obesity[30] and the tracking of poor health throughout adulthood, and obesity is a major contributor to many preventable causes of morbidity.[44] In one study, the risk of adult obesity was higher for older obese children, those with more severe obesity, and those with obese parents.[45] Some data suggest that BMI ≥ 99th percentile is particularly associated with excess adiposity, obesity comorbidities, and tracking of obesity into adulthood.[30] Although there is variation in the estimates among studies examining the question of persistence, it appears that approximately 40% of obese children become obese adults.[42,46,47]

5.4.1 Cardiovascular Disease

Obese and overweight youth are more likely to have cardiovascular risk factors resulting in cardiac structural and hemodynamic alterations.[30] It is estimated that almost all severely obese youth have at least one of these risk factors.[30] Analyses have suggested, however, that there is little evidence that childhood BMI is an independent risk factor for adult cardiovascular risk once adult BMI is taken into consideration.[48]

Obesity is the leading cause of hypertension in childhood[49] with a relative risk of 2.5 to 3.7 in overweight children and adolescents.[43] Systolic blood pressure correlates positively with BMI, skinfold thickness, and waist-to-hip ratios in children.[49] Obesity is associated with greater ventricular mass.[43] The presence of atherosclerotic changes has been documented in obese adolescents.[43] In obese children, there is evidence of early endothelial dysfunction, with intimal medial thickening in the carotid, and early coronary and aortic fatty streaks and fibrous plaque.[50,51] Autopsy data from the Bogalusa Heart and the Pathobiological Determinants of Atherosclerosis in Youth studies have demonstrated that the extent of aortic and coronary atherosclerosis is positively related to severity of obesity in childhood and adolescence.[52,53]

5.4.2 Dyslipidemia

Childhood obesity is associated with dyslipidemia, with the most common abnormality being elevated triglycerides and decreased high-density lipoprotein cholesterol.[43] Elevated low-density lipoprotein (LDL) cholesterol is also seen in obese children; however, the association between LDL cholesterol and adiposity is weaker.[54] BMI is also positively associated with likelihood for LDL particle size <25.5 nm.[55] There is some evidence to suggest that even though the majority of cardiovascular disease occurs in adulthood, the atherosclerotic process begins in childhood and progresses with age.[56] Childhood dyslipidemia has been shown to persist and to be a predictor of adult dyslipidemia, adult carotid intimal media thickness, and other cardiovascular disease risks.[57] In one study, the strongest predictors of adult lipid and lipoprotein levels were the corresponding levels of these measures in childhood and the development of adiposity assessed by BMI.[58]

5.4.3 Impaired Glucose Homeostasis

Obesity is commonly accompanied by insulin resistance and hyperinsulinemia, which precede and play a major role in the development of type 2 diabetes mellitus (T2DM).[59]

In children, total body fat and visceral fat are positively associated with fasting insulin,[60–62] and impaired insulin sensitivity may worsen with duration of obesity.[63] In one report, 21% of obese adolescents and 25% of obese children had impaired glucose tolerance (2-hour glucose value ≥140 and <200 mg/dL during an oral glucose tolerance test),[64] although most studies report much lower prevalence.[65] The increasing incidence of pediatric T2DM parallels the increasing prevalence of obesity. It has been estimated that 16% of all new cases of pediatric-onset diabetes among adolescents are now T2DM.[66] Development of T2DM adds on higher risk for cardiovascular disease than obesity alone. Among Pima Indians, the onset of T2DM during childhood or adolescence has been associated with a markedly earlier age for development of end-stage renal disease and a significant increase in mortality rate before age 55 years.[67]

5.4.4 Metabolic Syndrome

The metabolic syndrome refers to the clustering of insulin resistance, hypertension, dyslipidemia, and obesity, and this condition has been associated with increased risk of cardiovascular disease and T2DM in adults.[68] Metabolic syndrome is more prevalent in obese individuals, particularly in those with central adiposity.[68] There is no clear definition of the metabolic syndrome in pediatrics, but a number of criteria have been proposed, derived from the adult criteria but using percentile-based cut points for children.[43] Increasing BMI and insulin resistance during childhood are strong predictors of the metabolic syndrome.[69,70] In a study using NHANES 1999–2002 survey data, the overall prevalence of metabolic syndrome among U.S. adolescents ages 12 to 19 years ranged from 2.0% to 9.4% depending on the definition used, whereas among obese adolescents, the prevalence ranged from 12.4% to 44.2%.[71] The clinical utility of the metabolic syndrome in pediatrics remains debatable; however, and unlike in adults, the definition does not reflect outcomes-based variables or cut points.[43] There is also quite limited stability for the diagnosis of metabolic syndrome among children and adolescents.[72]

5.4.5 Pulmonary Comorbidities

It is estimated that up to 33% of obese children have obstructive sleep apnea (OSA),[73–75] which is characterized by snoring, nocturnal hypoxemia, and excessive daytime somnolence.[75] Among severely obese adolescents, 55% have polysomnographic findings consistent with OSA.[75] OSA results from airway narrowing from adenotonsillar hyperplasia/hypertrophy, fatty infiltration of upper airway structures, and fatty infiltration in the subcutaneous fat depot in the neck and cervical structures. Increased adiposity in the abdominal wall and cavity and thorax may also cause a mechanical decrease in lung volume and oxygen reserve and increase the work of breathing during sleep.[75] If left untreated, OSA may result in endothelial dysfunction and other longer-lasting vascular consequences including pulmonary hypertension and *cor pulmonale*.[75] Central hypoventilation syndrome also has been described in obese children.[75] Unlike patients with OSA, however, patients with hypoventilation syndrome will have daytime occurrence of hypercapnia and hypoxemia, which may lead to polycythemia, pulmonary hypertension, and *cor pulmonale*.[75]

5.4.6 Asthma Exacerbation

Pediatric studies have documented an association between obesity and asthma.[76] The exact mechanism for this association has not been elucidated, and it has not been clearly demonstrated whether obesity worsens the severity of asthma symptoms or whether weight reduction would result in improvement of pulmonary function in children.[76] Children with asthma have systemic inflammation that may be exacerbated by the inflammatory process from the obese state; increased airway inflammation is associated with worsening asthma symptoms.[76] Although there are no data examining the effect of weight loss on asthma in children, an adult randomized control trial showed improvement of pulmonary function in asthmatics following weight loss.[76]

5.4.7 Gastrointestinal Comorbidities

Gastroesophageal reflux, nonalcoholic fatty liver disease (NAFLD), cholelithiasis, and gallstones are increased among obese pediatric patients. A 13% prevalence of gastroesophageal reflux has been observed in obese children.[77] NAFLD has been shown to occur in 2.6%–25% of obese children and adolescents from small epidemiological studies using indirect diagnosis tests such as liver enzymes or ultrasound,[78] while an autopsy study reported a 9.6% prevalence in children ages 2–19 years and a higher prevalence among obese children (38%).[79] NAFLD is characterized by accumulation of macrovesicular fat in hepatocytes.[80] NAFLD can potentially progress to nonalcoholic steatohepatitis or to hepatic fibrosis and cirrhosis.[78] NAFLD histology shows more fibrosis in children than adults.[81] A definitive diagnosis of NAFLD can be made only by histology from a liver biopsy, limiting population-based estimates. Gallstones also have been shown to be more common in obese adolescents, with a higher prevalence observed in obese girls.[82]

5.4.8 Orthopedic Complications

A higher frequency of musculoskeletal discomfort and/or impairment of mobility has been documented in obese children and adolescents.[83] Tibia vara (Blount's disease) and slipped capital femoral epiphysis (SCFE) are the most common orthopedic problems in obese children,[43] resulting from mechanical stress on the developing skeletal system. Blount's disease usually occurs in severely obese boys ages 9 years or older and presents with bowing of the tibia and abnormal gait. SCFE presents with a waddling gait, limitation of hip movement, and/or pain in the hip or knee joints. SCFE occurs more commonly among obese African-American males.[84] Obese children also have increased risk of forearm

fractures,[85] but the exact reason is not clear. They may be caused simply by the greater force exerted on bones during a fall by an obese child.[83]

5.4.9 Psychosocial

Obese children are more likely to have psychological distress including low self-esteem, higher rates of anxiety disorders, body image disturbance, and depressive symptoms.[86,87] There is also some evidence suggesting increased risk for obesity among depressed youth.[88] In a longitudinal cohort study, depression in late adolescence among girls was associated with a greater than twofold increased risk for obesity in adulthood.[88] Obese children and adolescents reported significantly lower health-related quality of life compared to their normal-weight peers, and they rated their health-related quality of life as low as that of children being treated for cancer.[89] Experiences of teasing and bullying have been shown to be higher among obese children and adolescents.[90,91] Weight-related teasing may result in unhealthy weight-control behaviors such as binge eating, which could cause further weight gain among overweight and obese youth.[92]

5.4.10 Puberty

Obesity is associated with early onset of thelarche[93,94] and slightly earlier menarche among girls.[95–101] In contrast, obese boys are more likely to have delayed onset of gonadarche.[102,103] Excess adipose tissue results in elevated estrogenic effects because of several factors, including greater aromatase expression in adipose tissue, low levels of sex hormone-binding globulin, and possibly other contributors such as high-fat diets.[104]

5.4.11 Hyperandrogenism and Polycystic Ovary Syndrome

Among girls, peripubertal obesity is associated with significant hyperandrogenism, which is particularly marked in the prepubertal and early pubertal period.[105] Elevated insulin levels are thought to be the mechanism leading to hyperandrogenism.[105] Excess adiposity may thus cause polycystic ovary syndrome and may be associated with anovulation resulting in irregular menses (oligomenorrhea or amenorrhea), elevated androgens with or without clinical hyperandrogenism (hirsutism, acne, and male-pattern hair loss), and cystic ovaries. In adults, 30%–75% of women with polycystic ovary syndrome have obesity.[106]

5.4.12 Mortality

Some[107,108] but not all[109] studies have suggested that pediatric obesity has a unique impact on subsequent mortality. For example, in 1992, Must et al.[107] found that adolescent obesity was independently associated with an increased risk of mortality among 508 men in the Harvard Growth Study first examined at ages 13–18 years (between 1922 and 1935), but Gray et al.[109] found no evidence for an independent effect of high BMI in early adulthood on cardiovascular mortality risk in a study of 18,995 participants in the Harvard Alumni Study first examined between 1916 and 1950. Projection analysis by Olshansky et al.[110] predicted a shorter life span for the current generation of U.S. children, largely because of obesity and all its related comorbidities.

5.5 CONCLUSION

Although BMI is an imperfect measure of childhood adiposity, it is clear that the prevalence of pediatric obesity has increased dramatically since the 1960s in the developed world and is an increasingly common problem in developing nations. Pediatric obesity causes considerable morbidity during childhood and, particularly because obesity is so frequently persistent into adulthood, is associated with significant cardiovascular morbidity and greater mortality. Development of effective methods to prevent and treat pediatric obesity should be given the highest priority.

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6 Obesity in Older Adults in the United States

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CONTENTS

6.1 INTRODUCTION

Between 2010 and 2050, the American older adult population aged 65 years and older is projected to grow from 40.2 million to 88.5 million.[1] Similar to estimates in the entire adult population, in 2007–2010 over a third of adults aged 65 years and older were obese, which represents over 13 million adults.[2] Because both aging and obesity contribute to the increased use of health-care services,[3,4] health-care expenditures for America's older adult population are expected to rise.[3,4] Recent data suggest that the rise in obesity levels that began in the 1980s and 1990s may have slowed down or leveled off.[5] However, the anticipated demographic shift may lead to a large number of obese older adults even without an increase in age-specific obesity prevalence.

In this chapter, we present the epidemiology of obesity among older American adults, focusing on data from the United States. We first define obesity in older adults and provide a brief overview of body composition changes that are associated with aging. This is followed by a description of sarcopenic obesity. Obesity prevalence, trends, and disparities among older adults in the United States are also included, followed by a presentation of estimates of dietary intake and physical activity in the United States.

6.2 DEFINITION AND MEASUREMENT OF OBESITY IN OLDER ADULTS

Obesity is characterized as the excessive accumulation of adipose tissue that is of sufficient magnitude to impair health.[6] Measuring adiposity or body fatness in populations and individuals can be difficult. Underwater weighing, or hydrodensitometry, has generally been considered the gold or reference standard for measuring body fatness. However, hydrodensitometry is expensive and time consuming and is logistically difficult to implement in population studies.[7] Dual-energy x-ray absorptiometry (DXA) imaging can also be used to measure body fatness. DXA technology relies on the differential absorption of x-rays by different tissue types. The differences are captured by a detector and are used to estimate fat mass. Similar to underwater weighing, this method is also expensive.

Because direct measures of body fatness are difficult to implement and are expensive, anthropometric indices such as body mass index (BMI) are often used in epidemiologic studies. BMI, which is a composite index of weight accounting for height (BMI = weight [in kilograms]/height^2 [in meters]), is a common measure used to define obesity in all adults.[8] Current guidelines define adult obesity as a BMI of 30.0 or higher, regardless of age.[6] Obesity can be further subdivided into grade 1 obesity (BMI = 30.0–34.9), grade 2 obesity (BMI = 35–39.9), and grade 3 or extreme obesity (BMI $\geq$ 40).[6]

BMI has two major limitations: first, BMI does not discriminate between muscle mass and fat mass,[9] and second, BMI does not provide information on body fat location.[9] In addition to these limitations, assessing body composition in older people using BMI is challenging.[9–12] This is due, in part, to changes in body composition associated with healthy aging.[10,11,13] As adults age, loss of bone mineral density and fat-free lean mass occur.[10,11,13–17] Moreover, fat mass increases

and there is a redistribution of fat deposits.[13–17] As a result, at any given BMI value the amount of body fat, in particular visceral abdominal fat, is greater in older adults than in younger adults.[8,18] Because visceral abdominal fat is more predictive of morbidity and mortality compared with peripheral adiposity, some studies have recommended the use of waist circumference, a proxy measure of abdominal adiposity, as a substitute for or in addition to BMI.[12,19,20] However, both BMI and waist circumference are highly correlated and have been shown to be equally predictive of the risk for morbidity and mortality,[21,22] and BMI is still widely used to assess obesity among older adults.

6.3 SARCOPENIC OBESITY

Aging is accompanied by increased fat infiltration in muscle, which leads to loss in muscle quality and strength.[17,23,24] This loss of muscle strength can lead to poor or reduced physical function.[17,23,24] The age-associated loss of skeletal muscle mass and muscle function (strength or performance), which contributes to the development of frailty and disability, is referred to as sarcopenia.[15,25]

Sarcopenia can be present in older adults with or without obesity. When sarcopenia is present in the context of obesity, it is generally referred to as sarcopenic obesity or obesity/muscle impairment geriatric syndrome.[13,26] Although low levels of physical activity may, in part, explain both obesity and sarcopenia,[13,26,27] there is also evidence that obesity may contribute to the development of sarcopenia.[13,26] For example, studies have shown that fat mass promotes the production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, which have catabolic effects on muscle and can contribute to a decline in muscle mass and strength.[13,26,28]

The main consequence of sarcopenia is disability from loss of mobility.[13,26] However, identifying the consequences of sarcopenic obesity is challenging because of the lack of consensus on the definition of this body composition phenotype.[13,26] Because BMI cannot detect sarcopenic obesity, the effect of sarcopenic obesity on morbidity and mortality may be underestimated.[13,26]

6.4 DESCRIPTIVE EPIDEMIOLOGY OF OBESITY, MACRONUTRIENT INTAKE, AND PHYSICAL ACTIVITY

The data presented in Figures 6.1–6.4 and Table 6.1 are from the 2007–2010 U.S. National Health and Nutrition Examination Survey (NHANES). Some of the estimates cited are based on a previously published report of NHANES data.[29] NHANES is a continuous survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention to assess the health and nutritional status of the U.S. noninstitutionalized population. NHANES consists of an in-home interview followed by a standardized physical examination at a mobile examination center.

We examined obesity prevalence by sex, age, race and ethnicity, and socioeconomic status. Extreme obesity, compared to lower grades of obesity, is associated with the most severe health complications[30]; for this reason, we chose to present obesity prevalence by grade in Figure 6.1. Age was categorized as 65–74 years and 75 years and over. Because

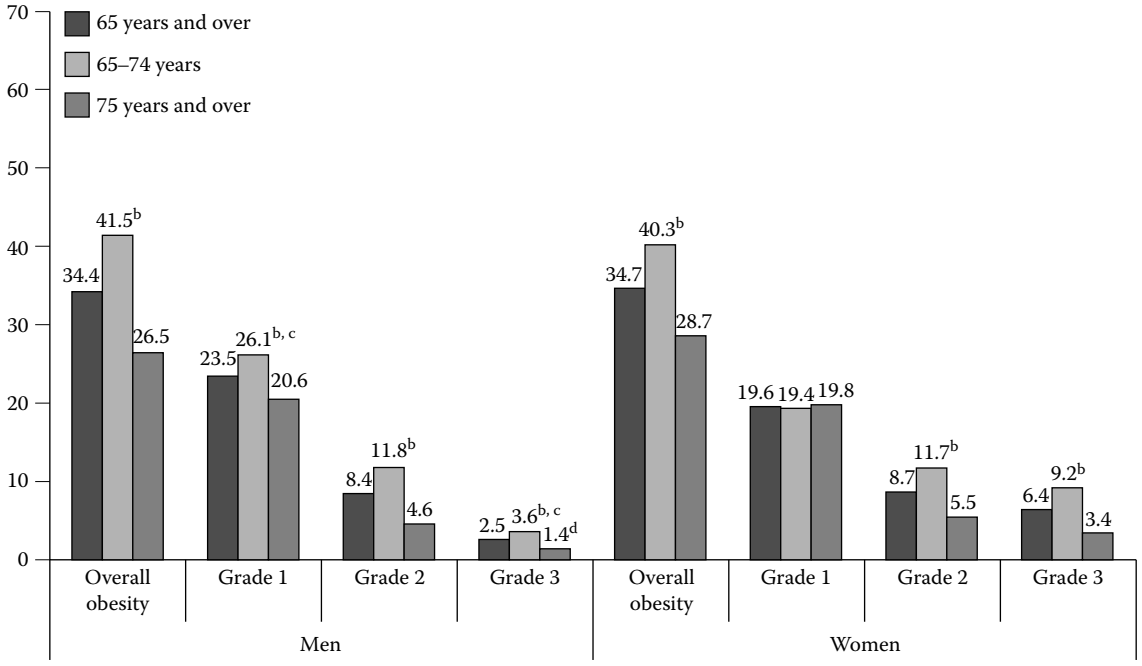

FIGURE 6.1 Prevalence of overall obesity, grade 1 obesity, grade 2 obesity, and grade 3 obesity by sex and age in U.S. adults 65 years and over in 2007–2010. [b] Significantly different from those 75 and over of the same sex (*t*-test, $p < .05$). [c] Significantly different from women of the same age (*t*-test, $p < .05$). [d] Does not meet standard of reliability (Relative Standard Error > 30). Definitions: Overall obesity BMI ≥ 30; grade 1 BMI 30 to < 35; grade 2 BMI 35 to < 40; grade 3 BMI ≥ 40. (Courtesy of National Health and Nutrition Examination Survey [NHANES].)

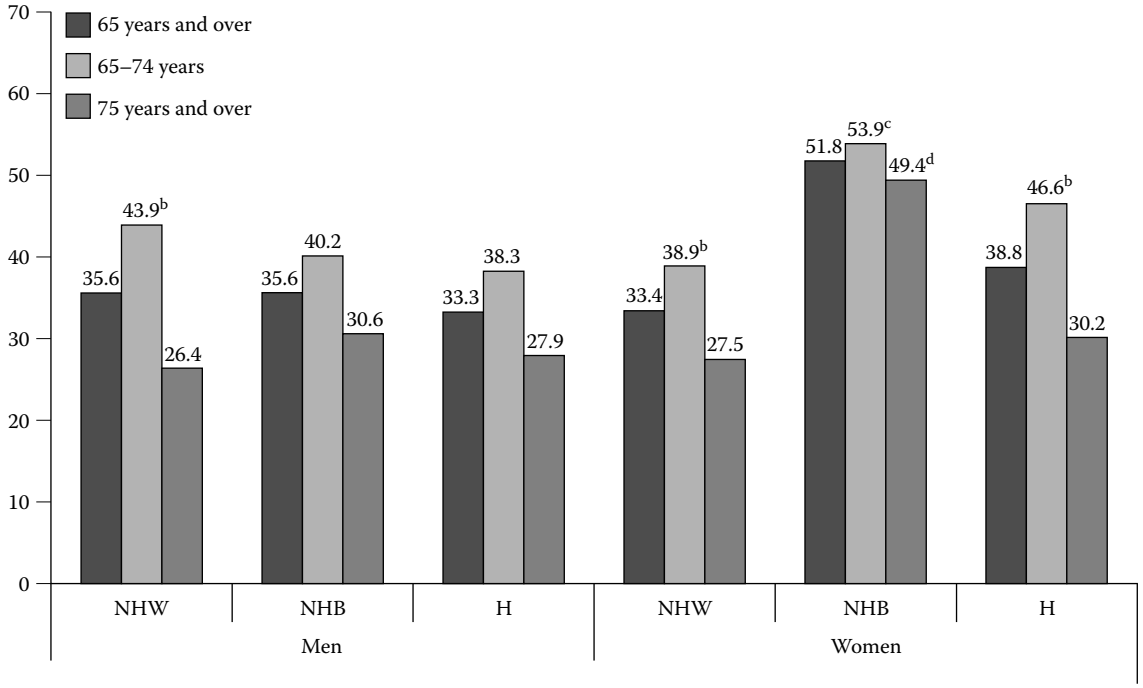

FIGURE 6.2 Prevalence of obesity by race/ethnicity, sex, and age in American adults 65 years and over in 2007–2010. [b] Significantly different from those 75 years and over (*t*-test, $p < .05$). [c] Significantly different from non-Hispanic white women of the same age (*t*-test, $p < .05$). [d] Significantly different from non-Hispanic white and Hispanic women of the same age (*t*-test, $p < .05$). Abbreviations: NHW: Non-Hispanic White, NHB: Non-Hispanic Black, H: Hispanic. (Courtesy of National Health and Nutrition Examination Survey [NHANES].)

racial and ethnic disparities in obesity prevalence have been reported for American adults aged 20 years and over, we sought to determine the prevalence of obesity by race and ethnicity among older adults in Figure 6.2. Race/ethnic groups were categorized as non-Hispanic white, non-Hispanic black, Hispanic, and others (including individuals of Asian descent, American Indians and Alaska Natives, and multiracial participants). Socioeconomic status has also been shown to be associated with obesity.[31,32] In Figure 6.3, we present obesity prevalence by two measures of socioeconomic status, family income to poverty ratio (FIPR) and educational attainment. FIPR is an index representing the ratio of family income to poverty.[33] We categorized FIPR into tertiles (lowest, T1 [FIPR: 0% to <130%]; medium, T2 [130% to <350%]; and highest, T3 [≥350%]). Income eligibility for participation in the Supplemental Nutrition Assistance Program (formerly known as the Food Stamp Program) is 130% of the poverty level (<130% FIPR).[34] The level of education attained was classified based on self-report as less than high school, completed high school or general equivalency diploma, some college, and college graduate.

Next, we examined physical activity and energy intake by race and ethnicity. Participation in leisure time moderate-to-vigorous physical activity (MVPA) was self-reported and assessed using two questions. First, participants were asked, "Now I would like to ask you about sports, fitness, and recreational activities. Do you do any vigorous-intensity sports, fitness, or recreational activities that cause large increases in breathing or heart rate like running or basketball for at least 10 minutes continuously?" Subsequently, participants were asked, "Do you do any moderate-intensity sports, fitness, or recreational activities that cause a small increase in breathing or heart rate such as brisk walking, bicycling, swimming, or golf for at least 10 minutes continuously?" Respondents were classified as nonparticipants in leisure time MVPA if they answered "no" to both questions.

The examination included standardized measurements of weight and height and a 24-hour dietary recall interview. Data from a single in-person 24-hour dietary recall interview were used to estimate mean daily total caloric intake and mean daily percentage of kilocalories consumed from protein, carbohydrate, total fat, and saturated fat.

Statistical analyses included adjustment for the complex sample design and included sample weights. Total prevalence and mean estimates for all adults aged 65 years and older were age adjusted using the direct method to the 2000 U.S. standard population using two age groups: 65–74, and 75 and over.

The focus of this chapter is on comparing obesity prevalence, macronutrient intake, and physical activity between the age groups (65–74 vs. 75+ years). Differences in prevalence or means between sociodemographic groups were evaluated using a univariate *t*-statistic or a linear test of trend at the $p < .05$ significance level with appropriate degrees of freedom.

6.5 OBESITY

6.5.1 Prevalence

In 2007–2010, more than a third of American adults of 65+ years were obese.[2] The prevalence was 34.4% among men and 34.7% among women.[2] For both men and women, the prevalence of obesity was higher among those aged 65–74

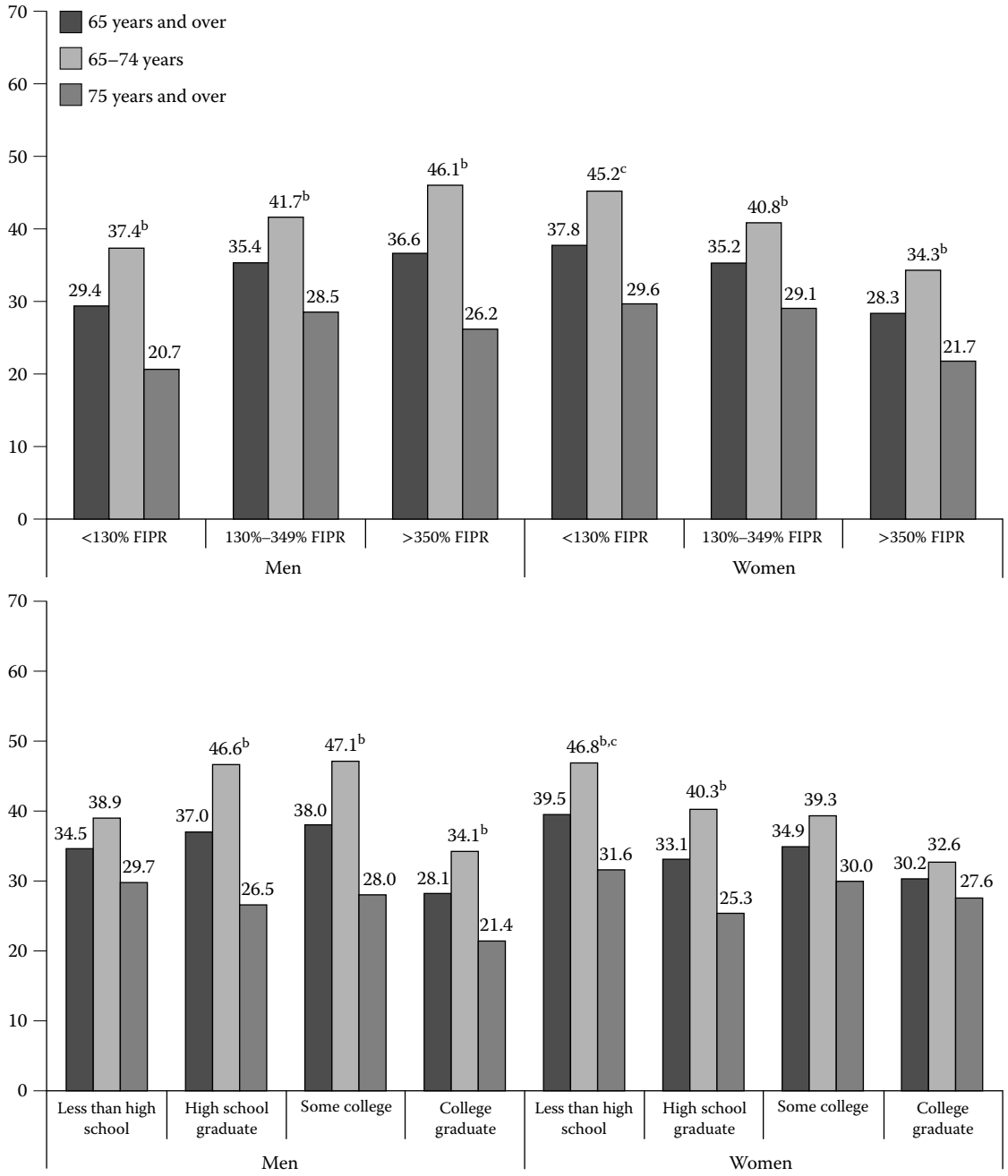

FIGURE 6.3 Prevalence of obesity among adults aged 65 and over by sex and (a) income and (b) education: United States, 2007–2010. [b] Significantly different from those 75 years and over (*t*-test, $p < .05$). [c] Significant linear trend among women 65–74 years of age (*t*-test, $p < .05$). Abbreviations: FIPR: Family income to poverty ratio. (Courtesy of National Health and Nutrition Examination Survey [NHANES].)

years than among those aged 75+ years (Figure 6.1). About 42% of men aged 65–74 years and 27% of those aged 75 years and older were obese. Among women, about 40% of those aged 65–74 years and 29% of those aged 75 years and older were obese.

The prevalence of obesity varies by grade of obesity. The majority of obese older men and women have BMI values between 30 and 35 (grade 1 obesity) (Figure 6.1). Among men 65–74 years of age 26.1%, 11.8%, and 3.6% were classified as grade 1, grade 2, and grade 3 obese compared to 20.6%, 4.6%, and 1.4% in those aged 75+ years. Among women 65–74 years of age 19.4%, 11.7%, and 9.2% were classified as grade 1, grade 2, and grade 3 obese compared to 19.8%, 5.5%, and 3.4% in their older counterparts, that is, 75+ years of age. The prevalence of obesity was lower in those aged 75 years and older for all grades of obesity except for the prevalence of grade 1 obesity among women. Approximately 19% of women aged 65–74 years and 75+ years had BMIs between 30 and 35 or grade 1 obesity.

The only differences in obesity prevalence between men and women occurred in adults 65–74 years of age. The prevalence of grade 1 obesity was higher in men than in women

(26.1% vs. 19.4%), and that of grade 3 obesity was higher in women than in men (9.2% vs. 3.6%).

6.5.2 Ethnic and Sociodemographic Differences in Obesity Prevalence

Racial and ethnic disparities in obesity prevalence have been reported in all adult American women.[5] Obesity prevalence in non-Hispanic white, non-Hispanic black, and Hispanic older adults of 65 years and over can be seen in Figure 6.2. Among both adults aged 65–74 years and 75+ years, no race/ethnic disparities in the prevalence of obesity were observed among men. In contrast, in 2007–2010 the prevalence of obesity varied significantly by race/ethnic group among women in both age groups. In women 65–74 years of age, the prevalence of obesity was highest among non-Hispanic black women (53.9%) compared to 38.9% among non-Hispanic white women and 46.6% among Hispanic women. Similarly, in women 75 years and over the prevalence of obesity among non-Hispanic black women was 49.4%, versus 30.2% in Hispanics and 27.5% in non-Hispanic whites.

Socioeconomic status, as measured by educational attainment and/or income, has been shown to be associated with obesity.[31,32] Previous analyses of the older American population have shown no significant trends in the prevalence of obesity among men by educational attainment in either age group.[2] In women 65–74 years of age, obesity prevalence decreased with increasing educational attainment (Figure 6.3). Almost half of women 65–74 years of age with less than a high school degree were obese compared to about a third of college graduates. Among women 75 years and over, there were no differences in obesity prevalence by educational attainment (Figure 6.3). The prevalence of obesity was lower among those aged 75 years and older regardless of educational attainment for both men and women (Figure 6.3). Similar to the patterns observed by educational attainment, the prevalence of obesity did not vary significantly by income among all older men or either age group in 2007–2010, although this may be due to a lack of statistical power (Figure 6.3). For example, in those 65–74 years of age 37.4% of men with income below 130% of the poverty line were obese compared to 41.7% of those living between 130% and 350% of the poverty line and 46.1% of those at or above 350% of the poverty line. Among older American women, obesity prevalence decreased with increasing income for women 65–74 years of age but not among those 75 years and older. Of those living below 130% of the poverty line 45.2% were obese versus 40.8% of those living between 130% and 350% of the poverty line and 34.3% of those living at or above 350% of the poverty line. In all income groups, the prevalence of obesity among those 75 years of age and older was lower than among those 65–74 years of age except among women living below 130% of the poverty line.

6.5.3 Trends

Previous analyses have demonstrated an increase in obesity prevalence among older adults from 22% in 1988–1994 to 32% in 2007–2008.[35] However, between 1999 and 2010, obesity prevalence significantly increased among older men but not among older women.[2] In men 65–74 years of age, obesity prevalence increased from 31.6% in 1999–2002 to 33.0% in 2003–2006 to 41.5% in 2007–2010. In men 75 years and older, the prevalence increased from 17.7% in 1999–2002 to 24% in 2003–2006 to 26.5% in 2007–2010. Among women 65–74 years and 75+ years, no significant changes were observed between 1999–2002 and 2007–2010.

6.6 MACRONUTRIENT INTAKE AND PHYSICAL ACTIVITY

Studies have documented that energy intake decreases substantially with age.[36–39] Concurrently, all major components of total energy expenditure also decrease with age, including physical activity, basal metabolic rate, and thermic effect of food.[14,40–43] As a result, increases in total fat mass have been attributed to a decline in total energy expenditure.[36,37] Studies have shown that interventions combining diet and exercise in older obese adults improve muscle strength and result in fat loss.[44,45] On the other hand, physical inactivity and inadequate intake of dietary protein have been linked to the development of sarcopenia.[13,46,47] Thus diet and physical activity patterns in older adults remain pertinent in relation to obesity and body composition.

6.6.1 Macronutrient Intake

Data from the United States show that macronutrient intake tends to decrease with age. In 2007–2008, the mean daily energy intakes for all adult men and women, 20 years and older, were 2504 and 1771 kcal, respectively.[48] In older adults, mean energy intake is lower. For men, the means were 2045 kcal among those 65–74 years of age and 1797 kcal among those 75 years of age and over in 2007–2010, with a difference of 248 kcal between the two older age groups (Table 6.1). Among men, the average energy intake decreased with age among all race/ethnic groups. Among women, mean energy intakes were 1607 kcal in those aged 65–74 years and 1476 kcal in those aged 75 years and older. The average energy intake decreased significantly with age overall and among non-Hispanic white women only.

Older adults who follow a dietary pattern consistent with current guidelines to consume higher amounts of low-fat dairy products, fruit, whole grains, poultry, fish, and vegetables are more likely to have improved quality of life and survival.[49,50] Dietary recommendations related to the intake of total and saturated fat in older adults are the same as those for all adults. All adults, including older adults, are encouraged to consume 20%–35% of kilocalories from fats and less than 10% of kilocalories from saturated fatty acids.[51] Overall, among all adult men 33.6% of energy intake was consumed as fat and approximately 11.0% of kilocalories were consumed as saturated fat.[48] Among all adult women, 33.5% of total energy intake was from fats and 11.1% of kilocalories were from saturated

TABLE 6.1
Macronutrient Intake: Total Energy and Percentage of Energy from Protein, Carbohydrate, Total Fat, and Saturated Fat by Sex, Race/Ethnicity, and Age in the United States in 1999–2010

	65- to 74-Year-Olds				75 Years and Over			
	All	Non-Hispanic White	Non-Hispanic Black	Hispanic	All	Non-Hispanic White	Non-Hispanic Black	Hispanic
Men								
Energy (kcal) (se)[a]	2045 (25.0)	2088 (29.8)[b]	1913 (57.1)	1967 (66.4)	1797 (40.2)	1839 (42.3)[b,c]	1595 (89.8)	1496 (71.2)
Proteins (%kcal) (se)	16.3 (0.2)	16.1 (0.2)[c]	17.4 (0.6)	17.1 (0.4)	15.9 (0.2)	15.8 (0.2)	15.8 (0.9)	16.2 (0.6)
Carbohydrates (%kcal) (se)	47.5 (0.4)	47.0 (0.5)[c]	45.9 (1.0)[c]	49.7 (0.9)	50.4 (0.5)	50.1 (0.5)[c]	49.9 (1.4)	53.9 (1.3)
Total fat (%kcal) (se)	34.4 (0.4)	35.1 (0.5)[c]	33.9 (0.6)	31.9 (1.0)	33.2 (0.5)	33.6 (0.5)[c]	34.4 (0.9)[c]	29.3 (0.8)
Saturated fat (%kcal) (se)	11.0 (0.2)	11.3 (0.2)[b,c]	10.4 (0.2)	10.3 (0.4)	10.9 (0.2)	11.1 (0.2)[c]	10.7 (0.5)	9.6 (0.5)
Women								
Energy (kcal) (se)[d]	1607 (26.1)	1645 (31.6)[c]	1502 (86.8)	1411 (40.0)	1476 (32.2)	1501 (37.5)[b]	1342 (65.2)	1378 (61.4)
Proteins (%kcal) (se)	16.1 (0.2)	16.0 (0.3)[c]	16.5 (0.6)	17.0 (0.3)	15.7 (0.2)	15.5 (0.2)	16.4 (0.7)	16.2 (0.5)
Carbohydrates (%kcal) (se)	50.4 (0.5)	49.8 (0.5)[c]	49.1 (1.0)[c]	54.8 (0.7)	51.6 (0.4)	51.3 (0.4)[c]	51.6 (1.4)	54.6 (1.5)
Total fat (%kcal) (se)	33.9 (0.4)	34.4 (0.5)[c]	34.8 (0.7)[c]	29.8 (0.6)	33.4 (0.4)	33.8 (0.5)[c]	32.9 (0.8)	30.7 (1.3)
Saturated fat (%kcal) (se)	11.2 (0.2)	11.5 (0.3)[b,c]	10.5 (0.3)[c]	9.5 (0.3)	11.0 (0.1)	11.3 (0.2)[b]	10.1 (0.3)	10.4 (0.5)

Source: Courtesy of National Health and Nutrition Examination Survey (NHANES).

Note: Data are based on one 24 hour dietary recall interview. kcal = Kilocalories, se = standard error.

[a] Significantly different from those 75 years and over of the same race/ethnic group (*t*-test, $p < .05$).

[b] Significantly different from non-Hispanic black.

[c] Significantly different from Hispanic.

[d] Significantly different from those 75 years and over for women overall and among non-Hispanic white women (*t*-test, $p < .05$).

fat.[48] In older adults, percentage energy intake from total fats and saturated fats was similar to those observed in the entire adult population. For example, among men 65–74 years of age, 34.4% of kilocalories were from total fats and 11.0% were from saturated fats (Table 6.1). Among both men and women, the percentage of energy intake from fats and saturated fats did not decrease with age in any of the race/ethnic groups.

Although comprehensive short-term nitrogen balance studies suggest that the requirement for dietary protein is not different between younger and older adults,[52] some studies suggest that a protein intake moderately greater than the recommended dietary allowance may be beneficial to enhance muscle protein anabolism and reduce loss of muscle mass in older adults.[52,53] Overall, 15.9% of energy intake among all adult men and 15.5% among all adult women were consumed as protein.[48] As was observed for total and saturated fats, percentage energy intake from proteins was similar to those observed in the entire adult population. For example, among older men 16.3% of energy was from proteins in those 65–74 years of age and 15.9% in those 75 years and over (Table 6.1). In both men and women, energy intake from proteins did not decrease with age for any of the race/ethnic groups.

6.6.2 Physical Activity

The benefits of physical activity in relation to body composition, chronic disease prevention, and reduced depression are well known.[35,54–57] In older adults, physical activity can be particularly important in that it can improve quality of life.[35,56,57] Physically active older adults can have enhanced mobility, and strength training in older adults may lead to better balance and a reduced risk of falls.[35,56,57]

Data from the United States show that in 2010 only 11% of older adults met the 2008 federal physical activity guidelines, although this percentage has increased since 1998. There are significant differences in the percentage who meet the guidelines by age and race/ethnicity.[35]

In 2007–2010, about 57% of all men 65 years and over and about 67% of all women 65 years and over reported no leisure time physical activity at all (Figure 6.4). Women were more likely to report no leisure time physical activity. More than half of men and almost 61% of women 65–74 years of age reported no leisure time physical activity compared to about 63% of men and just over 74% of women 75+ years of age. The percentage of those who did not report any leisure time physical activity increased with age for both men and women and in all racial and ethnic groups except among Hispanic men.

6.7 CONCLUSIONS

In 2007–2010, more than one-third of older American adults were obese. Obesity prevalence, however, was lower among those 75 years and older compared with adults aged 65–74 years. Trends in obesity prevalence, along with race/

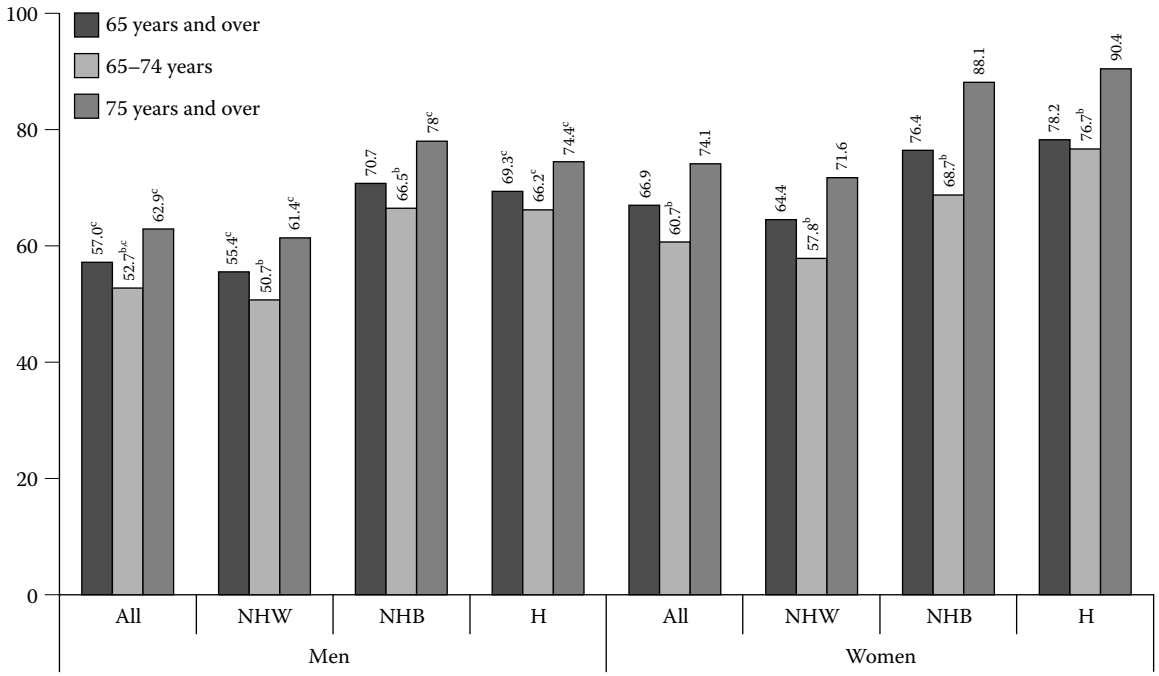

FIGURE 6.4 Prevalence of no leisure time physical activity by race/ethnicity, sex, and age in American adults 65 years and over in 2007–2010. [b] Significantly different from those 75 years and over (*t*-test, $p < .05$). [c] Significantly different from women of the same age (*t*-test, $p < .05$). Abbreviations: NHW: Non-Hispanic White, NHB: Non-Hispanic Black, H: Hispanic. (Courtesy of National Health and Nutrition Examination Survey [NHANES].)

ethnic disparities in obesity prevalence, were similar in the two age groups. In contrast, differences in obesity prevalence by income did vary between the two age groups. An inverse association was seen among women 65–74 years of age but not among women 75 years and older. Differences between the two age groups were also seen in energy intake and physical activity levels. In general, energy intake and physical activity decreased with age.

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7 Gender, Ethnic, and Geographic Variation in Adiposity

Timothy Olds and Carol Maher

CONTENTS

7.1 SEX DIFFERENCES IN BODY FAT AND BODY FAT DISTRIBUTION

Differences in body size and shape between males and females are referred to as "sexual dimorphism." Physical differences in stature and shape are the first indicators that allow us to distinguish between men and women, and we are biologically programmed to be acutely sensitive to these markers. In addition to size differences, at any given body mass index (BMI), women generally have higher levels of total body fat and lower levels of fat-free mass, and hence they weigh less and are shorter.[1] So-called "essential" body fat, the lowest level of body fat compatible with health, is often said to be 4%–6% in men and 8%–12% in women. This has been empirically verified in men in the Minnesota Starvation Experiment[2] and more recently by Friedl et al.,[3] but to our knowledge, there have been no parallel experiments in women. These differences appear to be quasi-universal in human populations. In a study of 96 preindustrial populations, Wells[4] found that women had a greater mean triceps skinfold thickness in all but one population group and a greater mean subscapular skinfold in all but two. Similar sexual dimorphism in body composition is found in many animal species, including mammals, snakes, and waterfowl. The evolutionary driver of these differences appears to be sexual selection. Men with a higher fat-free mass and women with an adiposity-defined female body shape have higher reproductive success.[5,6]

In spite of having lower levels of body fat, health risk is greater for men than for premenopausal women at any given BMI because of the differential risk associated with different patterns of fat distribution. Vague[7] initially compared android (apple-shaped) and gynoid (pear-shaped) patterns. Women have greater deposits of gluteo-femoral fat that is cardioprotective,[8] less abdominal fat, and hence lower waist-hip ratios. Extremity skinfolds (calf, front thigh, and triceps) are especially large in women relative to men and generally increase with overall levels of body fat (Figure 7.1). Central skinfolds (supraspinale, subscapular, and abdominal) are more similar in men and women and across weight-status categories. The ratio of extremity fat (e.g., triceps skinfold) to central fat (e.g., subscapular skinfold) is therefore higher in women.

Whole-body laser scanning allows a comparison of the distribution of segmental volumes in men and women. Table 7.1 shows mean segmental volumes (as a percentage of whole-body volume) in 340 Australian men and women, selected to represent a range of weight-status categories.[9] Women have relatively larger lower and upper leg volumes

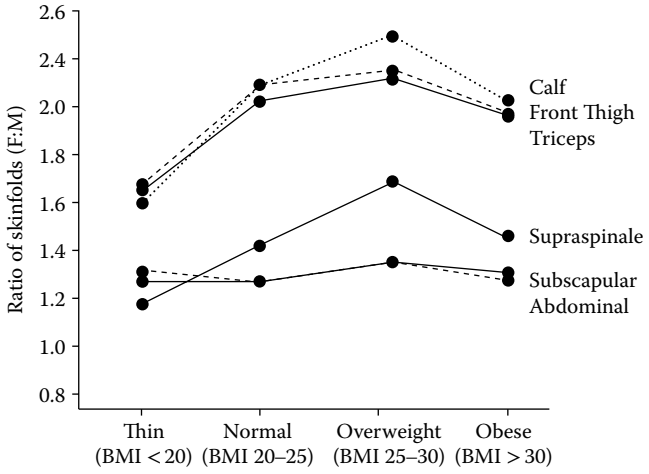

FIGURE 7.1 Ratio of female:male skinfold thicknesses at various sites according to weight-status category. (Unpublished data from Australian Anthropomorphic Database, University of South Australia, Adelaide, South Australia, 2013.)

TABLE 7.1
Mean Segmental Volumes for Normal Weight, Overweight, and Obese Australian Males (M) and Females (F), Expressed as a Percentage of Whole-Body Volume as Determined by 3D Laser Scanning

	Normal Weight			Overweight			Obese		
	F	M	F:M Ratio	F	M	F:M Ratio	F	M	F:M Ratio
Lower leg	11.8	11.2	1.05	11.2	11.0	1.02	10.5	10.7	0.98
Upper leg	25.9	22.1	1.17	25.9	22.2	1.17	25.1	21.4	1.17
Torso	46.7	50.4	0.93	47.8	51.0	0.94	49.8	53.6	0.93
Upper arms	4.7	5.2	0.90	4.8	5.3	0.91	4.7	4.9	0.96
Lower arms	3.6	4.2	0.86	3.4	4.2	0.81	3.2	3.8	0.84
Head & neck	7.4	7.2	1.03	7.0	6.6	1.06	6.7	5.7	1.18

Source: Burton R et al., *Am J Hum Biol 2013;40(1):64–69.*

but smaller torso and upper and lower arm volumes than men. That is, women's volume distribution is "bottom heavy," and men's is "top heavy." As BMI increases, female:male volume ratios remain fairly stable.

Sexual dimorphism has a genetic basis.[10] Differences in both the amount and distribution of body fat are largely hormonally driven, particularly by estrogen levels. Estrogen-deficient and postmenopausal women and ovariectomised rats have lower levels of gluteo-femoral fat. Estrogen deficiency appears to both stimulate hyperphagia (by, among other mechanisms, increasing ghrelin secretion) and reduce energy expenditure. Energy intake, for example, varies by about 1 MJ/day across the menstrual cycle, mirroring estrogen concentrations.[1] Although there are body composition differences between boys and girls well before puberty,[11,12] and indeed at birth,[13] sudden shifts in gender-specific patterns of fat distribution occur at puberty (Figure 7.2). There is a rapid increase in the triceps:subscapular skinfold ratio (a marker of peripheral vs. central fat distribution) at about the age of puberty, stabilizing in early adulthood.

In addition to biological drivers, socioeconomic factors also play a role. In developed countries, higher social status is almost invariably associated with greater thinness in women, and upward social mobility is associated with reductions in BMI.[14] Social class differences in BMI in developed countries are much stronger for women than for men. In most prenutrition transition cultures,[15] by contrast, and in some minority cultures in developed countries, well-rounded female bodies are seen as both desirable and a marker of high social status. In addition, data from the Dutch "Hunger Winter" of 1944 suggest that childhood nutritional deficiency has a larger rebound effect on girls than on boys.[16]

7.2 DIFFERENCES AROUND THE WORLD

Because the vast majority of available studies use BMI as a metric, and BMI typically shows a correlation of about 0.7–0.8 with measured body fat,[17] we focus here on global BMI data, comparing the prevalence of overweight and obesity in men and women. We have used the International Obesity Taskforce (IOTF) BMI cutoffs (25 $kg \cdot m^{-2}$ for overweight, and 30 $kg \cdot m^{-2}$ for obesity). In Caucasians, a BMI of 30 equates to about 25% body fat in young adult males and about 35% body fat in young adult females,[18] although these values will differ by ethnic group.[18]

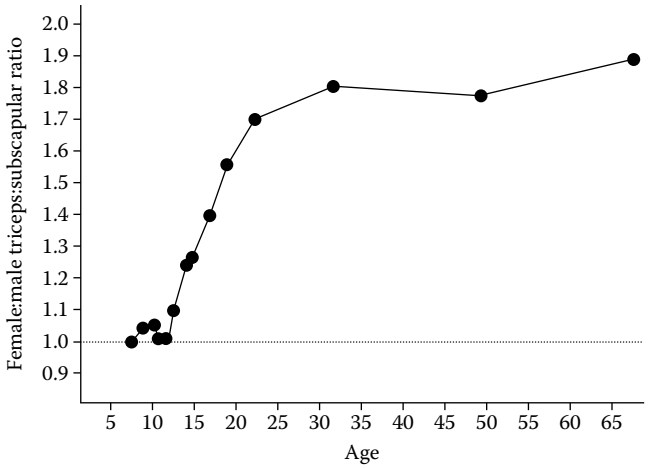

FIGURE 7.2 Changes in the ratio of male to female triceps:subscapular skinfold ratio across the life span. (Unpublished data from Australian Anthropomorphic Database, University of South Australia, Adelaide, South Australia, 2013.)

7.2.1 Overall Prevalence of Obesity

The World Health Organization (WHO) provides estimates of the global prevalence of overweight and obesity (https://apps.who.int/infobase/Comparisons.aspx; Table 7.2). Prevalence of obesity ranges from <0.3% in Ethiopia, Eritrea, Bangladesh, Sri Lanka, and Nepal to >50% in the South Pacific island nations (Nauru, Cook Islands, Micronesia, Tonga, Niue, and Samoa). Linking the WHO data to World Bank estimates of contemporaneous gross domestic product (GDP, per capita, in purchasing power parity dollars, i.e., the amount of money required to purchase the same goods), it is possible to explore the associations between obesity and economic characteristics (Table 7.2). Overall levels of obesity rise until a per capita GDP of about $5000, after which point GDP is unrelated to levels of overweight or obesity (Figure 7.3). At high per capita incomes, countries can have very low (<5% for Japan, Singapore) or very high (>30% for the United States, Kuwait, and United Arab Emirates) obesity prevalence. Northern European countries fare better than their equally wealthy Western Pacific and North American counterparts.

7.2.2 Sex Differences in Prevalence

The prevalence of obesity in women is greater than that in men in 173 of 192 countries, the median ratio being 2.1 (interquartile range 1.4–3.5). Female:male obesity ratios vary widely across regions (5.1 in Africa, 2.5 in Southeast Asia, 2.2 in the Middle East/North Africa, 2.1 in the Americas, 1.7 in the Western Pacific, and 1.4 in Europe). The highest values (>19) are found in Kenya, Zimbabwe, Ivory Coast, Indonesia, and Uganda, and the lowest (≤0.9) in Japan, Denmark, Belgium, Cambodia, and Lithuania.

7.2.2.1 Associations with Per Capita Income

There is a strong, negative linear relationship between the log of female:male obesity prevalence ratios and the log of GDP ($r = -0.62$, $p < .0001$). As GDP increases, the "obesity gap" between women and men becomes smaller (Figure 7.4). This may result from less childhood nutritional deficiency and hence a lesser adiposity rebound, poorer health literacy in women in developing countries, or greater pressure for female thinness in developed consumer cultures.[19]

7.2.2.2 Associations with Fertility

In addition to, and independently of, the per capita GDP, the log of the sex prevalence ratio is positively related to the national fertility rate ($r = 0.59$, $p < .0001$). Fertility rates have been taken from World Bank data for 2005.[20] The five countries with the highest fertility rates (Niger, Uganda, Somalia, Mali, and Burundi; fertility rates >6.2 children per woman) also have very high sex prevalence ratios (>3.7). Since women typically accumulate fat at each pregnancy,[21] high fertility rates may be associated with high levels of female obesity.

7.2.2.3 Associations with the Distribution of Income

Finally, the distribution of income within a country affects the sex prevalence ratio, independently of both per capita GDP and the fertility rate. The distribution of income is characterized by the Gini index, a coefficient ranging from 0 (perfect equality) to 100 (all income in the hands of a single family). Gini index values measured as close as possible to 2005 were taken from the Central Intelligence Agency's *World Factbook*.[22] As income becomes more inequitably distributed, the sex gap in obesity becomes larger, even when GDP is taken into account ($p < .0001$). The most equitable countries (Sweden, Hungary, Denmark, and Norway) with Gini index values ≤25 all have gender ratios ≤1.02, while the most inequitable countries, with Gini index values ≥63 (Namibia, Seychelles, South Africa, Lesotho, and Botswana), all have gender ratios ≥2. The significance of the Gini index persists even when the atypical Scandinavian countries are excluded from the analysis. Income inequality has been found to correlate with a wide array of social deficits, including overall obesity levels and the status of women.[23]

If, however, we look at overweight (BMI 25–29.9 $kg \cdot m^{-2}$), as opposed to obesity, the picture is quite different. The median female:male prevalence ratio for overweight is 1.0

TABLE 7.2
Gini index, Per Capita Gross Domestic Product ($ PPP for 2005), Fertility Rate, Obesity, and Overweight Prevalence for Men and Women and the Gender Prevalence Ratio for 192 Countries

Country	Gini index	Per Capita GDP ($ PPP)	Fertility Rate	Obese (F, %)	Overweight (F, %)	Obese (M, %)	Overweight (M, %)	F:M Ratio
Afghanistan	29.4	748	5.4	2.1	18.7	0.7	33.8	3.0
Albania	26.7	6107	1.5	23.8	28.7	18.6	29.5	1.3
Algeria	35.3	7095	1.8	16.2	33.2	6.4	31.0	2.5
Andorra	.	3640	1.4	31.2	37.5	17.1	24.1	1.8
Angola	.	2829	6.0	8.7	28.5	2.4	21.4	3.6
Antigua	.	18,556	2.1	25.3	36.8	12.4	10.4	2.0
Argentina	45.8	10,833	2.3	37.8	33.4	37.4	22.1	1.0
Armenia	30.9	4096	1.4	19.8	33.0	12.1	29.9	1.6
Australia	30.5	32,719	1.8	29.1	37.4	28.4	47.3	1.0
Austria	26.0	33,626	1.5	21.8	33.4	23.1	44.7	0.9
Azerbaijan	33.7	4496	2.0	24.9	31.9	15.4	21.7	1.6
Bahamas	.	26,351	2.0	29.5	36.4	16.0	47.1	1.8
Bahrain	.	28,068	1.9	37.9	31.6	21.2	28.7	1.8
Bangladesh	33.2	1165	2.6	0.2	6.5	0.2	8.2	1.0
Barbados	.	17,965	1.7	57.2	26.1	22.0	41.7	2.6
Belarus	27.2	8541	1.3	32.2	37.7	16.2	16.1	2.0
Belgium	28.0	32,181	1.7	10.7	32.2	14.8	46.4	0.7
Belize	.	6254	3.2	21.0	36.6	9.0	57.9	2.3
Benin	36.5	1147	5.3	12.1	31.7	1.5	20.4	8.1
Bhutan	.	3480	2.2	16.5	33.1	6.7	31.0	2.5
Bolivia	58.2	3772	3.0	40.2	33.0	19.4	43.0	2.1
Bosnia	36.2	6240	1.3	21.5	29.5	13.8	42.8	1.6
Botswana	63.0	11,542	2.5	17.7	35.8	6.9	34.7	2.6
Brazil	51.9	8509	1.9	24.5	35.8	12.4	38.0	2.0
Brunei	.	48,377	1.9	29.7	35.5	16.6	41.5	1.8
Bulgaria	45.3	9819	1.4	19.0	26.5	17.0	20.7	1.1
Burkina Faso	39.5	1007	6.1	1.7	17.7	0.6	14.5	2.8
Burundi	42.4	346	6.2	2.2	18.9	0.2	8.9	11.0
Cambodia	40.0	1508	2.8	0.4	13.4	0.5	19.9	0.8
Cameroon	44.6	1986	4.2	13.8	32.0	10.1	33.8	1.4
Canada	32.1	35,033	1.5	25.7	33.8	25.5	17.3	1.0
Cape Verde	.	2702	2.5	15.1	32.9	5.8	29.8	2.6
CAR	61.3	672	4.6	1.5	18.5	0.1	7.9	15.0
Chad	.	1374	5.1	2.6	20.3	0.6	14.4	4.3
Chile	52.1	12,168	1.9	39.1	34.2	24.3	40.2	1.6
China	41.5	4115	1.5	3.6	28.4	4.1	40.9	0.9
Colombia	56.0	7305	2.2	26.1	35.0	19.6	5.0	1.3
Comoros	.	1053	4.7	9.6	31.1	1.9	22.4	5.1
Congo	.	3381	5.7	3.5	23.3	0.5	13.3	7.0
Cook Islands	.	.	2.4	73.4	16.9	72.1	21.3	1.0
Costa Rica	50.3	9042	1.9	30.5	33.3	17.5	39.7	1.7
Cote d'Ivoire	41.5	1666	3.9	6.2	29.8	0.3	12.4	20.7
Croatia	27.0	15,346	1.4	17.6	30.7	20.1	43.4	0.9
Cuba	.	.	1.4	31.5	35.7	20.1	42.4	1.6
Cyprus	29.0	24,431	1.5	24.7	38.3	11.4	8.7	2.2
Czech Rep	31.0	20,362	1.2	22.1	27.2	20.2	29.9	1.1
Denmark	24.8	33,193	1.8	8.3	33.1	12.0	23.5	0.7
Djibouti	.	1840	2.7	7.4	27.1	1.8	60.5	4.1
Dominica	.	9259	2.1	52.6	28.2	25.8	31.6	2.0
Dominican Rep	48.4	6380	2.4	38.7	33.0	11.2	51.7	3.5
DRC	.	274	5.2	1.1	14.7	0.10	5.6	11.0

TABLE 7.2 (*Continued*)
Gini index, Per Capita Gross Domestic Product ($ PPP for 2005), Fertility Rate, Obesity, and Overweight Prevalence for Men and Women and the Gender Prevalence Ratio for 192 Countries

Country	Gini index	Per Capita GDP ($ PPP)	Fertility Rate	Obese (F, %)	Overweight (F, %)	Obese (M, %)	Overweight (M, %)	F:M Ratio
Ecuador	50.5	6510	2.4	19.1	36.4	7.7	46.2	2.5
Egypt	34.4	4491	3.0	48.0	28.0	22.0	11.5	2.2
El Salvador	46.9	5702	2.1	20.2	36.6	8.5	45.6	2.4
Equatorial Guinea	.	24,813	4.9	18.4	33.9	7.9	33.1	2.3
Eritrea	.	596	4.5	0.1	6.2	0.0	3.5	.
Estonia	31.3	16,548	1.4	8.4	25.4	8.6	28.0	1.0
Ethiopia	30.0	636	6.0	0.0	3.7	0.2	8.4	0.0
Fiji	.	4323	2.6	37.1	32.4	10.7	36.8	3.5
Finland	26.8	30,708	1.8	19.4	35.1	20.9	46.2	0.9
France	32.7	29,534	2.0	7.6	29.3	9.0	30.5	0.8
Gabon	.	13,014	4.6	19.2	33.0	3.4	26.8	5.7
Gambia	50.2	1159	4.2	3.6	23.4	0.5	12.3	7.2
Georgia	40.8	3611	1.5	17.1	36.7	6.1	22.2	2.8
Germany	27.0	31,115	1.4	22.1	35.0	22.9	52.8	1.0
Ghana	39.4	1208	3.5	5.9	26.6	4.8	30.8	1.2
Greece	33.0	24,348	1.4	26.4	36.8	30.3	10.4	0.9
Grenada	.	10,031	2.2	23.6	36.8	11.0	45.6	2.2
Guatemala	55.1	4062	3.3	36.8	34.1	20.5	42.3	1.8
Guinea	39.4	971	5.1	7.1	27.8	1.3	19.0	5.5
Guinea-Bissau	.	1017	4.5	3.7	21.4	0.6	12.3	6.2
Guyana	44.6	2536	2.3	19.4	36.4	7.9	55.8	2.5
Haiti	59.2	1023	3.1	21.1	36.6	1.3	62.2	16.2
Honduras	57.7	3277	3.1	16.7	35.8	6.2	47.7	2.7
Hungary	24.7	16,975	1.5	16.1	31.3	15.8	42.3	1.0
Iceland	28.0	34,889	2.0	25.3	38.4	18.5	2.9	1.4
India	36.8	2300	2.6	2.0	16.1	1.7	18.4	1.2
Indonesia	36.8	3102	2.3	3.9	23.2	0.2	9.7	19.5
Iran	44.5	9228	1.9	29.5	30.7	10.0	46.9	3.0
Iraq	.	2990	3.7	19.1	34.5	8.3	65.0	2.3
Ireland	33.9	38,896	2.0	10.4	33.5	11.7	33.3	0.9
Israel	39.2	23,390	2.7	25.9	33.4	17.9	75.5	1.5
Italy	32.0	28,280	1.4	13.7	26.3	14.4	33.1	1.0
Jamaica	45.5	7027	2.2	48.3	30.7	7.7	52.4	6.3
Japan	37.6	30,310	1.2	1.1	15.1	2.3	27.5	0.5
Jordan	39.7	4334	3.4	37.9	27.5	19.6	41.3	1.9
Kazakhstan	26.7	8699	1.9	11.0	27.9	7.9	68.2	1.4
Kenya	42.5	1346	4.2	2.2	21.1	0.1	7.6	22.0
Kiribati	.	2342	2.8	46.1	31.0	33.6	42.5	1.4
Kuwait	.	48,783	2.2	55.2	25.2	29.0	7.9	1.9
Kyrgyzstan	33.4	1728	2.6	14.2	29.7	5.0	24.8	2.8
Laos	36.7	1685	3.1	12.6	36.6	3.3	31.6	3.8
Latvia	35.2	13,053	1.3	15.0	29.7	9.7	41.8	1.6
Lebanon	.	9595	1.8	27.4	29.3	14.9	35.3	1.8
Lesotho	63.2	1195	2.9	36.1	34.7	2.3	27.2	15.8
Liberia	38.2	338	5.1	13.4	32.0	4.8	27.9	2.8
Libya	.	14,015	3.0	24.9	34.9	12.7	44.5	2.0
Lithuania	35.5	14,211	1.3	13.9	30.0	16.8	18.1	0.8
Luxembourg	26.0	68,320	1.8	17.8	38.4	13.6	9.4	1.3
Macedonia	44.2	7880	1.6	24.3	33.1	5.9	.	4.1
Madagascar	47.5	869	5.0	2.9	21.2	1.5	16.0	1.9

(*Continued*)

TABLE 7.2 (*Continued*)
Gini index, Per Capita Gross Domestic Product ($ PPP for 2005), Fertility Rate, Obesity, and Overweight Prevalence for Men and Women and the Gender Prevalence Ratio for 192 Countries

Country	Gini index	Per Capita GDP ($ PPP)	Fertility Rate	Obese (F, %)	Overweight (F, %)	Obese (M, %)	Overweight (M, %)	F:M Ratio
Malawi	39.0	645	5.4	2.4	22.8	0.8	15.6	3.0
Malaysia	46.2	11,544	2.7	11.0	31.2	1.7	21.3	6.5
Maldives	.	5221	1.8	25.0	25.8	7.7	28.9	3.3
Mali	40.1	885	6.4	8.4	30.0	1.0	17.1	8.4
Malta	26.0	20,965	1.5	36.5	31.1	28.1	36.0	1.3
Marshall Islands	.	.	3.4	18.5	36.2	7.3	35.7	2.5
Mauritania	39.0	1638	4.3	26.9	31.7	5.3	30.1	5.1
Mauritius	39.0	10,158	1.8	22.3	34.5	8.0	36.8	2.8
Mexico	51.7	12,191	2.3	41.0	32.0	30.1	24.9	1.4
Micronesia	.	3054	2.7	75.3	15.8	69.1	24.0	1.1
Moldova	38.0	2362	1.3	14.8	35.9	4.8	55.4	3.1
Monaco	.	.	1.5	29.9	37.7	15.9	81.0	1.9
Mongolia	36.5	2862	2.2	36.6	37.8	14.5	39.6	2.5
Morocco	40.9	3508	2.2	23.1	34.4	3.7	47.0	6.2
Mozambique	45.6	670	5.5	3.4	23.5	0.2	10.1	17.0
Myanmar	.	1062	2.3	11.3	35.7	2.7	29.6	4.2
Namibia	70.7	5205	2.5	6.1	28.3	0.4	13.1	15.3
Nauru	.	.	3.1	80.5	12.5	84.6	15.3	1.0
Nepal	47.2	954	2.5	0.3	9.6	0.3	10.7	1.0
Netherlands	30.9	35,104	1.7	12.9	33.2	11.7	62.2	1.1
New Zealand	36.2	25,305	2.1	39.9	34.3	28.9	45.0	1.4
Nicaragua	40.5	2336	2.1	41.1	32.0	15.9	34.8	2.6
Niger	34.0	610	7.6	3.4	21.7	0.9	16.3	3.8
Nigeria	43.7	1750	4.7	8.1	28.7	3.0	23.0	2.7
Niue	.	.	.	64.7	22.0	40.7	40.2	1.6
North Korea	.	.	2.0	12.9	36.8	3.4	32.1	3.8
Norway	25.0	47,626	1.8	10.7	35.1	12.8	68.1	0.8
Oman	.	21,047	2.9	17.0	33.8	7.7	53.2	2.2
Pakistan	30.6	2145	3.2	5.0	24.5	1.6	36.1	3.1
Palau	.	12,911	1.7	59.4	25.1	35.0	42.2	1.7
Panama	56.1	9167	2.5	22.2	36.7	9.9	57.2	2.2
PNG	50.9	1866	3.5	6.1	27.9	3.4	31.9	1.8
Paraguay	53.2	3901	2.1	19.6	36.4	8.0	40.0	2.5
Peru	51.0	6387	2.5	37.7	32.4	17.7	23.8	2.1
Philippines	45.8	3051	3.2	5.5	28.1	1.1	21.1	5.0
Poland	34.2	13,784	1.2	18.0	26.3	12.9	80.2	1.4
Portugal	38.5	21,369	1.5	17.7	33.5	15.5	27.5	1.1
Qatar	41.1	69,512	2.4	31.6	34.3	18.7	27.8	1.7
Romania	28.8	9370	1.3	12.0	28.6	5.5	71.7	2.2
Russia	39.9	11,853	1.4	23.6	28.1	9.6	25.7	2.5
Rwanda	46.8	840	4.9	1.6	20.1	0.1	8.0	16.0
Saint Kitts	41.3	14,963	1.8	25.8	36.8	12.8	54.4	2.0
Saint Lucia	.	8916	1.8	41.7	32.4	9.8	67.7	4.3
Saint Vincent	.	8852	1.9	21.6	36.7	9.5	46.4	2.3
Samoa	.	3831	3.2	60.9	23.2	42.2	38.9	1.4
San Marino	.	.	1.5	29.7	37.7	15.7	6.5	1.9
Sao Tome	.	1416	5.1	5.7	24.8	1.2	16.3	4.8
Saudi Arabia	.	20,406	3.4	36.4	29.5	23.0	37.5	1.6
Senegal	.	1675	4.8	11.8	29.2	2.0	17.2	5.9
Serbia	30.0	8525	1.4	20.6	27.9	17.7	43.5	1.2
Seychelles	65.8	17,352	1.9	43.2	30.6	21.3	42.5	2.0

TABLE 7.2 (*Continued*)
Gini index, Per Capita Gross Domestic Product ($ PPP for 2005), Fertility Rate, Obesity, and Overweight Prevalence for Men and Women and the Gender Prevalence Ratio for 192 Countries

Country	Gini index	Per Capita GDP ($ PPP)	Fertility Rate	Obese (F, %)	Overweight (F, %)	Obese (M, %)	Overweight (M, %)	F:M Ratio
Sierra Leone	62.9	647	4.9	16.0	33.1	3.5	22.8	4.6
Singapore	48.1	45,374	1.1	2.9	23.8	1.4	22.7	2.1
Slovakia	26.0	16,175	1.4	25.3	37.6	12.0	12.1	2.1
Slovenia	23.8	23,476	1.3	27.6	38.1	13.9	44.0	2.0
Solomon Islands	.	2073	3.6	17.1	35.8	6.4	34.3	2.7
Somalia	.	.	6.4	3.4	20.6	0.6	53.4	5.7
South Africa	65.0	8597	2.3	36.8	31.7	7.6	33.7	4.8
South Korea	31.0	22,783	1.2	14.6	36.4	8.3	43.2	1.8
Spain	32.0	27,377	1.5	17.3	32.5	17.3	74.1	1.0
Sri Lanka	49.0	3515	2.2	0.2	7.7	0.2	8.9	1.0
Sudan	.	1613	4.8	6.5	26.0	1.5	56.4	4.3
Suriname	.	6129	2.0	19.6	36.5	8.1	53.1	2.4
Swaziland	50.4	4516	3.1	16.5	35.4	6.1	33.4	2.7
Sweden	23.0	32,703	1.8	12.4	34.8	13.3	41.1	0.9
Switzerland	33.7	35,784	1.4	20.6	38.3	13.9	67.2	1.5
Syria	.	4133	2.9	24.6	35.0	12.4	45.5	2.0
Tajikistan	32.6	1500	2.9	12.6	34.8	3.6	29.9	3.5
Tanzania	37.6	1065	4.2	3.6	25.1	0.8	16.0	4.5
Thailand	42.0	6675	1.7	11.1	28.8	2.6	30.9	4.3
Timor-Leste	31.9	700	3.1	17.7	33.4	7.5	32.0	2.4
Togo	.	858	4.7	7.3	28.2	1.4	19.5	5.2
Tonga	.	4139	3.7	78.1	14.0	64.0	27.4	1.2
Trinidad	.	20,058	1.7	52.7	28.1	19.1	34.8	2.8
Tunisia	40.0	7182	1.9	32.6	28.8	7.7	48.8	4.2
Turkey	43.6	11,465	2.1	32.5	33.2	10.8	37.1	3.0
Turkmenistan	40.8	4762	2.2	15.0	30.5	9.3	38.8	1.6
Tuvalu	.	.	3.1	26.2	36.7	13.1	41.3	2.0
Uganda	45.7	911	6.7	1.9	22.0	0.1	8.1	19.0
Ukraine	27.5	5583	1.3	19.4	29.1	7.4	33.8	2.6
UAE	.	66,855	2.4	42.0	29.6	24.5	32.5	1.7
UK	34.0	32,738	1.8	26.3	37.5	23.7	44.1	1.1
USA	45.0	42,569	2.0	48.3	28.4	44.2	15.2	1.1
Uruguay	45.3	9683	1.9	29.8	34.6	25.7	29.3	1.2
Uzbekistan	36.8	2001	1.9	17.6	32.3	7.1	34.9	2.5
Vanuatu	.	3500	2.4	31.4	35.8	16.2	44.0	1.9
Venezuela	39.0	9924	2.4	33.0	34.3	29.5	14.4	1.1
Vietnam	37.6	2161	1.9	0.7	11.5	0.0	7.5	.
Yemen	37.7	2234	4.6	6.2	26.0	2.0	45.9	3.1
Zambia	50.8	1158	6.0	1.5	18.5	0.1	8.2	15.0
Zimbabwe	50.1	2413	3.6	16.7	33.9	0.8	15.9	20.9

Source: The World Bank, *World Development* Indicators, The World Bank, Washington, 2012; Central Intelligence Agency, *The World Factbook*, Central Intelligence Agency, Washington.

Notes: Overweight does not include obesity. CAR, Central African Republic; DRC, Democratic Republic of the Congo; PNG, Papua New Guinea; PPP, purchasing power parity; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America.

(IQ range 0.7–1.6) and is <1 in Europe, the Middle East, and the Americas. Furthermore, this ratio is unrelated to both GDP and the Gini index and only weakly associated with fertility rates ($r = 0.19$, $p = .03$). Economic factors therefore seem to have a greater gender effect at the extremes of BMI.

When entered in a joint model, per capita GDP ($p = .004$), fertility rate ($p = .01$), and the Gini index ($p = .0004$) are all independently related to the gender prevalence ratio for obesity and together explain 48% of the observed variance.

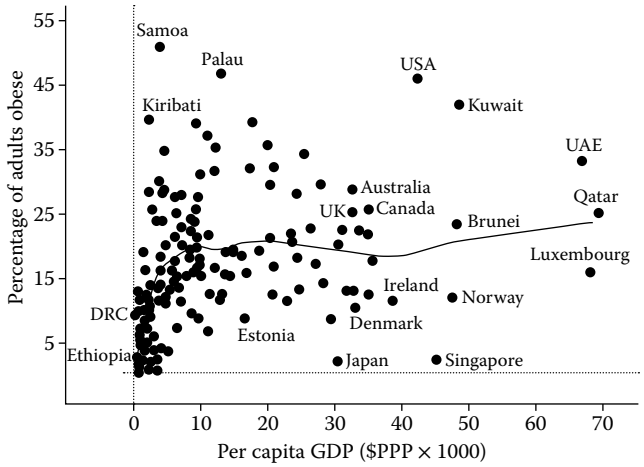

FIGURE 7.3 Relationship between average adult obesity prevalence and per capita gross domestic product (GDP) across 146 countries. The line is the Lowess curve of best fit. DRC, Democratic Republic of Congo; PPP, purchasing power parity (GDP adjusted for the amount of money required to purchase the same goods); UAE, United Arab Emirates. (Data from The World Bank, *World Development Indicators*, The World Bank, Washington, DC, 2012.)

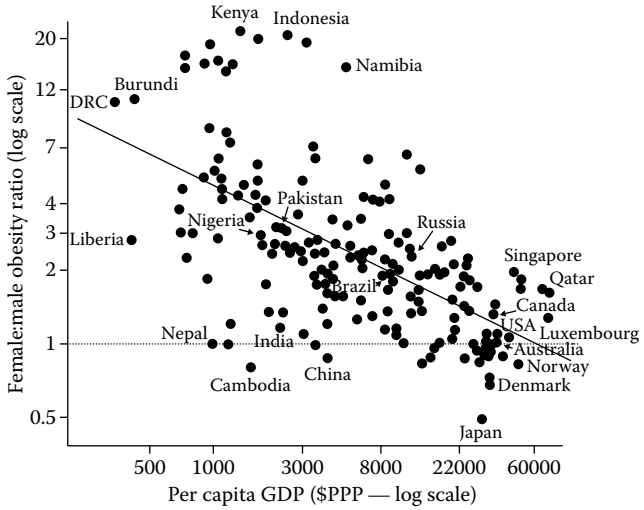

FIGURE 7.4 Relationship between female:male obesity prevalence ratio and per capita gross domestic product (GDP) across 180 countries. DRC, Democratic Republic of Congo; PPP, purchasing power parity (GDP adjusted for the amount of money required to purchase the same goods). (Data from The World Bank, *World Development Indicators*, The World Bank, Washington, DC, 2012.)

7.2.2.4 Associations with Geography and Climate

Body shape and stature in both sexes are associated with climate, probably reflecting heat loss arising from differences in body surface area to mass ratio. Populations near the equator tend to be more linear in shape,[24] while stature peaks at latitudes of about 40°–50°.[25] In an analysis of sex-related body composition differences in 96 preindustrial populations, Wells[4] recently found that sexual dimorphism in both fat mass and fat-free mass increases as the climate becomes colder. Wells argues that in cold climates, women invest energy in building up fat stores, and men in building up fat-free mass.

Latitude is an (imperfect) proxy for mean annual temperature. In modern societies, the sex prevalence ratio increases in countries closer to the equator ($r = 0.48$, $p < .0001$), but this appears to be an artifact of the lower GDPs, greater inequality of income distribution, and higher fertility rates of equatorial (largely African) countries, as well as the opposite socioeconomic characteristics of northern European countries. When latitude is entered as a predictor of the sex prevalence ratio with GDP, Gini index, and fertility rates, it is no longer significant.

7.2.3 Ethnic Differences in Prevalence

While the rates of overweight and obesity vary among countries, it is also clear that prevalence within countries can vary on the basis of ethnicity. We have compiled such data for 21 different countries in Table 7.3. Overweight and obesity have been defined according to IOTF cutoffs unless otherwise indicated. Where multiple data sets were available for one country, the study with the largest sample size and more recent time frame for data collection is presented.

Wherever possible, we have presented the prevalence for obesity and overweight separately and calculated the female to male ratio.

TABLE 7.3
Ethnic Prevalence of Obesity Alone, Overweight Alone, and Obesity/Overweight Combined and the Gender Prevalence Ratio in 21 Countries

Country	Ethnic Groups	Obese (%)	OB F:M Ratio	Overweight (%)	OW F:M Ratio	OB & OW Combined (%)	OB & OW F:M Ratio
Australia[26]	Australian Aboriginals	.	.	.	.	77.1	.
Barbados[27]	African origin	26.0	.	64.7	.	90.7	.
Brazil[28]	White	13.6	0.9	33.6	0.8	47.2	0.8
	Black	17.2	1.0	33.2	0.8	50.4	0.9
	Mixed	13.7	1.1	32.2	0.8	45.9	0.8
Canada[29]	White	17.0	0.9	34.0	0.6	51.0	0.7
	E/SE Asian	2.7	1.0	19.3	0.5	22.0	0.6
	W Asian/Arab	11.0	1.3	34.0	0.6	45.0	0.7
	S Asian	8.0	1.1	31.0	0.7	39.0	0.8
	Latin American	14.0	0.9	38.0	0.7	52.0	0.7
	Black	15.0	1.8	34.0	0.8	49.0	1.0
	N American Aboriginal	28.0	1.1	35.0	0.8	63.0	0.9
China[30]	Han	1.9	2.3	19.4	1.5	21.3	1.6
	Mongolian	2.2	1.7	23.9	1.5	26.1	1.5
Cyprus[31]	Greek	.	.	.	.	45.6	0.5
	Foreigners and mixed	.	.	.	.	36.9	0.4
England[32]	Black Caribbean	28.5	1.3	37.5	0.8	66.0	1.0
	Black African	27.5	2.2	38.5	0.7	66.0	1.1
	Indian	17.0	1.4	37.0	0.9	54.0	1.0
	Pakistani	21.5	1.9	37.0	0.9	58.5	1.1
	Bangladeshi	11.5	2.8	36.0	0.9	47.5	1.2
	Chinese	7.0	1.3	24.0	0.6	31.0	0.7
	Irish	23.0	0.8	39.5	0.9	62.5	0.9
Fiji[33]	Melanesian	52.3	1.4	32.4	0.8	84.8	1.1
	Indian Fijian	22.1	2.9	33.7	1.0	55.9	1.5
Ghana[34]	Akan	6.0	.	18.0	.	24.0	.
	Ga-Adangbe	14.6	.	18.3	.	32.9	.
	Ewe	6.6	.	22.0	.	28.6	.
	Guan	2.9	.	7.8	.	10.7	.
	Gurma	0.9	.	8.0	.	8.9	.
	Mole-Dagbon	1.4	.	8.0	.	9.4	.
	Grusi	2.2	.	9.8	.	12.0	.
	Mande-Busanga	1.1	.	8.0	.	9.1	.
Israel[35]	Israeli Jew	20.4	1.2	38.2	0.7	58.6	0.9
	Israeli Arab	31.8	1.8	41.4	0.7	73.3	1.0
Italy[36]	Senegalese	Males only 5.3	.	Males only 21.1	.	Males only 26.4	.
	Moroccan	9.3	3.3	44.4	1.0	53.7	1.4
	Tunisian	Males only 13.3	.	Males only 33.3	.	Males only 46.6	.
	Pakistani	Males only 0.0	.	Males only 25.6	.	Males only 25.6	.
	Kosovar	36.3	1.3	32.1	1.1	68.4	1.2
	Roma	21.7	0.4	34.3	0.9	56.0	0.7
Malaysia[37]	Malay	16.6	.	29.8	.	46.4	.
	Chinese	8.7	.	28.5	.	37.2	.

(*Continued*)

TABLE 7.3 (*Continued*)
Ethnic Prevalence of Obesity Alone, Overweight Alone, and Obesity/Overweight Combined and the Gender Prevalence Ratio in 21 Countries

Country	Ethnic Groups	Obese (%)	OB F:M Ratio	Overweight (%)	OW F:M Ratio	OB & OW Combined (%)	OB & OW F:M Ratio
	Indian	17.7	.	33.2	.	50.9	.
	Other Burnis	11.2	.	27.3	.	38.5	.
	Other	8.1	.	20.8	.	28.9	.
Netherlands[38]	S Asian (Hindustani-Surinamese)	22.1	1.8	41.5	0.9	63.6	1.1
	African (African Surinamese)	34.2	2.5	35.9	0.8	70.1	1.3
	Dutch	15.2	1.1	37.0	0.8	52.2	0.9
New Zealand[51]	European	25.5	1.0	49.0	0.7	67.4	0.8
	Samoan[a]	66.4	1.3	28.1	0.7	94.4	1.1
	Cook[a]	50.8	3.0	46.5	0.4	97.2	1.1
	Tongan[a]	69.3	1.3	29.7	0.6	99.0	1.0
	Niuean[a]	63.9	1.6	32.1	0.6	96.0	1.1
Norway[39]	Turkish	37.3	2.0	44.3	0.6	81.6	1.1
	Sri Lankan	13.8	2.3	49.0	1.0	62.8	1.2
	Iranian	16.2	1.5	49.9	0.7	66.1	0.8
	Pakistani	29.9	1.8	48.6	0.7	78.6	1.0
	Vietnamese	2.9	1.2	28.7	0.6	31.6	0.6
Singapore[40]	Malay	24.0	1.4	.	.	.	.
	Chinese	7.9	0.5	.	.	.	.
	Indian	16.9	1.6	.	.	.	.
South Africa[41]	African	21.4	5.3	23.7	1.4	45.1	2.3
	Mixed	18.3	3.4	24.7	1.1	43.0	1.7
	Indian/Asian	16.2	2.4	26.3	1.2	42.4	1.5
	White	20.7	1.3	30.9	0.7	51.6	0.9
South Korea[43]	Chinese	.	.	.	.	16.7	.
	Filipino	.	.	.	.	22.0	.
	Vietnamese	.	.	.	.	7.8	.
	Other Asian	.	.	.	.	19.2	.
Sweden[44]	Swedish	16.7	0.9	.	.	.	.
	Other European	27.3	0.7	.	.	.	.
	Middle Eastern	37.4	1.3	.	.	.	.
Switzerland[45]	Swiss	14.8	.	34.4	.	49.4	.
	German	12.0	.	34.8	.	46.8	.
	Italian	21.3	.	48.0	.	69.3	.
	French	9.9	.	33.9	.	43.8	.
	Spanish	20.6	.	42.8	.	63.4	.
	Portuguese	19.0	.	43.1	.	62.1	.
	Former Yugoslavia	29.9	.	52.9	.	82.8	.
USA[46]	Non-Hispanic White	22.7	.	40.3	.	63.0	.
	Non-Hispanic Black	35.8	.	38.0	.	73.8	.
	Non-Hispanic Asian	6.1	.	35.6	.	41.7	.
	Non-Hispanic American Indian	29.2	.	38	.	67.2	.
	Hispanic	27.7	.	41.8	.	69.5	.

Notes: E, East; N, North; S, South; USA, United States of America; W, West.

[a] Pacific Island–specific definitions applied (i.e., overweight BMI ≥ 26 to < 32; obese BMI ≥ 32).

Of the countries in Table 7.3 reporting prevalence of overweight and obesity in ethnic groups, prevalence of obesity ranged from lows of 0% among the male Pakistani population in Italy and 0.9% for the Gurma population in Ghana to highs of 69.3% and 66.4%, respectively, for the Tongan and Samoan populations in New Zealand. Furthermore, when combined obesity and overweight was considered, the rate was greater than 90% in particular ethnic groups in some countries, namely, the Pacific Island populations in New Zealand: Samoa, Cook Islands, Tonga, Niue, whose combined obese and overweight rates were 94.4%, 97.2%, 99.0%, and 96.0%, respectively, as well as the African-origin population in Barbados (90.7%).

7.2.3.1 Sex Differences in Prevalence in Ethnic Groups

Out of the 49 ethnic groups for which the female-to-male ratio for obesity could be calculated, in 40 cases, the ratio was >1 (i.e., the prevalence of female obesity exceeded male obesity in over 80% of ethnic groups). Interestingly, the reverse pattern was seen for the ratio of female to male overweight: out of the 43 ethnic groups, in 35 cases, the ratio was <1 (i.e., the rate of male overweight exceeded the rate of female overweight in over 80% of cases). The highest female-to-male ratios for prevalence of obesity were apparent in ethnic populations of African origin (e.g., the African-origin population in South Africa = 5.3 and the Moroccan population in Italy = 3.25), which is consistent with the gender differences already noted. The few instances of low ratios typically occurred in ethnic populations of European origin (e.g., the Roma population in Italy = 0.40 and the "other European" population in Sweden = 0.68) and in the Chinese-origin population in Singapore (0.48).

7.2.3.2 Differences in Prevalence between Ethnic Immigrants and the Prevalence in Their Adopted and Origin Countries

We have attempted to determine whether there were patterns in the prevalence of obesity between ethnic groups of shared origin that have settled in different countries; however, patterns are mixed. In general, ethnic groups of South and East Asian origin typically fared well compared with their adoptive countries (i.e., their rates of overweight and obesity were relatively lower than the overall rates in their adoptive countries). Ethnic groups of West Asian origin (e.g., India and Pakistan) showed mixed patterns, comparing favorably in some adoptive countries (e.g., England and Canada) but relatively poorly in others (e.g., the Netherlands and Norway). To illustrate this, the Pakistani immigrant population obesity rate in England was 21.5% (compared with the overall rate of 25.0%), while in Norway it was 29.9% (compared with the overall rate of 11.8%). A standout example of ethnic populations' obesity rates comparing unfavorably to their adoptive country's was the Pacific Island populations in New Zealand, whose obesity rates ranged from 50.8% to 69.3%, compared with 34% for the overall New Zealand population. There was also a common pattern for ethnic populations of African origin settling outside Africa to have obesity rates exceed those of their adoptive countries.

Examination of how obesity rates for migrant ethnic populations compared with those of their countries of origin provides another insight into ethnic variation in adiposity. Overall, in 36 out of 47 possible comparisons, the obesity rates were higher for migrant ethnic populations than for their origin countries (mean change = +8.1%, SD 12.9%). This was particularly marked for populations of African origin as well as migrant populations of Indian origin. Some exceptions to this pattern were the Mongolian population in China and the Cook Islander population in New Zealand, for whom the ethnic group-specific obesity rates were around 20% lower in their adoptive countries than prevalence in their countries of origin.

7.2.3.3 Prevalence of Obesity in Indigenous Populations

Indigenous ethnic groups form part of the population in many geographic areas of the world. Adiposity data for such populations are available in Table 7.3 for Australian Aboriginal people, Canadian Aborigines, U.S. Native Americans, and New Zealand Maoris. In each of these cases, rates of obesity are relatively high compared with the overall prevalence of obesity and overweight in the respective countries.

7.2.4 Reasons for Ethnic Differences in Prevalence of Obesity

Numerous factors are likely to contribute to the ethnic differences in prevalence of obesity, including genetic, socioeconomic, and cultural factors. Here, we briefly describe such key factors. However, it is important to recognize that these factors are complex and interact with each other; thus, full exploration of these issues is beyond the scope of this chapter.

7.2.4.1 Ethnic Differences in Body Shape, Build, and Composition

First, it is clear that body shape, build, and composition can vary on the basis of ethnicity. For example, Asian people typically have relatively short limbs in relation to their trunks, compared with Caucasian people, while people of African and Australian Aboriginal descent have relatively long limbs.[17,47] Certain ethnic groups are characterized by having large frames, such as people from the Pacific Island region.[48] Furthermore, there are differences in the extent and distribution of body fat among ethnic groups; for example, at a given BMI, African-Americans are more likely to have lower percentage body fat than white Americans and are likely to have less visceral fat but more subcutaneous fat that their white counterparts.[49]

Given these ethnic differences in body composition, it has been advocated that ethnicity should be taken into account in the application of common measures of adiposity, such as electrical bioelectrical impedance and BMI. In the case of bioelectrical impedance, the accuracy of body composition measurement has

been shown to vary on the basis of ethnicity, and as such, a variety of ethnic-specific correction algorithms have been proposed by manufacturers and researchers.[50] In the case of BMI, the IOTF cutoffs for obesity and overweight (≥30 and ≥25, respectively) have been developed primarily based on observational studies of morbidity and mortality conducted in Europe and the United States.[17] However, research shows that these cutoffs underestimate and overestimate obesity prevalence and cardiovascular risk, in certain ethnic populations. For example, people of the Pacific Islands have greater fat-free mass and lower percentage fat at any given BMI compared with their Caucasian counterparts.[51] In recognition of this, New Zealand has used ethnic-specific BMI cutoffs for obesity and overweight (≥32 and ≥26, respectively) for Pacific Island populations since 1997.[51] Conversely, people of Asian descent tend to have greater percentage body fat than their Caucasian counterparts at any given BMI.[52] Furthermore, a relatively high percentage of Asians have BMI < 20, without good reason to suggest that undernutrition is endemic.[53] Based on these observations, an expert panel assembled by the WHO proposed that in Asian populations, the BMI cutoff for normal weight should be shifted from <20 to <18.5.[52] The panel advised that many Asian people have heightened cardiovascular risk at BMIs substantially lower than the international overweight cut point (≥25), but that because of variation between different Asian populations, the international cut points for obesity and overweight should be retained.[52]

7.2.4.2 Socioeconomic Factors

The socioeconomic position of minority ethnic groups within a society is also likely to influence the prevalence of obesity in these subpopulations. In many countries, ethnic populations are commonly relatively disadvantaged.[54] In developing countries, socioeconomic disadvantage has historically been associated with malnutrition and low prevalence of obesity.[55] However, this is changing as countries pass through the nutrition transition. With increased abundance of food and increased availability of processed foods, often with high-fat content and poor nutritional value, obesity is becoming more prevalent among disadvantaged groups and may even co-occur with malnutrition.[55] In developed countries, obesity is more prevalent among people from socioeconomically disadvantaged backgrounds.[56] This is believed to occur because of various interacting factors, including lack of access to health insurance and health services, differing family structure, lack of education regarding nutrition, different attitudes toward food and physical activity, limited resources (financial and transport) to access recreational physical activity opportunities, reduced availability of nutritious foods, and neighborhood environments unsupportive of physical activity (e.g., because of poor infrastructure or safety concerns).

In the case of recent migrant ethnic populations, their changed economic circumstances may contribute to the differences in prevalence of obesity commonly observed between adoptive and origin countries. Migrants are frequently attracted to countries with stronger economies and with opportunities for work, education, and a better way of life.[57] As we saw under "Associations with per capita income," obesity prevalence increases with GDP (to a point). Thus, it is not surprising that populations migrating from relatively poor countries to relatively wealthy countries typically experience increases in the rates of obesity.

7.2.4.3 Cultural Factors

Finally, cultural factors, beliefs, and attitudes play an important role in ethnic differences in obesity. Ethnic groups are influenced by the culture of their adoptive countries (including diet preferences, access to health services, educational opportunities, and lifestyle factors), which may help explain the differences in obesity prevalence seen between ethnic groups of shared origin settling in different countries. It is also clear that cultural perceptions about weight status vary between ethnicities. For example, Paeratakul et al.[58] analysis of data from 5440 U.S. adults found that white people were more accurately able to self-perceive overweight and obese status compared with blacks or Hispanics. Similarly, a New Zealand–based study from Sundborn et al.[51] found that while people from the Pacific Islands were able to self-report their weight with similar accuracy to people from European backgrounds, they were far less likely to accurately perceive themselves as overweight or obese. Of those who self-reported being "underweight," 6.7% and 63.5% of European and Pacific Islanders were actually overweight or obese, respectively. Of those who self-reported being the "right weight," 26.6% of Europeans and 90.4% of Pacific Islanders were overweight or obese. These results reveal vastly differing perceptions of what constitutes "healthy" or "normal" weight status.

Desirability of different body shapes also differs among ethnicities. Among white people, there is a strong desire for a slender body shape and dissatisfaction with higher weight statuses.[59] Among black people in the United States, there is still a desire for thinness; however, overweight body shapes may be viewed as being attractive, and overweight individuals are less dissatisfied with their body shape than their white peers.[59,60] In contrast, heavier body shapes are the more desired body shapes among particular ethnic groups. For example, Holdsworth et al.[61] showed that among Senegalese women, overweight is the most desirable body shape and is associated with perceptions of femininity, good health, likelihood of marriage, and having enough money. It has been observed that many economically developing societies idealize heavier body shapes, possibly because of the association between body fat and resource security.[62]

7.3 CONCLUSION

In conclusion, there are sex, geographic, and ethnic differences in adiposity. The median ratio of female to male obesity prevalence is 2.1:1, although this varies widely across countries and appears to be due in part to weight gain and retention related to childbearing. Prevalence of obesity ranges from <0.3% in countries such as Ethiopia, Eritrea, Bangladesh, Sri Lanka, and Nepal to >50% in the South Pacific island nations. Overall levels of obesity are related to a country's wealth to a

point (approximately $5000 per capita GDP), after which GDP is unrelated to levels of overweight or obesity. Furthermore, prevalence of obesity varies between ethnic populations. With some exceptions, obesity rates are generally higher among ethnic groups in their adoptive countries compared with their countries of origin. This appears particularly true for populations of African and Indian origin. It is likely that biological, socioeconomic, climate, and cultural factors contribute to the sex, geographic, and ethnic differences in adiposity.

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Part II

Biological Determinants of Obesity

8 Genetic Component to Obesity
Evidence from Genetic Epidemiology

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CONTENTS

8.1 INTRODUCTION

Obesity is a complex and heterogeneous condition resulting from multiple genetic and environmental factors each interacting in a variety of ways. For example, obesity can develop as a consequence of adversely regulated metabolic pathways (e.g., catecholaminergic pathways, leptin signaling pathways, insulin signaling pathways, lipid oxidation pathways), each being potentially influenced by a number of genetic determinants. Furthermore, the expression of genetic propensities may depend on synergistic relationships among genes (epistasis), exposure to certain environmental stimuli (gene-by-environment interactions) such as nutritional or activity backgrounds, developmental stage, epigenetic events, or sex of the individual. Given the multiplicity of factors underlying the predisposition to obesity, complex modeling approaches such as those used in genetic epidemiology have been used to uncover genetic and environmental factors, to explore how those factors act and interact, and to estimate the magnitudes of those effects. Based on designs that depend on predictable underlying biological relationships (e.g., degree of relatedness between family members), these models provide inferences about genes. They do not depend on direct measures of the genes, but they rather infer genetic effects based on biological modeling.

In this volume, three chapters are devoted to the current status of our knowledge regarding the role of genetic variation and epigenetic mechanisms in the predisposition to obesity (Chapters 8 through 10), and in the second volume of the *Handbook of Obesity*, Chapter 8 focuses on single-gene disorders causing obesity. In this chapter, we briefly review some of the basic genetic epidemiological methods and then summarize the evidence accumulated on phenotypes of obesity.

8.2 OVERVIEW OF METHODS IN GENETIC EPIDEMIOLOGY

8.2.1 Multifactorial Model

A multifactorial model is required to describe complex traits. Multifactorial models can incorporate multiple genes and

environmental factors, as well as interactions among and between them. The basic multifactorial model posits that an obesity phenotype (P) is caused by genetic (G) and environmental (E) effects (P = G + E), usually expressed as variance components ($V_P = V_G + V_E$). The genetic component can be further partitioned into separate additive versus nonadditive (dominance [D] deviations) effects ($V_G = V_A + V_D$). Similarly, the environmental component can be stratified into factors that are shared (or common [C]) among family members and those that are not shared or are residual (R) ($V_E = V_C + V_R$). Thus, the total phenotypic variance of a trait may be expressed as $V_P = V_A + V_D + V_C + V_R$.

8.2.2 Heritability or Familial Aggregation

In general terms, heritability is the extent to which individual differences in trait expression can be attributed to genetic differences. Defined statistically, heritability (h^2) is the percent of the total phenotypic variance that is due to genetic factors (e.g., $h^2 = V_G/V_P$). In general, *broad sense* genetic heritability is the proportion of the total phenotypic variance that is due to all genetic effects ($h^2_B = (V_A + V_D)/V_P$), while *narrow sense* heritability is the proportion due only to the additive genes ($h^2_N = V_A/V_P$). *Multifactorial* heritability is the percentage of variance that is due to all shared familial effects, both genetic and common environmental ($h^2_M = (V_A + V_D + V_C)/V_P$), while *cultural* heritability is the percentage of variance due to common environmental sources ($h^2_C = V_C/V_P$). The genetic component (V_G) can consist of one or more genes, ranging from *polygenic* (many genes) to *oligogenic* (several genes) to a single *major gene*. Polygenic effects are defined as a large number of genes each having a small, linear (additive) effect that has a Gaussian (normal) distribution. The effect due to each gene tends to be small, and measuring the contribution of genes with very small effect size requires unusually large studies. Under genetic epidemiological models, the contribution of polygenes is estimated only in the aggregate across all genes simultaneously.

8.2.3 Study Design

The most commonly used study designs in genetic epidemiology are nuclear families (parents and their biological offspring), extended families or pedigrees (grandparents, parents, offspring, cousins, etc.), and twins. Other study designs, such as adoptive families, can be quite powerful but are not often used because of the rarity of their occurrence. As study design issues are extensively covered elsewhere,[1–5] they are only briefly reviewed here.

Nuclear families (father, mother, and one or more offspring) yield three types of familial correlations: parent-offspring, sibling, and spouse. Genetic assumptions are that parent-offspring and sibling pairs share half their genes and that spouse pairs share no genes by descent. Advantages of the nuclear family designs are their accessibility and apparent generalizability to the population. Modeling assumptions are that there is random mating; that the genetic variation is additive with no dominance or epistasis; that there is no common or shared environmental variance; and that there is no genotype–environment interaction or correlation. In practice, these assumptions are not often met, particularly for a condition such as obesity. For example, family members typically share both genes and environments (e.g., dietary intake), so the heritability is likely to be multifactorial (additive genetic plus common environmental). The extended family or pedigree study design is an extension of the nuclear family design that incorporates additional relationships such as cousins and grandparents. Pedigrees allow for greater precision in estimating the familial variance components and a somewhat better ability to disentangle the genetic from common environmental effects. A quick formula for verifying whether there is a heritable component based on family data is to simply double the parent-offspring or sibling correlation, because, by definition, members of these pairs of relatives share half of their genes.

The twin design includes both monozygotic (MZ) and dizygotic (DZ) twins. MZ or identical twins share 100% of their genes. DZ or fraternal twins share on average half of their genes (same as regular siblings). The assumptions underlying twin designs include equal environments between MZ versus DZ twins, no dominance deviations, and that the twins are representative of the general population. However, these assumptions are not always met. For instance, DZ twins may be more similar than regular siblings, because they share more common environmental effects due to shared age as well as shared prenatal and early postnatal conditions. Although the twin design can resolve genetic versus common environmental sources of variance using maximum likelihood methods to model dominance and common environmental variance components,[6] it tends to produce higher heritability estimates than other study designs. Advantages of explicit twin modeling are the ability to test whether the modeled parameters are significant and a relatively clean separation of the genetic versus cultural heritabilities. The primary maximum likelihood modeling software used for twin studies currently is Mx or OpenMX for use with R.[7]

Several cautionary issues need to be raised concerning heritability estimates. First, researchers typically report "heritability" assuming that it is genetic in origin. However, as briefly discussed earlier, the degree to which heritability is genetic is a function of the study design that was used. That is, nuclear family members share both genes and common environments, and so it may be difficult to disentangle these two sources of variance. Second, heritability is not an absolute measurement and can vary considerably across studies from the same population.[8] Because it is a proportion of variance, heritability can vary to the extent that the genetic or environmental variances are different across populations. For example, if an inbred or isolated population has a smaller genetic variance than a random mating population, then the heritability may be smaller in the inbred population. On the other hand, heritability can be larger if the environmental variance is minimized, as would occur in intervention studies where measurements are taken under standardized environmental

conditions. Thus, heritability can vary substantially across populations or under any circumstances when the relative importance of the genetic versus environmental components of the total trait variance differs.

In summary, the primary advantages of genetic epidemiological methods are that they inform on whether the trait under observation has a familial and perhaps a genetic component, indicate the most likely mode of transmission of the genetic component(s), and provide an estimate of the magnitude of the effect with respect to the total trait variance. Complex traits like obesity are likely to be influenced by many genetic and environmental factors, as well as the interactions among and between them. Consequently, it is unlikely that we will discover anything close to "the gene" that explains most of the variation for the common form of obesity. Rather, we expect genetic effects to be composed of oligogenic and polygenic determinants. Combined genetic epidemiological approaches that model inferred genetic effects, as well as effects due to measured genes (i.e., linkage and association) (see Volume 1, Chapter 9), have much greater power to identify genes with small and large effect sizes and to disentangle the interplay among multiple underlying processes.

8.3 GENETIC EFFECTS ON PHENOTYPES OF OBESITY

8.3.1 Body Mass Index

The first strong evidence suggesting that obesity may be inherited was published in 1923 by Davenport,[9] who studied the distribution of body build of adult offspring from various types of parental mating and found a clear correlation between the body builds of parents and offspring, suggesting a role for genetic factors for body type. Since the publication of this seminal paper, multiple twin, adoption, and family studies have clearly demonstrated that excess body mass, most often assessed using the body mass index (BMI = weight [kg]/height [m^2]), is influenced by genetic factors (see Refs. [10–13] for reviews).

Data from large studies have clearly shown that BMI aggregates in families.[14–17] Following numerous early studies (e.g., von Verschuer, 1927[18]; Newman et al., 1937[19]), Stunkard et al., using data from twin[20,21] and adoption[22] studies, showed more than 20 years ago that BMI was heritable. Since then, a plethora of studies using various study designs have confirmed the presence of a significant heritability component to obesity. A detailed review of twin and family studies of BMI published up to 1997 and including information on more than 25,000 twin pairs and 50,000 biological and adoptive family members found weighted mean correlations of 0.74 for MZ twins, 0.32 for DZ twins, 0.25 for siblings, 0.19 for parent-offspring pairs, 0.12 for spouses, and 0.06 for adoptive relatives.[23] These results are consistent with a substantial role of genetic factors in explaining interindividual differences in BMI, with heritability estimates in the range of 50% to 80% based on twin data and 20% to 50% based on family studies. These estimates have been confirmed in more recent studies.[24–27] For example, a 2008 twin study examined the heritability of BMI in a large sample of more than 5000 twin pairs aged 8–11 years and found a high heritability of 77% with a small shared environment effect of 10%.[26] The strong genetic influence on childhood obesity was confirmed in a meta-analysis of nine twin studies, including twins aged 1–18 years, with heritabilities in the range of 60% to 90%.[27] More recently, a meta-analysis of over 8000 MZ and nearly 10,000 DZ twins confirmed that the heritability of BMI was high and remained high (60%–80%) across the life span from preadolescence, through young adulthood, and into late adulthood, and that the contribution of unique environmental influences increased with age from 14% to 40%. The contribution of common environmental factors was small in preadolescence (15%) and nonsignificant in young and late adulthood.[25]

Results from twin studies have suggested that family environment plays a small role in causing obesity. This finding remains controversial considering that several environmental determinants of obesity related to diet (e.g., type of food served, frequency of meals, snacking) and physical activity energy expenditure (television viewing, computer games, other screen time, participation in sports, etc.) are directly under the control of or are strongly influenced by parents, particularly in young children. This conclusion regarding parental control is based on the assumption often made in genetic epidemiological studies that children in the same family experience a rather similar environment. Recent research indicates that this may not be the case always and suggests that the presence of within-family variation may lead to an underestimation of the role of family environment in determining susceptibility to obesity. The role of within-family variation in obesity was recently investigated by examining the degree to which BMI varies between twin and non-twin siblings.[28] Using data from the Children of the National Longitudinal Survey of Youth 1979, the authors compared the distribution of the sibling differences in percentile BMI for various types of siblings and a set of random matches. As expected, identical twins were the most similar but still had a mean difference in BMI of 12 percentile points, compared to 28 percentiles for non-twin siblings.[28] These results indicate significant variation in BMI between siblings, even between identical twins, and suggest that failure to take into account this within-family variation may explain the relatively low shared-family environment effect observed in genetic epidemiological studies of obesity.

In general, heritability estimates derived from family studies[16,17,29–31] have been lower (20%–50%) than those derived from twin studies. For example, the largest family study of BMI, based on a Norwegian sample of first- and second-degree relatives that included a total of 23,936 spouse pairs, 43,586 parent–offspring pairs, 19,157 sibling pairs, and more than 2400 second-degree relatives, estimated the heritability of BMI at 0.39.[17] More recently, a study conducted in England on 22,297 subjects from 9237 households reported a lower heritability of 19% for BMI.[32] The lower heritability estimate reported in that study could be explained by the fact that the study sample included a large number of unrelated individuals within households, which led to better estimates of the

proportion of variance due to additive genetic effects versus shared environmental contributions due to within-household effects.

A recent systematic review of twin and family studies illustrates the heterogeneity in the BMI heritability estimates and emphasizes that coefficients derived from twin studies are higher than those derived from family studies,[8] as we did in the previous version of this publication.[33] The authors identified 88 independent heritability estimates from 31 twin studies (total of 140,525 twins) and 27 estimates from 25 family studies (42,968 family members). The distribution of the reported estimates of BMI heritability is shown in Figure 8.1. Estimates from twin studies ranged from 0.47 to 0.90 (median value of 0.75), whereas those derived from family studies ranged from 0.24 to 0.81 (median value of 0.46). Meta-regression analyses were performed to determine the impact of demographic (age, sex, ethnic origin) and methodological (sample size, choice of variance component model, method used to determine zygosity, measured versus self-reported BMI) factors on this heterogeneity. Results revealed that age category, type of variance component model, method of zygosity assignment, and BMI measurement explained 47% of the heterogeneity in heritability estimates derived from twin studies, although these effects were not significant for heritability estimates derived from family studies.[8]

Sex differences in the genetic effects for BMI have been tested in a few studies; some have found evidence of sex differences, with higher estimates in women than in men,[34,35] while others have not.[36,37] One of the largest studies addressing this issue was done in a sample of about 37,000 twin pairs aged 20–29 years (20,608 pairs) and 30–39 years (16,930 pairs) from eight countries.[38] Overall, variation in BMI was largely explained by additive genetic effects (60%–80%), and sex differences in estimates of variance components were strong and consistent across age groups and countries. Genetic and environmental determinants of fluctuations in BMI were recently investigated in a sample of 14,763 twins and their family members.[39] Fluctuation of BMI was calculated as the difference between the highest and lowest BMI in more than 28,000 subjects aged 18–80 years. In males, genetic effects accounted for 34% of the variance in BMI fluctuation and were largely due to additive genetic effects, while in females, genetic effects accounted for 43% of the variance and were largely due to dominant genetic effects.[39] These results suggest a lower heritability for the fluctuation in BMI than for BMI at a given time; however, this should be interpreted with caution because of the potentially greater error of measurement in assessing BMI fluctuation, as subjects were asked to report their height and their lowest and highest weights in that particular study.

Another way to estimate the importance of genes in the development of obesity is to calculate the familial risk. The risk of becoming obese when a first-degree relative is overweight or obese can be quantified using a statistic called the lambda coefficient (λ_R) or the standardized relative risk ratio. Lambda is defined by the ratio of the risk of being obese when a biological relative proband is obese compared to the risk in the population at large, that is, the overall prevalence of obesity.[40] Estimates of λ_R based on BMI data from twin and family studies have suggested that the risk of obesity, as defined by the 90th BMI percentile, is about two to three times higher for an individual with a family history of obesity. This risk tended to increase with the severity of the obesity, with estimates of λ_R of about 3 to 6 for the 95th percentile cut-off point.[41] Similar results have been reported in the National Health and Nutrition Examination Survey (NHANES) III. Data obtained from 2349 first-degree relatives of 840 obese probands and 5851 participants of NHANES III showed that the prevalence of obesity (BMI $\geq$ 30) is twice as high in families of obese individuals as in the population at large.[42] Moreover, the risk of extreme obesity (BMI $\geq$ 45) is about seven to eight times higher in families of extremely obese subjects. Data from the 1981 Canada Fitness Survey, which included 15,245 participants aged 7 to 69 years, showed that the familial risk of

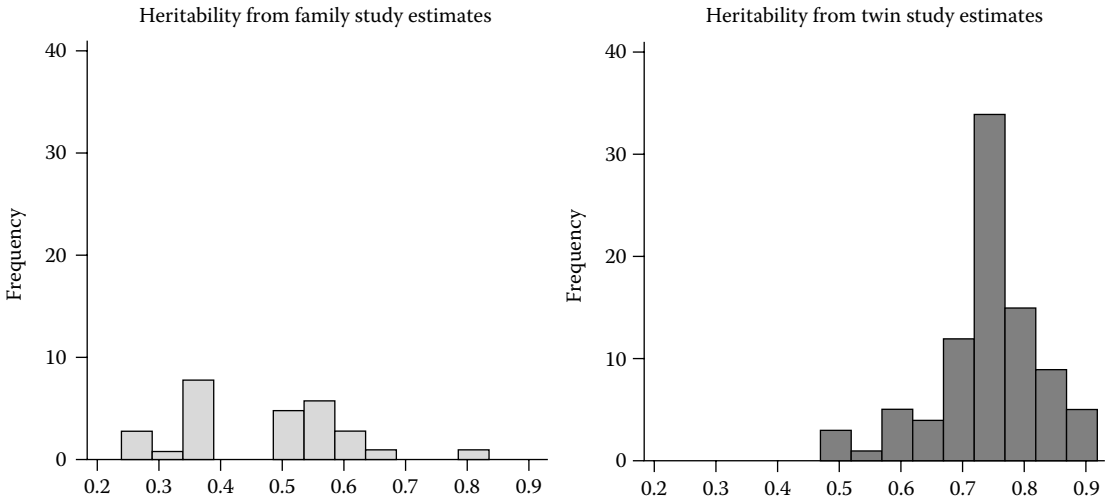

FIGURE 8.1 Distribution of reported estimates of heritability for BMI from family (left panel) and twin (right panel) studies. (Adapted from Elks CE, den Hoed M, Zhao JH et al., *Front Endocrinol*, 3, 29, 2012.)

obesity was five times higher for relatives in the upper 1% distribution of BMI than in the general Canadian population.[14] However, the latter study suggested that the familial risk was not entirely due to genetic factors as the spouses of probands were also characterized by an elevated risk.

8.3.2 Body Composition

Although there are fewer studies of fat mass (FM) and fat-free mass (FFM) than of BMI, it is well established that these body composition measures also have significant additive genetic components. The first heritability estimates for body composition measures were derived from the Quebec Family Study (QFS) using several types of relatives by descent or adoption.[29] The results revealed that 50% to 55% of the variance in FM and percent body fat was transmissible from parents to offspring, but the additive genetic effect was in the range of 20% to 35%. These global estimates are consistent with those reported in Mexican-American families (18%–35%),[43] in the HERITAGE Family Study (55%–62%),[44,45] and in Hispanic children (31%).[46] More recently, large family studies have confirmed these results but also have suggested that the heritabilities for some measures tend to vary by sex. For example, Zillikens et al.[37] measured body composition in more than 2500 individuals from a genetically isolated population in the Netherlands and found significant heritabilities (consistent with earlier data) for BMI (44%), lean mass (57%), FM (46%), and percent body fat (42%). Evidence for sex-specific genetic effects was found, resulting in marginally higher heritabilities in women than men for lean mass (64% vs. 59%) and percent body fat (54% vs. 42%).

8.3.3 Fat Distribution Traits

Body fat distribution, especially truncal abdominal fat, has been associated with the development of obesity-related metabolic complications and risk of diabetes and cardiovascular diseases.[47] A large number of studies have examined the contribution of genetic factors for various fat distribution phenotypes derived from anthropometric measures and, as reviewed elsewhere,[12,48–50] found that the pattern of fat distribution is influenced by genetic factors, generally to a larger extent than overall body fatness. For a phenotype like the waist-to-hip circumference ratio (WHR), heritability estimates vary from 28% to 60%.[12] Another measure of fat distribution is the trunk-to-extremity skinfold ratio, sometimes analyzed as a simple ratio or as a principal component. This approach was used in QFS, and heritability estimates of 30% and 48% were observed for the trunk-to-extremity skinfold ratio adjusted for BMI and a principal component indexing truncal abdominal fat, respectively.[51] In recent years, a large number of studies performed in various populations have reported heritability estimates for waist circumference. Estimates derived from twin studies have ranged from 48% to 77%[26,52–55] while those derived from family studies have ranged from 39% to 63%.[37,56–64] The largest twin study based on more than 5000 twin pairs aged 8–11 years reported a heritability of 77% for waist circumference,[26] which is higher than estimates of 40% to 54% reported in two other studies based on about 2500 adult subjects.[37,55] It is noteworthy that in most studies waist circumference was not adjusted for BMI in order to obtain an estimate of fat distribution independent of body mass. After adjustment for BMI, the heritability of waist circumference is generally attenuated, as observed in QFS with heritability estimates of 46% and 29% before and after adjustment for BMI, respectively.[51]

A few studies have reported heritability estimates of fat distribution using imaging techniques such as dual-energy x-ray absorptiometry (DXA) or computed tomography. Heritability of abdominal visceral fat (AVF) measured by computed tomography was first reported in the QFS[65] and HERITAGE[44] family studies, and after adjustment for total body fatness, significant genetic effects (48%–56%) were found in both the studies. Other family studies, which used DXA measurements to assess fat distribution, have reported heritability estimates in the range of 33% to 63% for the amount of fat in the trunk.[37,66,67] Results from the largest family study (2500 members from 22 extended Dutch pedigrees) revealed heritability estimates of 43% for android FM and 49% for gynoid FM.[37] Sex-specific analyses revealed that heritability estimates were only marginally significantly higher in women than men for android FM (54% vs. 43%) and for the android-to-gynoid FM ratio (60% vs. 50%).

8.3.4 Multivariate Associations among Indices of Adiposity

Although the measures of body mass, body composition, and fat distribution have substantial heritable components, there are important questions about whether there is any evidence for shared genetic variation among the individual traits. There is ample evidence for shared genetic factors between measures of total fat and fat distribution, as reviewed by Katzmarzyk et al.[68] In QFS, a shared familial effect ranging from 29% to 50% was observed between total body fatness and AVF,[69] whereas no common familial effects were observed between FM and the trunk-extremity skinfold ratio.[30] High genetic correlations ranging from about 0.60 to 0.90 have been reported between BMI and waist circumference and WHR.[59,62,67] These results suggest that some of the genes that influence total adiposity may also influence fat distribution traits. On the other hand, Nguyen et al.[70] found no evidence of common genetic effects between FM and lean mass. An interesting multivariate finding is that there is little evidence for common or shared genes underlying the covariation in BMI and FM.[30,71] This is an important observation because BMI is almost universally used as a surrogate for total adiposity.

8.3.5 Ectopic Fat Accumulation

A growing body of evidence suggests that ectopic fat deposition plays a key role in the development of obesity-related metabolic complications and diseases.[72–75] Only two studies have investigated the contribution of genetic factors in ectopic fat

distribution despite evidence that fat accumulation in organs like the heart, the liver, the muscle, or the kidney contributes to the risk of obesity-related diseases independently of overall body fatness. In the first study, data from 471 subjects in eight large multigenerational Afro-Caribbean families (3535 relative pairs) were used to assess the contribution of genetic factors in skeletal muscle fat infiltration, which was assessed by measuring muscle density at the calf level using quantitative computed tomography. Calf cross-sectional total adipose tissue (TAT expressed in millimeters squared), subcutaneous adipose tissue areas expressed in percent of TAT (%SAT), and muscle density (milligram/centimeters cubed) were computed and used as phenotypes for genetic analyses. After adjustment for age, gender, and BMI, the three phenotypes showed significant genetic effects, with heritability estimates of 59%, 29%, and 35% for TAT, %SAT, and muscle density, respectively.[76] In the second study, an ectopic fat depot associated with chronic kidney disease and characterized by high renal sinus fat accumulation (fatty kidney) was investigated in 2946 participants from the Framingham Heart Study.[77] Renal sinus fat (centimeters squared) was quantified in the right kidney based on single-slice abdominal multidetector computed tomography and adjusted for age, BMI, and visceral adipose tissue. The heritability of renal sinus fat was 39% ($p < .0001$) and remained the same after further adjustment for BMI (39%) or visceral adipose tissue (40%). Sex-specific analyses revealed approximately similar heritability estimates in men and women, with values ranging from 43% to 47% in the latter compared to 49% to 55% in the former.[77]

8.4 BEHAVIORAL AND BIOLOGICAL TRAITS IN THE CAUSAL PATHWAYS LEADING TO FAT DEPOSITION

8.4.1 Caloric and Macronutrient Intake

Considering the role of energy intake in the etiology of obesity, one important question is whether there are individual differences in the regulation of appetite and satiety, as well as in caloric intake and macronutrient preference, and whether there is evidence for the contribution of genetic factors. A more extensive review of the role of genetic variation for these traits can be found in other publications.[78–81] A major challenge in such studies is that for any dietary nutrient, there is considerable day-to-day intraindividual difference in the amount consumed.[82] This makes it more difficult to delineate the nature of the genetic variance.

A large number of family and twin studies have tested hypotheses regarding the role of a genetic contribution to human variation in caloric intake, macronutrient consumption, and taste preference. The reader is referred to recent reviews for the details of such studies.[78–81,83,84] The main lessons from these observational studies are that there is a substantial degree of familial aggregation in the pattern of caloric and macronutrient intake, and that all these traits are commonly characterized by a significant genetic component.[79,81] For caloric and macronutrient intake assessed generally by methods such as dietary recalls, food frequency questionnaires or 3- to 7-day dietary records, the genetic variance ranges from about 20% to 40% of the total trait variance adjusted for age, sex, and other appropriate concomitants.

However, as illustrated in Table 8.1, the correlation patterns for energy intake and for carbohydrate, fat, and protein intake as percentages of energy suggest that the nature of human variation in these traits is heterogeneous and complex. These data are from QFS and were derived from a 3-day dietary record obtained on relatives by descent or adoption.[85] The correlation patterns and a more formal path analysis exploration of the coefficients reveal evidence for a common familial environment effect for total caloric intake, as well as for the percentage of energy derived from each of the macronutrients. Strong correlations between spouses also suggest the presence of some assortative mating and potentially common familial environmental effects. The higher correlations in DZ twins compared to regular siblings and to parents and their offspring are likely the result of both genetic and common environmental effects. Also of importance in the data of Table 8.1 is the fact that all correlations are highest in MZ twins, an indication that there is a substantial genetic component for all four traits.

In their 2010 review of the genetic basis of taste preference, Reed and Knaapila[80] argued that while food contains nutrients and calories that animals need to produce heat and energy, it may also contain harmful parasites, bacteria, or chemicals. To guide food selection, the senses of taste and smell have evolved to alert us to the bitter taste of poisons and the sour taste and repugnant smell of spoiled foods. But food choices are also motivated by seeking pleasant nutrients,

TABLE 8.1
Correlations for Various Pairs of Relatives by Descent or Adoption for Energy and Macronutrient Intake

Variable	Foster Parent–Adopted Child	Siblings by Adoption	Spouses	Parent-Offspring	Siblings	DZ Twins	MZ Twins
Energy intake/kg	0.29	0.21	0.31	0.26	0.30	0.58	0.69
CHO (%)	0.08	0.21	0.50	0.29	0.37	0.49	0.70
Lipid (%)	0.18	0.04	0.45	0.31	0.36	0.59	0.61
Protein (%)	0.22	0.22	0.28	0.27	0.38	0.55	0.71

Source: Pérusse L, Tremblay A, Leblanc C et al., *Am J Clin Nutr,* 47, 629–3, 1988.

such as fat and sugar. Studies in humans and animals have suggested that the liking of sugar and fat is influenced by the genotype. Reed and Knaapila[80] illustrated the progress made in defining genes and alleles associated with the positive and negative aspects of food and flavor using a ham and cheese sandwich that contains bread, onion, tomato, watercress, cheese, and ham. They hypothesized that people with sensitive alleles at key genes might differentially detect the mild sweetness of onion (*TAS1R3*), the savory glutamate taste of tomato (*TAS1R3*), the bitterness of watercress (*TAS2R38*), the smell of cheese (*OR11H7*), or the boar-taint odor of ham (*OR7D4*). Thus, it would be reasonable to conclude that combinations of alleles could contribute to the range of liking for the sandwich. People who can taste the pleasant components (and not the unpleasant ones) may experience the ham sandwich as a more pleasant food.[80]

Finally, a few family and twin studies[86–92] have focused on behavioral traits for eating such as restraint, disinhibition, and hunger as assessed in the Three-Factor Eating Questionnaire[93] and other similar instruments. These studies have revealed significant cross-sectional familial aggregation for these traits, but it remains unclear whether this familial aggregation is explained in total or in part by genetic components.[79] For instance, a 3-year longitudinal study of restrained eating in fathers, mothers, and adolescent boys and girls from 404 Dutch families did not find evidence of parental transmission of restrained eating across three time points.[94] The role of genetic determinants, if any, on these behavioral traits remains to be elucidated.

8.4.2 Daily Energy Expenditure

Of particular importance for the regulation of body weight are the key components of daily energy expenditure such as resting metabolic rate (RMR), thermic effect of food (TEF) consumed, relative rates of substrate oxidation, and the energy expenditures of spontaneous, work, and leisure-time physical activity, as well as sedentary time. The evidence for a genetic component for each of these traits is briefly reviewed here.

8.4.2.1 Resting Metabolic Rate

RMR accounts for the largest fraction (60%–70%) of the energy expended every day by sedentary individuals. FFM is the single largest determinant of RMR; it accounts for 50% and more of the RMR variation among people, but it may exert a much smaller or larger influence for a given individual. Adjusting RMR for age, sex, FFM, and FM accounts for a large fraction of the RMR variance, but there remains a residual of about 125 to 150 kcal/day of the energy expended at rest which is not accounted for.[95–98]

One important question is whether this unexplained variance in RMR is characterized by some forms of familial aggregation and whether there is any evidence for a genetic component. Few studies have addressed these issues. In one study of Pima Indians, comprised of 130 nondiabetics from 54 sibships, it was reported that family membership accounted for 11% of the variance in RMR.[95] We have reported data on twin resemblance in RMR in two small studies.[97,99] In both studies, MZ intraclass correlations for RMR adjusted for FFM or per kilogram of FFM were substantially higher, ranging from 0.64 to 0.77, than the same coefficients in DZ twins, which ranged from 0.30 to 0.44. Furthermore, the observations made in QFS are compatible with these twin data.[100] RMR was measured in 372 pairs of sibs from 169 families (mean age of 31 years, SD = 12). A maximum likelihood heritability estimate of 47% was obtained for RMR adjusted for age, sex, body mass, and body composition. Thus, there appears to be a substantial genetic component to the variance in RMR not explained by differences in age, sex, body mass, and body composition.

8.4.2.2 Thermic Effect of Food

The TEF is the component of daily energy expenditure associated with the energy cost of digestion, nutrient storage, and other processes following the consumption of food. One study dealt with TEF measured during 4 hours after a 1,000 kcal carbohydrate-rich meal in 21 pairs of DZ twins, 37 pairs of MZ twins, and 31 parent-offspring pairs.[97] Correlations for TEF (minus the energy expenditure at rest for 4 hours) reached 0.35 in DZ twins, 0.52 in MZ twins, and 0.30 in parent-offspring pairs. The heritability of TEF was estimated to be about 30%. The standard deviation of TEF over 4 hours reached 20 kcal. If one extrapolates to a daily caloric consumption of 2500 kcal with a mixed composition, a standard deviation of TEF of about 50 kcal would be predicted, which would yield 95% confidence intervals of plus or minus 100 kcal or 4% of the caloric intake. It is this fraction of the variance that includes the so-called facultative component of TEF which would be impacted by the heritability level and could influence body weight regulation. But the latter needs to be confirmed in other studies.

8.4.2.3 Energy Partitioning

We know little about the genetic determinants of nutrient partitioning in humans. Two indicators of energy partitioning are of particular interest: First, the propensity to gain more or less adipose tissue relative to lean tissue when body energy is gained as a result of positive energy balance and, second, the relative proportion of carbohydrates and lipids oxidized under standardized conditions. From rodent models and the animal husbandry literature, it is evident that there are strong strain differences in energy partitioning either during the growth period or during periods of weight gain under forced feeding or weight loss as a result of caloric deprivation.

In humans, our studies of long-term overfeeding and of negative energy balance performed with pairs of MZ twins have revealed strong within-MZ-twin-pair resemblance for the changes in the FM-to-FFM ratio, as well as in the respiratory exchange ratio (RER) under standardized conditions.[98,101,102]

In the overfeeding experiment with 12 pairs of MZ twins, the mean body weight gain was 8.1 kg, of which 5.4 kg was FM and 2.7 kg was FFM. Although the main gain in FM/FFM was 2:1, there were substantial differences among the 24 subjects. The correlation between the delta FM/FFM and

total body weight gain reached 0.61, indicating that those who gained more lean tissues were the low-body-mass gainers.[103] Moreover, there was a strong within-pair resemblance in the changes in FM/FFM induced by the overfeeding protocol.[101] The same phenomenon was observed in the study of MZ twins exposed to long-term negative energy balance.[102]

As for rates of substrate oxidation, MZ twins have more similar RER than DZ twins during standardized submaximal exercise.[97] In addition, when MZ twins were exposed to chronic overfeeding, significant within-pair resemblance was observed for baseline RER and for RER over 4 hours after a 1000 kcal mixed meal, as well as for the changes in RER after being overfed by 84,000 kcal over a 100-day period.[98] The latter observations reveal that even when energy intake, macronutrient composition of the diet, and physical activity level are standardized for more than 3 months, some adults are more successful than others at oxidizing more lipids than carbohydrates or modifying their profile of substrates oxidized with the goals of resisting the gain in adipose tissue. The within-pair resemblance strongly suggests that this ability to modulate the rates of substrates oxidized is influenced by genetic characteristics.[96]

8.4.2.4 Physical Activity Level and Sedentary Time

Numerous reports based on family or twin designs have been published on the role of genetic factors in physical activity level and indicators of sedentary behavior (see Refs. [104–107] for reviews). Likewise, a substantial body of data has been developed on spontaneous activity levels in rodents and other animal models.[108]

Most of the research based on nuclear families has used questionnaires to evaluate the level of physical activity. In a report of the 1981 Canada Fitness Survey, more than 18,000 individuals from 11,884 households across Canada completed a questionnaire on physical activity habits.[16] The evidence for a genetic component to human variation in activity level was deemed quite weak in this cohort. Based on 1610 members from 375 families of QFS, including nine types of relatives by descent or adoption, with activity level assessed by a 3-day activity record, the heritability level reached a maximum of 29%.[109] More recently, a report on heritability of activity levels in 1030 Hispanic children from 319 families was based on free-living assessment of activity by accelerometer.[110] The heritability coefficients reached 55% for total physical activity level, with a range from 46% to 57% for various levels of activity. In a recent report from the Baependi Heart Study in Brazil, heritability levels of 35% for weekly physical activity and about 14% for sedentary behavior were reported on the basis of assessments by questionnaires made in 1693 individuals from 95 extended families.[111]

In contrast, studies relying on the traditional twin study design have reported substantially higher heritability estimates. A detailed review of these studies is beyond the scope of this chapter. We will focus on the largest twin study reported to date. A cohort of 37,051 twin pairs from seven countries (Australia, Denmark, Finland, Norway, the Netherlands, Sweden, and the United Kingdom) was put together with data on exercise behavior derived from questionnaires.[112] The trait retained for analysis was a dichotomous variable representing exercisers (at least 60 minutes of activity per week at an intensity of four times the RMR and more) and nonexercisers. The average percentage of male and female exercisers was 44% and 35%, respectively, for the seven countries. The median heritability level for all seven cohorts was 62%, with a range from 27% (Norwegian males) to 71% (United Kingdom), as shown in Table 8.2. These elevated heritability estimates are quite comparable to those derived from other twin studies.[105]

One recent report dealt specifically with the genetic component of sedentary behavior.[113] Sedentary behavior was assessed from surveys about TV viewing time, electronic game playing time, and computer and Internet time, and a screen-viewing sedentary behavior trait was computed. Data were available in 5074 adolescent twins and siblings from 2777 families of the Netherlands. The genetic component of sedentary behavior reached 35% for boys and 19% for girls

TABLE 8.2
Heritability Estimates and Confidence Intervals for an Exercise Behavior Trait by Country for the Most Parsimonious Model

	A (95% CI)	C (95% CI)	E (95% CI)
Australia	48.2 (41.0, 54.9)	–	51.9 (45.2, 60.0)
Denmark	51.8 (47.0, 56.0)	–	48.2 (48.2, 52.5)
Finland	61.7 (57.8, 65.5)	–	38.3 (34.5, 42.2)
Netherlands	66.7 (60.9, 71.9)	–	33.3 (28.1, 39.1)
Norway (males)	26.5 (10.1, 46.8)	36.8 (18.9, 51.5)	36.7 (29.4, 44.7)
Norway (females)	56.4 (48.5, 63.6)	–	43.6 (36.4, 51.5)
Sweden	61.8 (58.1, 65.3)	–	38.2 (34.7, 42.0)
United Kingdom	70.5 (55.2, 82.3)	–	29.5 (17.7, 44.8)

Source: Stubbe JH et al., *PLoS One*, 1, e22, 2006.

Note: Based on 37,051 twin pairs from seven countries.

A, additive genetic factors; C, common environmental factors; E, unique environmental factors; 95% CI, 95% confidence interval.

around 12 years of age, but it increased to 48% in boys and 34% in girls at 20 years of age.

From these studies and others not reviewed herein, we conclude that there is a significant genetic component to spontaneous activity level, exercise participation, and the time spent in sedentary pursuits. The challenge is now to identify the genes and genomic variants responsible for these genetic effects.

8.5 GENOTYPE–ENVIRONMENT INTERACTIONS

8.5.1 Genetic Effect Modulated by Diet and Physical Activity in Observational Studies

Results obtained mainly from twin studies have provided evidence for the effects of interaction between genotype and environment in obesity, either by assessing the impact of diet or physical activity, taking into account genetic predisposition to obesity, or by assessing the modifying effects of diet or physical activity on the genetic variance of obesity-related traits. Using these approaches, evidence of interactions with both physical activity[114–117] and diet[117,118] has been reported. Heitmann et al.[114] investigated the impact of both physical activity and genetic factors on 6-year weight changes in 1571 MZ and 3029 DZ adult Finnish same-sex twin pairs. They found that associations between weight changes in twins A and B were significantly stronger for MZ than DZ twins, suggesting that genetic factors play a significant role in weight changes. Moreover, they found evidence of significant genotype–environment interaction in male MZ twins, as the genetic effects for the 6-year changes in body weight were observed at medium and high levels of physical activity only.[114] This interaction with physical activity level has been confirmed recently in three other twin studies that observed a reduced heritability of BMI among physically active individuals.[116,117,119]

The largest study based on 5037 twin pairs (2710 MZ and 2327 DZ pairs) from the Vietnam Era Twin Registry found that self-reported vigorous exercise significantly ($p < .001$) modified the additive genetic variance of BMI.[116] Age was also found to moderate the genetic effects on BMI and to operate synergistically with the modifying effects of exercise. As shown in Table 8.3, the heritability of BMI was smaller among subjects who reported vigorous exercise (0.50–0.66) compared to those who did not (0.61–0.72), and this reduction in the heritability increased with age, with a 6-, 9-, and 11-point decrease in heritability estimates of BMI in subjects with a mean age of 38, 41, and 44 years, respectively. These results suggest that physical activity may attenuate some of the genetic influences of obesity, which has recently been shown to be the case with susceptibility genes of obesity identified through genome-wide association studies[120,121] (see Volume 1, Chapter 9).

Protein intake was also found to modify the genetic and environmental component of BMI and waist circumference variance in male (but not in female) twins from Denmark.[117]

8.5.2 Heritability of the Response to Experimental Interventions

Studies undertaken in MZ twins have clearly shown that response to a caloric surplus or an energy deficit induced by exercise is genotype dependent. The overfeeding studies in which 12 pairs of male MZ twins ate a 1000 kcal/day caloric surplus, 6 days a week, during a period of 100 days, showed a significant within-pair resemblance for gains in body weight ($r = 0.55$), FM ($r = 0.50$), and AVF ($r = 0.72$).[101] The greater within-pair than between-pair response to the standardized caloric surplus suggests that the amount of weight gained in response to overfeeding is influenced by the genotype and thus heritable. In another experiment, seven pairs of young adult male MZ twins completed a negative energy balance protocol during which they exercised on cycle ergometers twice a day, 9 out of 10 days, over a period of 93 days while being kept on a constant daily energy and nutrient intake.[102] The mean total energy deficit caused by exercise above the estimated energy cost of body weight maintenance reached 58,000 kcal over the duration of the intervention. Even though there were large individual differences in response to the negative energy balance and exercise protocol, subjects with the same genotype were more alike in responses than subjects with different genotypes as shown by the intraclass coefficients for body weight ($r = 0.74$), FM ($r = 0.87$), and AVF ($r = 0.84$) changes.

These observations were supported by a weight-loss experiment performed with 14 pairs of premenopausal female MZ twin pairs who were subjected to 28 days of a very-low-calorie diet (1.6 MJ/day) in an inpatient metabolic unit.[122] Subjects lost on average 8.8 kg (SD = 1.9) with a range from 5.9 to 12.4 kg. Changes in weight were not randomly distributed among the 28 women. There was about 13 times more variability between

TABLE 8.3
Heritability of BMI by Self-Reported Vigorous Exercise and Age

	Age = 38 years		Age = 41 years		Age = 44 years	
	h^2	CI	h^2	CI	h^2	CI
No exercise	0.72	0.61–0.76	0.68	0.59–0.72	0.61	0.47–0.71
Vigorous exercise	0.66	0.50–0.74	0.59	0.44–0.70	0.50	0.29–0.67

Source: McCaffery JM et al., *Am J Clin Nutr,* 89, 1011–18, 2009.
Note: Data are from 8627 subjects from 2170 MZ and 2327 DZ twin pairs.
CI, 95% confidence interval.

pairs than within pairs of MZ twins for the changes in body weight. The similarity among members of twin pairs for the decreases in FM, as assessed from underwater weighing, was even more pronounced, with an F ratio of 17. The loss of FFM accounted on average for 24% of the weight loss, a value comparable to other weight-loss studies. High intrapair resemblance was also observed for an indicator of overall metabolic efficiency, suggesting that the response to therapeutic weight-loss regimens may be influenced by genetic variability.[123]

Results from family studies also suggest that the response of body weight and body fatness to interventions is influenced by genetic factors. In the HERITAGE Family Study, the heritability of body fat changes in response to 20 weeks of endurance exercise training was investigated in two reports. In one study, changes in the amount and distribution of subcutaneous fat in response to exercise training were characterized by moderate levels of familial aggregation, with significant spouse and sibling correlations but no evidence of parent-offspring correlations for subcutaneous fat and waist circumference.[124] This pattern of correlations indicates a cohort effect and suggests that genetic and/or environmental effects influencing the response to exercise training are age dependent. In the second study, the changes in total body fatness and AVF in response to exercise training were investigated using familial correlations to assess polygenic effects and segregation analyses to test for the presence of major gene effects.[125] The results provided little evidence of a polygenic effect, but segregation analyses revealed the presence of a putative dominant locus accounting for 31% of the variance for changes in total body fatness and a putative recessive locus accounting for 26% of the variance for changes in AVF adjusted for age, baseline AVF, and changes in total body fat.

More recently, the contribution of genetic factors to weight loss after Roux-en-Y gastric bypass surgery was investigated in a cohort of 848 patients by comparing weight loss within pairs of genetically related and genetically unrelated individuals.[126] By using genotype data from the Illumina 650Y BeadChip array and identity-by-descent methods, the authors were able to identify 13 first-degree relative pairs, defined as pairs of patients who shared approximately 50% of their genes. They also identified 10 pairs of individuals living together, but who were genetically unrelated and randomly paired the remaining individuals to form 397 genetically unrelated pairs. The mean within-pair difference in excess weight loss with surgery was 9% in first-degree relative pairs compared to 26% in cohabiting unrelated pairs and 25% in unrelated pairs. The intraclass correlation was significant for first-degree relatives ($r = 0.70$, $p = .02$) but not for the two other groups.[126] Another small case study of MZ twins showed that within-pair weight loss of three twin pairs who underwent Roux-en-Y gastric bypass was very similar.[127]

8.6 GENETIC COVARIATION BETWEEN OBESITY-RELATED TRAITS

Unlike the large number of studies that have shown that BMI and obesity are influenced by genetic factors, relatively few studies have investigated the contributions of shared genetic and environmental influences between obesity and traits known to influence body weight and body fatness, such as eating and physical activity habits, as well as between obesity and its comorbidities.

In QFS, we have examined the familial clustering of body fatness and traits related to the metabolic syndrome such as abdominal fat,[69] blood pressure (BP),[128] fasting glucose and insulin,[129] and blood lipids.[130] Results have revealed significant evidence of a shared genetic basis between body fat and abdominal fat (bivariate h^2 of 43%), diastolic BP (bivariate h^2 of 33%), and fasting glucose and insulin (bivariate h^2 of 10%), while no significant genetic covariation has been found between blood lipids and adiposity measures. More recently, genetic and environmental determinants of BP and BMI were investigated in 1243 MZ and 833 DZ Chinese twins.[131] Bivariate genetic analyses revealed significant genetic correlations between BMI and systolic ($r = 0.38$) and diastolic ($r = 0.48$) BP. The phenotypic correlations between BP and BMI were largely explained by genetic factors (82% for systolic BP and 86% for diastolic BP), which suggests that these traits share common genes. However, the estimates of the percentage of total BP variance explained by genetic effects common to BMI were drastically lower at 6% for systolic BP and 7% for diastolic BP.[131]

The effects of genetic factors on BMI, traits for eating behavior, and liking for sweet and fatty foods were examined in a cohort of 1,326 adult twins from the United Kingdom and Finland.[88] Significant heritability estimates were observed for traits related to eating behavior (10%–69%) and for the liking and use-frequency of fatty foods (24%–54%). Sex differences were noted in the heritability estimates of traits for eating behavior and liking for salty-and-fatty foods, with higher estimates in women than in men. Significant genetic correlations were observed between BMI and cognitive dietary restraint (0.16), uncontrolled eating (0.29), and emotional eating (0.51).[88] In another study, shared genetic effects of energy, macronutrient, and fruit and vegetable consumption with BMI were investigated in a cohort of parents and their adult offspring ($n = 1410$) 20 years after shared living in the same household.[132] Moderate heritability estimates were observed for protein intake (0.21) and fruit (0.26) and vegetable (0.32) consumption. Only fruit (–0.28) and vegetable consumption (–0.30) exhibited significant negative genetic correlations with BMI.[132] The negative genetic correlation between fruit and vegetable consumption and BMI suggests that a proportion of shared genes associated with low fruit and vegetable consumption may also be associated with higher BMI. The genetic correlations reported in these two studies[88,132] suggest that, in some individuals, the genetic predisposition to obesity may be explained by an inherited predisposition to loss of control over eating, to emotional eating, or to low fruit and vegetable consumption.

Shared genetic and environmental influences between physical activity and adiposity have been examined in a few studies. Mustelin et al.[133] studied 304 adult twins in whom sports participation and body composition were measured using the Baecke questionnaire and DXA, respectively.

They found that both genetic and environmental factors contributed to the covariation between sports participation and body fatness, with genetic factors accounting for 71% and 59% of the activity correlation with percent body fat and waist circumference, respectively. For both percent body fat (–0.50) and waist circumference (–0.27), the genetic correlation was negative, suggesting the presence of a common set of genes associated with a reduced propensity for vigorous physical activity and increased body fatness. In the previously mentioned study based on twin pairs who served in the military during the Vietnam War, no shared genetic effects were observed between vigorous exercise and BMI.[116]

8.7 CONCLUDING REMARKS

In summary, the evidence that there is a genetic component to BMI and the risk of obesity is strong. A similar conclusion can be reached for the genetic component of total adiposity, lean body mass, and several indicators of adipose tissue distribution. At this time, the evidence is less conclusive for traits related to ectopic fat deposition. Substantial genetic components are present for behavioral and biological traits, which are part of the causal pathways leading to adipose tissue expansion and increasing risk of obesity, including caloric and macronutrient intake, sedentary time, physical activity energy expenditure, RMR, TEF, and rates of substrate oxidation. More research is clearly warranted on these and other behavioral and biological endophenotypes.

A topic that has received some attention in recent years in the obesity genetics literature[134,135] is that of the large differences between the commonly cited heritability estimates for BMI and the small fraction of the variance accounted for to date by common variants, as identified in comprehensive and adequately powered genome-wide association studies (see Volume 1, Chapter 9 for a review of the latter). A first potential explanation for the discrepancy could be that the missing variance will eventually be accounted for by genomic features such as rare alleles, copy number variants, sequence variation in microRNAs and their binding sites, variants in other small and in larger RNAs, variants in the millions of genomic switches involved in the regulation of gene expression in specific tissues and organs, variation in imprinted sequences, methylation profiles at relevant CpG islands, and undoubtedly others. Another potential explanation could come from the notion that the current heritability estimates are highly inflated. In support of this view, a few studies have reported a substantially lower genetic component than traditional twin and family reports.[22,29,136] The issue is unlikely to be resolved without extensive population and genomic research.

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9 Genes and the Predisposition to Obesity

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CONTENTS

9.1 INTRODUCTION

Since the 1980s, the prevalence of obesity has more than doubled in the United States, where 36% of adults and 17% of children and adolescents are now obese.[1,2] The obesity epidemic has largely been fueled by a rapid globalization of the Westernized lifestyle,[3] and as such, it represents a public health challenge in both high- and low-income countries.[4] However, even in the most obesogenic of environments, some individuals experience more difficulties maintaining a healthy body weight than others, suggesting that nonenvironmental factors also contribute to obesity susceptibility.

Data from family and twin studies have provided evidence of a role for genetic factors in obesity susceptibility. In a recent meta-analysis of results from 88 independent twin studies and 27 family studies, genetic factors explained between 24% and 90% of the interindividual variation in body mass index (BMI).[5] The wide range of heritability estimates was partly explained by study design, with twin studies reporting substantially higher heritability estimates (median heritability 75%) than family studies (median heritability 46%). Also across twin studies, a wide range of heritability estimates was observed (47%–90%)[5]; nearly half of the heterogeneity in heritability was explained by population-level differences and study characteristics.[5] Despite the large heterogeneity, family and twin studies provided clear evidence of a genetic contribution to obesity susceptibility.

Here, we discuss the recent progress in obesity genetics. This chapter focuses on the discovery and confirmation of common variants by large-scale candidate gene and genome-wide association (GWA) studies (GWASs). The genome-wide

linkage approach, which has been largely unsuccessful in identifying loci for common obesity,[6] is not discussed here. Furthermore, we discuss the clinical relevance of these findings, along with implications for our understanding of the etiology of obesity and recommendations for future research.

9.2 EVIDENCE FROM CANDIDATE GENE STUDIES

In the hypothesis-driven candidate gene approach, current biological knowledge is used to select candidate genes for obesity susceptibility. Such candidacy is usually based on a confirmed role in regulating energy balance in animal studies or on previous implication of mutations in monogenic obesity. Previously, the candidate gene approach had limited success in identifying loci that were robustly associated with obesity-related traits. This was likely due to insufficient knowledge of the biology of energy metabolism, an often incomplete survey of the genetic variation in the candidate gene, and generally small study populations ($N < 1000$), resulting in low power to detect the small effect sizes that are anticipated for common obesity.

More recently, an increasing number of candidate gene studies have examined associations in larger samples ($N > 5000$), sometimes followed by a meta-analysis of all available evidence. These studies showed robust associations between obesity-related traits and variants in melanocortin 4 receptor (*MC4R*), β3-adrenergic receptor (*ADRB3*), proprotein convertase subtilisin/kexin type 1 (*PCSK1*), brain-derived neurotrophic factor (*BDNF*), lactase (*LCT*), melatonin receptor 1 B (*MTNR1B*), toll-like receptor 4 (*TLR4*), ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*), fibroblast growth factor receptor 1 (*FGFR1*), and leptin receptor (*LEPR*). Table 9.1 summarizes candidate gene studies that confirmed associations with obesity-related traits.

9.2.1 Melanocortin 4 Receptor

MC4R is expressed in the hypothalamus and plays a key role in food intake regulation and energy homeostasis.[7–9] *MC4R* mutations constitute the most common form of monogenic, early-onset obesity in humans,[10] with MC4R-deficient patients being characterized by hyperphagia.[10] These findings make *MC4R* a clear candidate gene for common obesity. Many

TABLE 9.1
Candidate Genes for Which Associations with Obesity-Related Traits Were Confirmed

Gene	Variant	Study Design	Population	Sample Size	EAF	Outcome	Reference
MC4R	I251L	Meta-analysis of results from 15 population-based studies and case–control studies of obesity	European, East Asian	11,435	1%	I251I homozygotes had a higher risk of obesity than 251L carriers (OR = 1.92, $p = 3.6 \times 10^{-5}$)	Stutzmann et al.[12]
	V103I	Meta-analysis of results from 37 studies	European, East Asian, African	19,822 cases, 35,373 controls	1%	V103V homozygotes had a higher risk of obesity than I103 carriers (OR = 1.27, $p < .0001$)	Wang et al.[11]
ADRB3	T64R	Meta-analysis of results from 97 studies	European, East Asian, other	44,833	18%	East Asian 64R carriers had a BMI 0.31 kg/m^2 higher than T64T homozygotes ($p = .001$)	Kurokawa et al.[15]
PCSK1	N221D	Meta-analysis of results from six case–control studies of obesity and one family study	European	13,659	5%	OR of obesity was 1.34 for each additional 221D-encoding allele ($p = 7.3 \times 10^{-8}$)	Benzinou et al.[22]
		Population-based cohort	European	20,249	6%	No associations with risk of obesity, BMI, or WC found ($p > .05$); an interaction with age for risk of obesity ($p = .02$) and BMI ($p = .01$) found, showing an association with both in individuals <59 years ($p = .02$) but not in individuals >59 years ($p > .6$)	Kilpeläinen et al.[23]
	Q665E/ S690T	Meta-analysis of results from six case–control studies of obesity and one family study	European	13,659	26%	OR of obesity was 1.22 for each additional minor allele ($p = 2.3 \times 10^{-12}$)	Benzinou et al.[22]
		Population-based cohort	European	20,269	27%	No associations with risk of obesity, BMI, or WC found ($p > .05$)	Kilpeläinen et al.[23]

TABLE 9.1 (*Continued*)
Candidate Genes for Which Associations with Obesity-Related Traits Were Confirmed

Gene	Variant	Study Design	Population	Sample Size	EAF	Outcome	Reference
BDNF	V66M	Meta-analysis of results from three population-based studies	European	10,109	20%	V66 carriers had a BMI 0.76 kg/m^2 higher than M66M homozygotes ($p < .001$)	Shugart et al.[28]
		Meta-analysis of results from three population-based studies	Korean	20,270	55%	Each additional V66-encoding allele was associated with a BMI increase of 0.17 kg/m^2 ($p = 5.6 \times 10^{-8}$)	Hong et al.[29]
LCT	C/T$-_{13910}$	Meta-analysis of eight population-based studies and one family study	European	31,720	80%–90%	T allele carriers had a BMI 0.06 kg/m^2 higher than C/C homozygotes ($p = 7.9 \times 10^{-5}$)	Kettunen et al.[35]
MTNR1B	G24E	Meta-analysis of results from two case–control studies of obesity	European	10,601	9%	OR of obesity was 1.20 for each additional 24E-encoding allele ($p = 8.3 \times 10^{-4}$), which was also associated with a BMI increase of 0.5 kg/m^2 ($p = 1.2 \times 10^{-5}$) and a WC increase of 1.2 cm ($p = 9.0 \times 10^{-6}$)	Andersson et al.[41]
TLR4	D299G/ T399I	One population-based cohort (METSIM) and one family-based cohort (TÜF/TULIP)	European	5327 in METSIM, 1482 in TÜF/TULIP	METSIM: 9% TÜF/ TULIP: 5%	299G/399I-encoding allele was associated with higher BF% under an additive model in METSIM ($p = .01$) and under a dominant model in TÜF/TULIP ($p = .03$)	Weyrich et al.[46]
ENPP1	K121Q	Meta-analysis of results from 10 case–control studies of obesity	European	11,372 cases, 12,952 controls	Cases: 13%–18%, controls: 11%–23%	Q121Q homozygotes had a higher risk of obesity than K121 carriers (OR = 1.25, $p = .021$)	Wang et al.[49]
FGFR1	rs7012413	Meta-analysis of four case–control studies of (extreme) obesity	European	4838 cases, 5827 controls	Cases: 30%–38%, controls: 27%–33%	OR of obesity was 1.17 for each minor T allele ($p = 1.8 \times 10^{-6}$)	Jiao et al.[52]
LEPR	rs9436746	Population-based cohort	European	5636	41%	OR of overweight was 1.13 for each additional minor A allele ($p = .003$)	Bender et al.[56]
	rs10889553	Population-based cohort	European	5636	2%	Each additional minor T allele was associated with a 1.65 cm larger WC ($p = .001$)	Bender et al.[56]

Notes: EAF, frequency of the obesity-susceptibility-increasing allele; WC, waist circumference.

studies have examined the association of common variants in *MC4R* with obesity-related traits. The most widely studied variants encode the amino acid changes V103I (rs2229616) and I251L. Meta-analyses of all available data have shown that carriers of the 103I-encoding allele had a 21% lower risk of obesity than V103V homozygotes,[11] whereas carriers of the 251L-encoding allele had a 48% reduced risk of obesity when compared with I251I homozygotes.[12]

9.2.2 β3-Adrenergic Receptor

ADRB3 is primarily expressed in visceral adipose tissue (VAT),[13] and it regulates lipolysis upon activation by the sympathetic nervous system.[14] A meta-analysis incorporating data of 44,833 individuals from 97 populations showed that East Asian carriers of the 64R-encoding allele (rs4994) had a 0.31 kg/m^2 higher BMI than T64T homozygotes. The 64R-encoding allele is more common in East Asians (frequency ~18%) than in Europeans (~7.5%), which may explain why an association was observed only in East Asians.[15] Associations with BMI did not reach genome-wide significance in a recent GWAS for BMI in East Asians.[16,17]

9.2.3 Proprotein Convertase Subtilisin/Kexin Type 1

PCSK1 encodes the prohormone convertase 1/3 enzyme, which is expressed in neuroendocrine cells and converts prohormones into their metabolically active forms.[18] Mutations in

PCSK1 result in human congenital prohormone convertase 1/3 deficiency, a syndrome characterized by obesity and dysfunction of the small intestine.[19–21] More recently, associations with obesity-related traits have been described for the common and moderately deleterious rs6232 (N221D) and rs6235 variants (tagging the Q665E-S690T pair). A meta-analysis of data from six case–control studies and one family study (N = 13,659) showed an odds ratio (OR) for obesity of 1.34 for each additional 221D-encoding allele in rs6232 and of 1.22 for each additional minor allele in rs6235.[22] Although a subsequent follow-up study could not confirm associations with obesity-related traits for rs6232 and rs6235 in a population-based study of 20,249 adults,[23] a 2012 GWAS for BMI in individuals of East Asian descent also identified a locus near *PCSK1*.[17] Although the latter locus is in low linkage disequilibrium (LD), that is, it correlates weakly with rs6232 and rs6235 variants ($r^2_{LD} < 0.03$), these results confirm the relevance of *PCSK1* for common obesity.

9.2.4 Brain-Derived Neurotrophic Factor

Bdnf mutant mice show a reduced expression of BDNF in the hypothalamus and are hyperphagic, obese, and hyperactive, suggesting a role for *BDNF* in the regulation of energy balance.[24–26] In humans, the 66M-encoding allele (rs6265) has been associated with impaired intracellular BDNF trafficking and a reduced activity-dependent secretion of BDNF in hippocampal neurons.[27] In 10,109 European women, M66M homozygotes had a significantly lower BMI (–0.76 kg/m^2) than carriers of the V66-encoding allele.[28] More recently, the association of V66M with BMI was confirmed in data from 20,270 Koreans.[29] In addition, GWASs confirmed associations with BMI for a locus harboring V66M in data from European (r^2_{LD} = 0.74)[30] and East Asian (r^2_{LD} = 1.00)[16,17] individuals.

9.2.5 Lactase

LCT is expressed in intestinal epithelial cells and encodes the lactase-phlorizin hydrolase enzyme, which catalyzes the digestion of the dairy sugar lactose. In most humans, LCT activity declines after weaning,[31] resulting in some degree of LCT nonpersistence (lactose intolerance). Interestingly, the T allele of the C/T$_{-13910}$ variant (rs4988235), located 10 kb upstream of *LCT*, has been shown to fully predict LCT persistence in some populations,[31–33] potentially by binding transcription factors more strongly than the C allele.[34] Given the dietary consequences of lactose intolerance, the C/T$_{-13910}$ variant was hypothesized to be associated with BMI.[35] In line with this, T allele carriers in C/T$_{-13910}$ had a BMI 0.06 kg/m^2 higher compared with C/C homozygotes in data from 31,720 Europeans.[35]

9.2.6 Melatonin Receptor 1 B

Growing evidence suggests that adequate regulation of circadian rhythm is essential for the regulation of appetite and food intake,[36] as well as for glucose metabolism.[37] Melatonin plays a role in the regulation of circadian rhythm,[38] and common variants in the gene encoding its receptor have been associated with fasting glucose and risk of type 2 diabetes.[39,40] Deep sequencing of *MTNR1B* in 200 individuals identified six nonsynonymous variants. Subsequent follow-up analyses of data from 10,601 population-based Europeans showed that each additional 24E-encoding allele of the G24E variant was associated with a 20% higher risk of obesity, a BMI increase of 0.5 kg/m^2, and a waist circumference (WC) increase of 1.2 cm.[41] Functional follow-up showed that ligand-independent constitutive signaling was decreased in 24E mutant MTNR1B.[41] The G24E-encoding variant was not available in recent meta-analyses of GWASs for obesity-related traits. Therefore, replication of the association is warranted.

9.2.7 Toll-Like Receptor 4

TLR4 is essential for increased inflammatory activity in adipocytes and macrophages following macrophage-induced adipose tissue lipolysis.[42] C3H/HeJ mice with a loss-of-function mutation in *Tlr4* have been shown to be resistant to diet-induced obesity.[43] In humans, evidence shows that *TLR4* expression in skeletal muscle is increased in obesity[44] and is downregulated after dietary restriction.[45] Each additional copy of the 299G allele of the nonsynonymous D299G variant (rs4986790), which is in perfect LD with the T399I variant (rs4986791), was associated with a higher body fat percentage (BF%) in data from 5327 individuals of the Metabolic Syndrome in Men (METSIM) cohort.[46] The association was confirmed in data from 1482 individuals of the Tübingen Family Study (TÜF)/Tübingen Lifestyle Intervention Program (TULIP) cohort. TÜF/TULIP carriers of the 299G-encoding allele also had proportionally more liver fat and VAT than D299D homozygotes, independently of BF%.[46]

9.2.8 Ectonucleotide Pyrophosphatase/ Phosphodiesterase 1

ENPP1 inhibits tyrosine kinase activity of the insulin receptor, thereby downregulating insulin signaling and reducing insulin sensitivity.[47] A meta-analysis of 15,801 obese cases and 26,241 controls previously showed that European Q121Q homozygotes in rs1044498 (K121Q) are at increased risk of type 2 diabetes when compared with carriers of the K121-encoding allele. Adjusting for BMI abolished the association, suggesting that the association with type 2 diabetes resulted from an association with BMI.[48] Another recent meta-analysis of published case–control studies for obesity (N = 24,324 Europeans) showed that Q121Q homozygotes were also at increased risk of obesity when compared with carriers of the K121-encoding allele (OR = 1.25, recessive model).[49] Future studies with large populations are required to confirm the relevance of K121Q in *ENPP1* for obesity.

9.2.9 Fibroblast Growth Factor Receptor 1

FGFR1 encodes a receptor tyrosine kinase that plays a role in hypothalamic regulation of food intake and physical activity.[50,51] In humans, *FGFR1* mRNA and protein levels in adipose

tissue were recently shown to be higher in obese women when compared with lean controls.[52] A single-nucleotide polymorphism (SNP) in intron 1 of *FGFR1* (rs7012413) was consistently associated with obesity in four separate cohorts, together comprising data from 4838 obese cases (BMI $\geq$ 30) and 5827 normal-weight controls (BMI < 25).[52] A meta-analysis of results from all four studies showed that each additional copy of the minor T allele in rs7012413 was associated with an increased risk of obesity. Each additional T allele was also associated with higher *FGFR1* mRNA levels in adipose tissue of a subsample ($N = 80$, $p = .018$).[52]

9.2.10 Leptin Receptor

Leptin is an adipocyte-derived hormone with circulating levels that correlate closely with fat mass. It also plays a key role in regulating energy metabolism through its hypothalamic receptor (LEPR).[53] *Lepr*-null mice (*db/db*) have been shown to be severely hyperphagic and to develop early-onset obesity and diabetes,[54] much like humans with loss-of-function mutations in *LEPR*.[53,55] So far, the SNPs encoding K109R, Q223R, and K656N in *LEPR* have been most widely studied in the context of common obesity. Recently, a meta-analysis of all available data could not confirm an association with obesity for any of the three variants.[56] Besides meta-analyzing all available data for K109R, Q223R, and K656N, the authors also examined associations of 15 tag SNPs that cover the *LEPR* region with obesity-related traits in data from 5636 adults of the Cohorte Lausannoise (CoLAUS).[56] Of these 15 SNPs, rs9436746 was associated with the risk of being overweight, and rs10889553 was associated with WC.[56] These variants are largely independent of K109R, Q223R, and K656N ($r^2_{LD} < 0.6$ for rs9436746; $r^2_{LD} < 0.02$ for rs10889553), were not associated with plasma leptin levels[56] and were at most in moderate LD with *LEPR* variants that had previously been identified in a GWAS for plasma soluble LEPR levels ($r^2_{LD} < 0.7$ for rs9436746; $r^2_{LD} < 0.02$ for rs10889553).[57] Additional efforts in large population-based cohorts are required to evaluate whether variants in *LEPR* are truly associated with obesity-related traits.

In summary, a growing number of large-scale candidate gene studies have identified common, mostly nonsynonymous variants in at least 10 candidate genes (*MC4R*, *ADRB3*, *PCSK1*, *BDNF*, *LCT*, *MTNR1B*, *TLR4*, *ENPP1*, *FGFR1*, and *LEPR*) that show associations with obesity-related traits (Table 9.1). Reassuringly, GWASs have confirmed associations with BMI for some of these loci (*MC4R*, *BDNF*, and *PCSK1*), whereas they have not done so for the remaining candidates. Lack of replication in GWASs may reflect a lack of coverage in the region (*MTNR1B*), a difference in the model of association (*ENPP1* and *LCT*), or the stringent significance threshold used in GWASs, which does not take into account a priori biological knowledge.

In addition to being sufficiently powered to identify common variants for obesity-related traits, large-scale candidate gene studies are also capable of refuting associations between variants in candidate genes and obesity-related traits. The candidate gene study for *LEPR* in CoLAUS discussed in Section 9.2.10 clearly illustrates the importance of studying all variation in a gene, as *LEPR* would have been discarded as irrelevant for obesity based on results from K109R, Q223R, and K656N alone.[56]

9.3 EVIDENCE FROM GENOME-WIDE ASSOCIATION STUDIES

Advances in the field of obesity genetics have largely been driven by technological developments, with improved technology allowing genotyping of many variants in many individuals simultaneously and in little time. These improvements have facilitated the development of catalogs with detailed information on human genetic variation, such as the Human Genome Project,[58] the International HapMap Project,[59] and, more recently, the 1000 Genomes Project.[60]

Since the first GWASs for obesity-related traits were reported in 2007, at least 50 loci have been identified that are robustly associated with BMI, BF%, WC, waist-to-hip ratio (WHR), VAT and subcutaneous adipose tissue (SAT), and early-onset and/or extreme obesity. These efforts have so far mainly focused on adults of European descent. However, studies in children and in individuals of East Asian and African descent are beginning to be reported as well. Table 9.2 lists loci that have shown genome-wide significant associations with obesity-related traits in GWASs.

9.3.1 Study Design of Genome-Wide Association Studies

A GWAS usually consists of (at least) two stages: a discovery stage and a follow-up stage. The discovery stage comprises the actual GWAS, in which individual studies examine the association between ~2.5 million SNPs and a continuous or dichotomous outcome. Results files of independent studies are subsequently meta-analyzed to obtain summary statistics that represent the association in all studies combined.

To avoid false-positive findings and to maximize the discovery of novel loci, the most significant SNPs within promising loci are taken forward for evaluation in an independent sample, ideally of a similar size as the discovery sample. SNPs for which associations reach $p < 5 \times 10^{-8}$ after a combined meta-analysis of both stages are considered "confirmed loci," representing an α of 0.05 after adjusting for 1 million independent tests.

Confirmed loci are often further examined in a third stage, in which associations with related traits or diseases are assessed.

9.3.2 Genome-Wide Association Studies for BMI

BMI provides an inexpensive and noninvasive proxy measure for overall adiposity and is available in many studies. So far, five waves of GWASs have identified variants in 32 loci that are robustly associated with BMI in Europeans and

TABLE 9.2
Loci That Showed Genome-Wide Significant Associations with Obesity-Related Traits in GWASs

SNP	Near Gene(s)	Chr	Alleles			Per Effect Allele Effect					Discovery Study
			Effect	Other	EAF	Beta	SE	r^2(%)	*N*	*p*	
BMI, individuals of European descent[a]											
rs1558902	*FTO*/**/****	16	a	t	0.42	0.39	0.02	0.34	192,344	4.80×10^{-120}	Frayling et al.,[61] Scuteri et al.[62]
rs2867125	*TMEM18****	2	c	t	0.83	0.31	0.03	0.15	197,806	2.77×10^{-49}	Willer et al.,[66] Thorleifsson et al.[67]
rs571312	*MC4R*/****	18	a	c	0.24	0.23	0.03	0.10	203,600	6.43×10^{-42}	Loos et al.,[63] Chambers et al.[64]
rs10938397	*GNPDA2*	4	g	a	0.43	0.18	0.02	0.08	197,008	3.78×10^{-31}	Willer et al.[66]
rs10767664	*BDNF*/****	11	a	t	0.78	0.19	0.03	0.07	204,158	4.69×10^{-26}	Thorleifsson et al.[67]
rs543874	*SEC16B*/****	1	g	a	0.19	0.22	0.03	0.07	179,414	3.56×10^{-23}	Thorleifsson et al.[67]
rs2815752	*NEGR1*	1	a	g	0.61	0.13	0.02	0.04	198,380	1.61×10^{-22}	Willer et al.,[66] Thorleifsson et al.[67]
rs713586	*RBJ/ADCY3/POMC/ */****	2	c	t	0.47	0.14	0.02	0.06	230,748	6.17×10^{-22}	Speliotes et al.[30]
rs12444979	*GPRC5B*	16	c	t	0.87	0.17	0.03	0.04	239,715	2.91×10^{-21}	Speliotes et al.[30]
rs7359397	*SH2B1*	16	t	c	0.40	0.15	0.02	0.05	204,309	1.88×10^{-20}	Willer et al.,[66] Thorleifsson et al.[67]
rs987237	*TFAP2B*****	6	g	a	0.18	0.13	0.03	0.03	195,776	2.90×10^{-20}	Speliotes et al.[30]
rs2241423	*MAP2K5**	15	g	a	0.78	0.13	0.02	0.03	227,950	1.19×10^{-18}	Speliotes et al. [30]
rs9816226	*ETV5/DGKG*	3	t	a	0.82	0.14	0.03	0.03	196,221	1.69×10^{-18}	Thorleifsson et al.[67]
rs7138803	*BCDIN3D/FAIM2****	12	a	g	0.38	0.12	0.02	0.04	200,064	1.82×10^{-17}	Thorleifsson et al.[67]
rs2287019	*QPCTL/GIPR**	19	c	t	0.80	0.15	0.03	0.04	194,564	1.88×10^{-16}	Speliotes et al.[30]
rs1514175	*TNNI3K****	1	a	g	0.43	0.07	0.02	0.02	227,900	8.16×10^{-14}	Speliotes et al.[30]
rs13107325	*SLC39A8*	4	t	c	0.07	0.19	0.04	0.03	245,378	1.50×10^{-13}	Speliotes et al.[30]
rs2112347	*FLJ35779*	5	t	g	0.63	0.10	0.02	0.02	231,729	2.17×10^{-13}	Speliotes et al.[30]
rs10968576	*LRRN6C*	9	g	a	0.31	0.11	0.02	0.02	216,916	2.65×10^{-13}	Speliotes et al.[30]
rs3817334	*MTCH2*	11	t	c	0.41	0.06	0.02	0.01	191,943	1.59×10^{-12}	Willer et al.[66]
rs3810291	*TMEM160*	19	a	g	0.67	0.09	0.02	0.02	233,512	1.64×10^{-12}	Speliotes et al.[30]
rs887912	*FANCL*	2	t	c	0.29	0.10	0.02	0.03	242,807	1.79×10^{-12}	Speliotes et al.[30]
rs10150332	*NRXN3*****	14	c	t	0.21	0.13	0.03	0.02	183,022	2.75×10^{-11}	Speliotes et al.[30]
rs13078807	*CADM2*	3	g	a	0.20	0.10	0.02	0.02	237,404	3.94×10^{-11}	Speliotes et al.[30]
rs11847697	*PRKD1*	14	t	c	0.04	0.17	0.05	0.01	241,667	5.76×10^{-11}	Speliotes et al.[30]
rs2890652	*LRP1B*	2	c	t	0.18	0.09	0.03	0.02	209,068	1.35×10^{-10}	Speliotes et al.[30]
rs1555543	*PTBP2*	1	c	a	0.59	0.06	0.02	0.01	243,013	3.68×10^{-10}	Speliotes et al.[30]
rs4771122	*MTIF3*	13	g	a	0.24	0.09	0.03	0.02	198,577	9.48×10^{-10}	Speliotes et al.[30]
rs4836133	*ZNF608*	5	a	c	0.48	0.07	0.02	0.01	241,999	1.97×10^{-9}	Speliotes et al.[30]
rs4929949	*RPL27A*	11	c	t	0.52	0.06	0.02	0.01	249,791	2.80×10^{-9}	Speliotes et al.[30]
rs29941	*KCTD15*	19	g	a	0.67	0.06	0.02	0.00	192,872	3.01×10^{-9}	Willer et al.,[66] Thorleifsson et al.[67]
rs206936	*NUDT3*	6	g	a	0.21	0.06	0.02	0.01	249,777	3.02×10^{-8}	Speliotes et al.[30]
BMI, individuals of East Asian descent[b]											
rs2206734	*CDKAL1*	6	c	t	0.59	0.04	0.01	0.06	62,245	1.40×10^{-11}	Okada et al.,[16] Wen et al.[17]
rs11142387	*KLF9*	9	c	a	0.46	0.03	0.01	0.04	62,245	1.30×10^{-9}	Okada et al.[16]
rs261967	*PCSK1*	5	c	a	0.41	0.04	0.01	0.07	27,715	5.13×10^{-9}	Wen et al.[17]
rs12597579	*GP2*	16	c	t	0.80	0.04	0.01	0.05	27,715	1.02×10^{-8}	Wen et al.[17]
Body fat percentage, individuals of European descent[c]											
rs2943650	*IRS1*	2	c	t	0.36	0.16	0.05	0.03	68,593	6.00×10^{-9}	Kilpelainen et al.[71]
rs534870	*SPRY2*	13	g	a	0.30	0.14	0.05	0.02	63,273	3.20×10^{-8}	Kilpelainen et al.[71]
Waist circumference, individuals of European descent[b]											
rs7826222	*MSRA*	8	g	c	0.18	0.04	0.01	—	80,210	8.89×10^{-9}	Lindgren et al.[76]
Waist-to-hip ratio adjusted for BMI, individuals of European descent[b]											
rs9491696	*RSPO3*	6	g	c	0.48	0.05	—	—	190,746	1.84×10^{-40}	Heid et al.[79]
rs6905288	*VEGFA*	6	a	g	0.56	0.04	—	—	172,559	5.88×10^{-25}	Heid et al.[79]

TABLE 9.2 (*Continued*)
Loci That Showed Genome-Wide Significant Associations with Obesity-Related Traits in GWASs

			Alleles			Per Effect Allele Effect					
SNP	**Near Gene(s)**	**Chr**	**Effect**	**Other**	**EAF**	**Beta**	**SE**	r^2(%)	***N***	***p***	**Discovery Study**
rs984222	*TBX15/WARS2*	1	g	c	0.64	0.03	—	—	186,790	8.69×10^{-25}	Heid et al.[79]
rs1055144	*NFE2L3*	7	t	c	0.21	0.04	—	—	190,781	9.97×10^{-25}	Heid et al.[79]
rs10195252	*GRB14*	2	t	c	0.60	0.04	—	—	179,568	2.09×10^{-24}	Heid et al.[79]
rs4846567	*LYPLAL1*	1	g	t	0.72	0.03	—	—	168,987	6.89×10^{-21}	Lindgren et al.[76]
rs1011731	*DNM3/PIGC*	1	g	a	0.43	0.03	—	—	169,112	9.51×10^{-18}	Heid et al.[79]
rs718314	*ITPR2/SSPN*	12	g	a	0.26	0.03	—	—	184,670	1.14×10^{-17}	Heid et al.[79]
rs1294421	*LY86*	6	g	t	0.61	0.03	—	—	179,343	1.75×10^{-17}	Heid et al.[79]
rs1443512	*HOXC13*	12	a	c	0.24	0.03	—	—	189,518	6.38×10^{-17}	Heid et al.[79]
rs6795735	*ADAMTS9*	3	c	t	0.59	0.03	—	—	161,642	9.79×10^{-14}	Heid et al.[79]
rs4823006	*ZNRF3/KREMEN1*	22	a	g	0.57	0.02	—	—	170,997	1.10×10^{-11}	Heid et al.[79]
rs6784615	*NISCH/STAB1*	3	t	c	0.94	0.04	—	—	185,887	3.84×10^{-10}	Heid et al.[79]
rs6861681	*CPEB4*	5	a	g	0.34	0.02	—	—	162,886	1.91×10^{-9}	Heid et al.[79]
						Waist-to-hip ratio, individuals of East Asian descent[d]					
rs2074356	*C12orf51*	12	c	t	0.85	—	—	—	16,703	7.80×10^{-12}	Cho et al.[77]
						Visceral-to-subcutaneous adipose tissue ratio, individuals of European descent[d]					
rs11118316	*LYPLAL1*	1	a	g	0.44	—	—	—	10,577	3.13×10^{-9}	Fox et al.[80]
						Visceral adipose tissue in women, individuals of European descent[d]					
rs1659258	*THNSL2*	2	a	g	0.92	—	—	—	5560	1.58×10^{-8}	Fox et al.[80]
						Extreme and/or early-onset obesity, individuals of European descent[e]					
rs1424233	*MAF*	16	a	g	0.48	—	—	—	3477 cases, 3827 controls	3.80×10^{-13}	Meyre et al.[82]
rs17150703	*TNKS/MSRA*	8	a	g	0.11	—	—	—	2319 cases, 3080 controls, 715 nuclear families	1.85×10^{-8}	Scherag et al.[84]
rs9568856	*OLFM4*	13	a	g	0.16	0.20	0.06	—	8348 cases, 12,401 controls	1.82×10^{-9}	Bradfield et al.[85]
rs9299	*HOXB5*	17	t	c	0.65	0.13	0.04	—	8348 cases, 12,401 controls	3.54×10^{-9}	Bradfield et al.[85]

Notes: Effect allele, obesity-susceptibility-increasing allele; EAF, frequency of the obesity-susceptibility-increasing allele; other allele, allele associated with lower obesity susceptibility; SE, standard error; SNP, single-nucleotide polymorphism. For each trait, summary statistics are shown as provided in the largest study to date (Speliotes et al. for BMI in Europeans, Okada et al. for BMI in East Asians [for rs2206734], Lindgren et al. for WC, Heid et al. for WHR adjusted for BMI [for rs4846567]); beta and SE are from stage 2/replication data only.

[a] Beta and SE expressed in kg/m^2.

[b] Beta and SE expressed in SD per effect allele (converted from percentage increase for rs261967 and rs12597579[17] using data from the *CDKAL1* locus, which is available in Okada et al.[16] and Wen et al.[17]).

[c] Beta and SE expressed in %.

[d] Beta and SE are available only for stage 1 or stage 1 + 2.

[e] Beta and SE are available only for stage 1 or stage 1 + 2 where missing and represent the natural log of the odds ratio where provided.

*Locus also reached genome-wide significance for association with BMI in East Asians.

**Locus also reached genome-wide significance for association with body fat percentage in Europeans.

***Locus also reached genome-wide significance for association with early-onset and/or extreme obesity in Europeans.

****Locus also reached genome-wide significance for association with waist circumference in Europeans.

in 4 loci that are robustly associated with BMI in East Asian individuals.

In the first wave, two GWASs independently identified associations with BMI for a locus in the fat mass and obesity-associated (*FTO*) gene. First, a GWAS for type 2 diabetes identified variants in intron 1 of *FTO* that were associated with the risk of type 2 diabetes. These associations were abolished after adjusting for BMI, suggesting mediation by adiposity.[61] Replication in data from 38,759 individuals confirmed the association between the lead SNP in *FTO* and BMI. Within weeks, the first GWAS specifically aiming to identify loci for BMI also identified the *FTO* locus in a discovery set of 4741 Sardinians and a follow-up stage with data from 2335 individuals.[62]

Quadrupling the size of the discovery stage ($N = 16{,}876$) in the second wave resulted in confirmation of the *FTO* locus and the discovery of one additional locus, located ~188 kb downstream of *MC4R*.[63] At the same time, a locus in high LD

with the near-*MC4R* locus ($r^2_{LD} > 0.75$) was also identified in an independent two-stage study with a discovery stage that included data from 2684 individuals of Asian-Indian ancestry and a follow-up stage with data from 11,955 individuals of Asian-Indian and European ancestry.[64]

In the third wave, the results of 15 GWASs were combined in the Genomic Investigation of Anthropometric Traits (GIANT) consortium, which aims to identify loci for anthropometric traits such as BMI, height, WC, and WHR.[65] Associations with BMI were confirmed for the *FTO* and near-*MC4R* loci, and six additional loci were identified after a combined meta-analysis of results from a discovery stage with data from 32,387 individuals and a follow-up stage with data from over 59,000 individuals.[66] The previously unanticipated loci were located near neuronal growth regulator 1 (*NEGR1*), near transmembrane protein 18 (*TMEM18*), in Src homology 2 (SH2B) adaptor protein 1 (*SH2B1*), near potassium channel tetramerization domain containing 15 (*KCTD15*), near glucosamine-6-phosphate deaminase 2 (*GNPDA2*), and in mitochondrial carrier 2 (*MTCH2*).[66] Simultaneously, results from 30,232 Europeans and 1,160 African-Americans were meta-analyzed at deCODE Genetics. After follow-up in a sample of 37,973 additional individuals, associations with BMI were confirmed for variants in or near *FTO*, *MC4R*, *NEGR1*, *TMEM18*, *SH2B1*, and *KCTD15*, as well as in four additional loci: in protein transport protein SEC16 homolog B (*SEC16B*); between ets variant 5 (*ETV5*) and diacylglycerol kinase, gamma 90kDa (*DGKG*); in *BDNF*; and between bicoid-interacting protein 3 homolog (BCDIN3) domain containing (*BCDIN3D*) and Fas (tumor necrosis factor receptor superfamily member 6) apoptotic inhibitory molecule 2 (*FAIM2*).[67]

In the fourth wave of GWASs for BMI, the GIANT consortium quadrupled its discovery stage to include data from 123,865 individuals. After a combined meta-analysis of the discovery stage and follow-up data from 125,931 additional individuals of European descent, associations with BMI were confirmed for 32 loci. These included the 12 previously identified loci, 2 loci that had already been identified in GWASs for WC (transcription factor–activating protein 2 [AP-2] beta [*TFAP2B*], neurexin 3 [*NRXN3*]), and 18 novel loci (Table 9.2).

Wave five comprised two large-scale GWASs that have recently examined associations with BMI in individuals of East Asian descent.[16,17] The Asian Genetic Epidemiology Network (AGEN) consortium[68] identified three novel loci for BMI after a combined meta-analysis of data from 83,048 individuals. These loci were located in cyclin-dependent kinase 5 (CDK5) regulatory subunit–associated protein-like 1 (*CDKAL1*), near *PCSK1*, and near glycoprotein 2 (*GP2*).[17] At the same time, researchers from RIKEN in Japan identified two loci for BMI, one in *CDKAL1* and one near Kruppel-like factor 9 (*KLF9*), after a combined meta-analysis of results from a discovery stage with data from 26,620 Japanese individuals and a follow-up stage with data from 35,625 East Asian individuals.[16] Associations with BMI were confirmed for previously identified loci in or near *FTO*, *MC4R*, *SEC16B*, *BDNF*, glutaminyl-peptide cyclotransferase-like (*QPCTL*)/gastric inhibitory polypeptide receptor (*GIPR*), rab and DnaJ domain containing (*RBJ*) (now known as *DNAJC27*, DnaJ homolog, subfamily C, member 27)/adenylate cyclase 3 (*ADCY3*)/proopiomelanocortin (*POMC*), and mitogen-activated protein kinase kinase 5 (*MAP2K5*).[16,17]

Two GWASs in individuals of African descent have not identified novel loci for BMI.[69,70] This likely reflects low statistical power due to small sample size, as these studies each included data from less than 2000 individuals in the discovery stage and had a combined discovery and follow-up data set of less than 5000 individuals.

Taken together, 5 waves of GWASs for BMI have identified 32 loci that show robust associations with BMI in adults of European descent and 4 additional loci that are consistently associated with BMI in adults of East Asian ancestry.

9.3.3 Genome-Wide Association Studies for Body Fat Percentage

Despite the advantages of using BMI as a measure of overall adiposity, BMI's most important shortcoming is that it cannot distinguish between fat mass and fat-free mass. In comparison, BF% provides a more accurate measure of adiposity.

So far, results from one meta-analysis of GWASs for BF% have been described, combining the results from 36,626 (discovery) and 39,576 (follow-up) individuals.[71] Besides the *FTO* locus, associations with BF% reached significance for gene loci near insulin receptor substrate 1 (*IRS1*) and near sprouty homologue 2 (*SPRY2*).[71]

9.3.4 Genome-Wide Association Studies for Body Fat Distribution

Epidemiological evidence has suggested that an excess of abdominally stored fat is associated with mortality, independently of overall adiposity.[72] WC and WHR are widely used as noninvasive measures to assess central adiposity. While WC and WHR are inexpensive and easily obtained, they do not allow the distinction between SAT and the metabolically more harmful VAT. Therefore, a further distinction between VAT and SAT is desirable to improve metabolic and cardiovascular risk prediction,[73,74] but these measures are scarcely available as they require computed tomography scans. Three waves of GWASs for body fat distribution have so far been reported: two waves of GWASs for WC and WHR and one wave for VAT, SAT, and their ratio (VAT/SAT).

In the first wave, three meta-analyses of GWASs described associations with WC[75,76] and WHR.[76,77]

- In an effort that was coordinated by the GIANT consortium, the *FTO* and near-*MC4R* loci were shown to be associated with WC, confirming a role for these loci in obesity susceptibility in data from 38,580 (discovery) and 70,689 individuals (follow-up).[76] Moreover, genetic variants in *TFAP2B*

and near methionine sulfoxide reductase A (*MSRA*) were also associated with WC, while a variant near lysophospholipase-like 1 (*LYPLAL1*) was significantly associated with WHR in women only.[76]

- In a second effort that was organized by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium,[78] associations with WC were assessed in a combined discovery and follow-up population of 70,014 individuals. In addition to the *FTO* and near-*MC4R* loci, a locus in *NRXN3* was shown to be associated with WC.[75]
- A third study identified a locus in chromosome 12 open reading frame 51 (*C12orf51*) (now known as HECT domain containing E3 ubiquitin protein ligase 4) that showed evidence of association with WHR in a two-stage GWAS including data from 16,703 Koreans.[77] The lead SNP in the *C12orf51* locus (rs2074356) is monomorphic in Europeans. The *TFAP2B*, near-*MSRA*, and *NRXN3* loci were also associated with BMI in the discovery studies[75,76] and thus appear to represent general adiposity loci, as was confirmed by a significant association with BMI in a subsequent study for the *TFAP2B* and *NRXN3* loci.[30] However, the near-*LYPLAL1* and *C12orf51* loci were not associated with BMI and appear to represent loci purely associated with body fat distribution.[76,77]

In the second wave of discoveries, the GIANT and CHARGE consortia combined efforts to focus on associations with body fat distribution independently of overall adiposity. Therefore, they examined associations with WHR adjusted for BMI in a discovery stage with data from 77,167 individuals. The near-*LYPLAL1* locus was confirmed and 13 additional loci were identified as being associated with WHR after follow-up of the most significant loci in data from an additional 113,636 individuals. None of the 14 loci were previously identified in GWASs for BMI. Secondary analyses showed that associations were significantly more pronounced in women than in men for 7 of the 14 loci.[79]

In the third wave of discoveries, a GWAS for computed tomography–derived VAT, SAT, and VAT/SAT ratio recently reported genome-wide significant associations with two loci in data from 5560 women and 4997 men from four population-based studies.[80] Interestingly, a locus near *LYPLAL1* was significantly associated with the VAT/SAT ratio in data from men and women combined, indicating that this locus affects the propensity to store fat viscerally rather than subcutaneously. A trend toward an association with the VAT/SAT ratio was also observed in data from men and women separately ($p < 1.0 \times 10^{-5}$). This VAT/SAT locus near *LYPLAL1* is only in low LD ($r^2_{LD} = 0.285$) with the female-specific locus near-*LYPLAL1* for BMI-adjusted WHR, suggesting that they may have independent and sex-specific effects. In addition to the near-*LYPLAL1* locus, a locus near threonine synthase-like 2 (*THNSL2*) was identified to be associated with VAT in women but not in men.

Taken together, GWASs for WHR adjusted for BMI, the VAT/SAT ratio, and VAT have so far identified 16 loci that are specifically associated with body fat distribution, but not overall adiposity. One additional locus was associated with WHR in East Asians but was monomorphic in Europeans.

9.3.5 Genome-Wide Association Studies for Early-Onset and Extreme Obesity

Individuals with early-onset or extreme obesity are anticipated to be enriched for variants that predispose to obesity in the general population. As such, GWASs that compare genotypes of cases with early-onset or extreme obesity with normal-weight or lean controls may prove an effective way of finding loci for common obesity. So far, results from four such studies have been reported.

Whereas the first study confirmed associations only for a locus in *FTO*,[81] the second GWAS for early-onset and extreme obesity confirmed associations with the *FTO* and near-*MC4R* loci and presented results for four additional loci based on results of a combined meta-analysis of results from a discovery and follow-up stage with data from 3447 obese cases and 3827 normal-weight controls.[82] Significant association was observed with early-onset and extreme obesity for a locus near v-maf musculoaponeurotic fibrosarcoma oncogene homolog (*MAF*),[82] whereas associations for loci in Niemann–Pick disease, type C1 (*NPC1*), near prolactin, and near phosphotriesterase related just failed to reach genome-wide significance. Associations of these loci with obesity-related traits could not be confirmed in data from up to 33,045 population-based adults and children, except for a nominally significant association of rs1805081 in *NPC1* with BF%.[83] As such, these loci may be specifically associated with early-onset and extreme obesity.

The third GWAS specifically aiming to identify loci for early-onset and extreme obesity included data from 2319 extremely obese children and adolescents, 3080 normal-weight or underweight controls, and 715 nuclear families with at least 1 extremely obese offspring. Associations with obesity status were confirmed for the *FTO*, near-*MC4R*, and near-*TMEM18* loci and reached significance for one additional locus near tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase (*TNKS*)/*MSRA*.[84] The *TNKS*/*MSRA* locus was not associated with BMI in the discovery study[84] or in the largest GWAS for BMI reported so far.[30] However, this locus is in low LD with the locus near *MSRA* ($r^2_{LD} = 0.047$, distance 114 kb), which was identified in a GWAS for WC that also showed suggestive evidence for association with BMI.[76]

A fourth GWAS specifically aimed to identify loci for common childhood obesity.[85] In data from 5530 obese children and 8318 lean controls from 14 studies, associations of the previously identified loci in or near *FTO*, *MC4R*, *TMEM18*, *SEC16B*, *BCDIN3D*/*FAIM2*, *RBJ*/*ADCY3*/*POMC*, and troponin I type 3–interacting kinase (*TNNI3K*) were confirmed. Furthermore, a meta-analysis that combined the GWAS results with those from additional 2818 obese cases and 4083 lean controls identified two novel loci that were associated

with obesity susceptibility in children. These loci, located near olfactomedin 4 (*OLFM4*) and in homeobox B5 (*HOXB5*), also showed evidence of association with extreme obesity during childhood[85] and showed suggestive evidence of association with adult BMI.[30] Associations of the *TNKS/MSRA* locus with childhood obesity were not confirmed after data from the original discovery study[84] were excluded from the meta-analysis.[85]

Taken together, four GWASs for early-onset and extreme obesity confirmed associations for loci in or near *FTO*, *MC4R*, *TMEM18*, *SEC16B*, *BCDIN3D/FAIM2*, *RBJ/ADCY3/POMC*, and *TNNI3K* and identified four loci that were not previously shown to be associated with obesity-related traits. Subsequent efforts, however, could not confirm associations for the loci near *MAF*[84] and *TNKS/MSRA*,[85] and only the near-*OLFM4* and *HOXB5* loci appear to be unequivocally associated with common childhood obesity.

9.4 CLINICAL RELEVANCE OF LOCI ESTABLISHED IN GENOME-WIDE ASSOCIATION STUDIES

9.4.1 Effect Sizes and Explained Variance of Established Loci

In spite of highly statistically significant associations, effect sizes of confirmed loci tend to be small. The largest effect size has been observed for the *FTO* locus, for which each effect allele increases BMI by 0.26–0.66 kg/m^2, corresponding with 750–1900 g of body weight for an adult 1.7 m tall.[30] Each additional effect allele in the *FTO* locus is also associated with BF% increases of 0.29% in men and 0.39% in women, which, based on participant characteristics of the discovery study, corresponds to ~240 g of fat in men and ~270 g of fat in women.[71]

When all 32 loci that have so far been identified in GWASs for BMI in Europeans are combined in a score, each additional effect allele on average increases BMI by 0.17 kg/m^2 or 490 g of body weight in an adult 1.7 m tall. Effect sizes are of a similar magnitude for the four BMI loci that were identified in East Asians (range 0.028–0.042 standard deviation [SD]/effect allele),[16,17] the two additional BF% loci (0.023–0.025 SD/effect allele),[71] and the 14 confirmed WHR loci (range 0.019–0.045 SD/effect allele).[79]

Together, lead SNPs of the 32 loci that were identified in Europeans explain ~1.45% of the variance in BMI (Table 9.2) and have a low predictive ability for obesity (area under the receiver operating characteristic curve 0.574).[30] The variance in BMI explained by the four loci discovered in the fifth wave of discoveries is higher in East Asians (range 0.04%–0.07%) than in Europeans (range 0.00%–0.01%).[17,30] The *FTO* locus explains more of the variance in Europeans (0.34%) than in East Asians (0.18%), likely because of a higher effect allele frequency in the former (42% vs. 17%).[17,30] The WHR loci together explain ~1% of the variance in WHR in men and women combined,[79] whereas the three known BF% loci together explain ~0.16% of the variance in BF%.[71]

9.4.2 Impact of Established Loci in Non-European Populations

In the fifth wave of GWAS studies for BMI, large-scale efforts by researchers from the AGEN consortium and RIKEN identified four novel loci in or near *CDKAL1*, *PCSK1*, *GP2*, and *KLF9* that showed evidence of association with BMI in East Asians.[16,17] In addition, associations with BMI were confirmed for previously identified loci in or near *FTO*, *MC4R*, *SEC16B*, *BDNF*, *QPCTL/GIPR*, *RBJ/ADCY3/POMC*, and *MAP2K5*.[16,17] Earlier replication efforts already convincingly confirmed associations with BMI in East Asians for loci in or near *GNPDA2*,[86,87] *KCTD15*,[86] *ETV5*,[86,87] *NEGR1*,[86] *TMEM18*,[87] and *MSRA*,[88] implying that associations with BMI can be generalized beyond European ancestry for at least 13 of the 32 loci that were identified as being associated with BMI in Europeans.[30] In line with this, the associations of the *FTO* and near-*MC4R* loci with BMI have now been convincingly confirmed in populations of South Asian[88] and African des cent.[67,69,89] Future studies with larger samples are required to assess whether associations of the remaining obesity-susceptibility loci can also be generalized.

9.4.3 Impact of Established Loci in Children and Adolescents

Before a targeted GWAS for common childhood obesity was published recently,[85] several follow-up studies had already examined whether the BMI-associated loci begin affecting obesity-related traits during childhood and adolescence. A meta-analysis including data from nearly 13,000 children showed that the effect of the *FTO* and near-*MC4R* loci is of similar magnitude in children and adolescents of European descent as in adults.[90] Longitudinal studies showed that the influence of these loci increases throughout childhood, peaks at around age 20 years, and subsequently weakens throughout adulthood.[91–93] The *FTO*[94,95] and near-*MC4R*[96,97] loci were also associated with measures of adiposity in children of Chinese and African descent.

For loci that were identified in the third wave of GWASs for BMI,[66,67] associations have been confirmed in children and adolescents of European descent for the loci in or near *TMEM18*,[90,98,99] *GNPDA2*,[90,98] *NEGR1*,[90,98] *SEC16B*,[90] *BCDIN3D/FAIM2*,[90] *BDNF*,[90,98] *KCTD15*,[90,98] and *ETV5/DGKG*.[98] These findings are in line with genome-wide significant associations of the loci in or near *TMEM18*, *SEC16B*, and *BCDIN3D/FAIM2*[85] in a recent meta-analysis of GWAS for childhood obesity.[85] In children of European descent, associations could previously not be confirmed for loci in or near *MTCH2* and *SH2B1*.[90,98] A longitudinal study in which 7146 children were followed from birth until age 11 years showed that a genetic predisposition score comprising 8 of the 12 BMI-associated loci identified in wave three is positively associated with BMI, weight, and height from as early as 6 weeks of age,[98] suggesting a role for these loci in growth and development. Loci in or near *TMEM18*, *SH2B1*, *BDNF*, *GNPDA2*, *BCDIN3D/FAIM2*, and *KCTD15* were

also associated with BMI and risk of obesity in Chinese children.[95,97,100]

All 32 BMI loci that were identified in the fourth wave of GWASs for BMI showed directionally consistent associations with BMI or risk of obesity in data from children and adolescents.[30] Of the loci that had not yet been identified in wave three,[66,67] associations for the loci in or near *RBJ/ADCY3/POMC*, *MAP2K5*, *TNNI3K*, solute carrier family 39, member 8 (*SLC39A8*), cell adhesion molecule 2 (*CADM2*), protein kinase D1 (*PRKD1*), polypyrimidine tract–binding protein 2 (*PTBP2*), mitochondrial translational initiation factor 3 (*MTIF3*), and ribosomal protein L27a (*RPL27A*) reached nominal significance.[30] These findings were further strengthened by genome-wide significant associations of the loci near *RBJ/ADCY3/POMC* and *TNNI3K* in a recent meta-analysis of GWAS for childhood obesity.[85]

Large-scale studies are required to establish the role of the BMI loci in childhood and adolescence, as the discovery study in adults was underpowered to confirm or refute associations in data from children and adolescents only. Unfortunately, associations with childhood obesity were not provided for 25 of the 32 loci that were previously identified as being associated with adult BMI.[85] Furthermore, no studies have so far assessed the role of the loci identified for BF% and WHR in children and adolescents.

9.4.4 Gene–Lifestyle Interactions

Obesity susceptibility results from an interaction between lifestyle factors and genetic predisposition.[101,102] The discovery of loci that are robustly associated with obesity susceptibility has increased interest in whether lifestyle can attenuate or exacerbate a genetic predisposition to obesity. Recently, a large-scale meta-analysis incorporating results from 218,166 adults showed that the effect size of each additional effect allele in *FTO* for BMI and risk of obesity is ~30% lower in physically active individuals than in physically inactive individuals.[103] In line with this, data from ~20,000 adults showed previously that each additional BMI-increasing allele across the 12 loci that were identified in wave three[66,67] has a ~60% lower effect size in physically active as compared with inactive individuals.[104] These results suggest that a healthy lifestyle can offset some of the genetic predisposition to obesity. The GWASs that have so far been reported for obesity-related traits have focused only on the main effects of genetic variants. Given the results described here, it seems likely that the true effects of established loci are larger in subgroups of the population with lifestyles that favor penetrance of their genetic predisposition.

9.4.5 Implications for the Etiology of Obesity

In spite of small effect sizes, the established obesity-susceptibility loci are anticipated to increase our understanding of the physiology underlying regulation of energy balance and body fat distribution by identifying previously unanticipated pathways. Ultimately, these loci may elucidate novel therapeutic targets. However, most established loci contain multiple genes, and deep-sequencing and fine-mapping efforts, as well as animal studies, are warranted to identify causal variants and genes within these loci. Only then can physiologists and biochemists start exploring their functional relevance for obesity susceptibility.

Most follow-up studies of obesity-susceptibility loci have focused on *FTO*. In mice, Fto was shown to be ubiquitously expressed, including in the hypothalamus.[105] A complete loss of Fto in mice led to postnatal growth retardation and a reduction in adiposity as well as fat-free mass.[106] In humans, homozygosity for a rare loss-of-function mutation in *FTO* (R316Q) also resulted in postnatal growth retardation as well as in abnormal development of several organ systems, including the central nervous system and the cardiovascular system.[107] While the presence of at least some functional FTO is vital for normal development, common variation in *FTO* plays a more subtle and currently incompletely understood role in regulating energy balance. So far, follow-up studies in humans have shown associations with appetite regulation and energy intake but not energy expenditure.[108–110] In mice, *Fto* expression in the arcuate nucleus of the hypothalamus was downregulated after a 48-hour fast and increased after 10 weeks of exposure to a high-fat diet.[111] Furthermore, an experimentally induced 2.5-fold overexpression of *Fto* in the arcuate nucleus reduced average daily food intake of mice by 14%, while knocking down *FTO* expression by 40% increased food intake by 16%. These results indicate that *FTO* may play an anorectic role in the central regulation of appetite.[111]

Of interest is that many loci that have been identified in GWASs for BMI map in or near genes that are highly expressed in the hypothalamus, supporting a role of these loci in the regulation of energy balance.[30,66,67] Furthermore, several loci harbor genes that are implicated in monogenic forms of obesity, such as *MC4R*,[53,112] *BDNF*,[53] *SH2B1*,[113] and *POMC*.[53,114]

Several loci that have been identified as being associated with BF%[71] and WHR[79] contain genes that likely influence adipocyte metabolism. For example, the BF%-decreasing allele of the near-*IRS1* locus is also associated with proportionally less SAT as opposed to VAT, at least in men.[71] Interestingly, the BF%-decreasing allele is also associated with higher triglyceride and lower HDL-cholesterol concentrations and with increased insulin resistance and risk of type 2 diabetes.[71] Furthermore, the WHR-increasing allele of the locus near the growth factor receptor-bound protein 14 (*GRB14*) is also associated with higher triglyceride and fasting insulin concentrations and with increased insulin resistance.[79] Finally, the locus near the ADAM metallopeptidase with thrombospondin type 1 motif, 9 gene (*ADAMTS9*) is also associated with insulin resistance in peripheral tissues[115] and with the risk of type 2 diabetes,[116] whereas the vascular endothelial growth factor A gene (*VEGFA*) is thought to play a role in adipogenesis.[117]

9.5 FUTURE RESEARCH

The obesity loci that have so far been identified in GWASs explain only a fraction of the predicted heritability. Identifying currently unanticipated loci, as well as causal

variants within established loci, will likely increase the explained variance in obesity-related traits substantially. Several strategies are anticipated to further increase our knowledge of obesity.

9.5.1 Extended Genome-Wide Association Studies

Metabochip is a customized array containing ~200,000 carefully selected SNPs, half of which reached subsignificant levels of association in previous GWASs of BMI, WHR, and a range of other metabolic and cardiovascular traits. The other half of the SNPs were selected to fine-map established loci. In addition, improved knowledge of human genetic variation acquired by large-scale sequencing efforts like the 1000 Genomes Project[118] has already led to the development of more dense genome wide arrays. These arrays cover variants with a minor allele frequency as low as 1% and provide improved coverage of common variants when compared with previously described arrays. Sequencing efforts like the 1000 Genomes Project also provide information on low-frequency variants and non-SNP variants that are associated with common obesity, such as copy number variants and insertions/deletion variants in or near *NEGR1*[66] and *SH2B1*,[113,119,120] as well as in the Prader–Willi syndrome–critical region on chromosome 15.[121] At the moment, 1000 Genomes information is used to reimpute existing data sets with GWA information, thereby increasing their resolution. Performing meta-analyses of existing GWASs that have been imputed using 1000 Genomes information, along with additional samples that have been genotyped using novel GWA arrays or Metabochip, will likely identify additional loci as well as causal variants within established loci.

9.5.2 Next-Generation Sequencing and Functional Follow-up

Next-generation sequencing efforts are anticipated to take gene discovery to the next level. Examining all available variants in extremes of the population may identify novel loci as well as identify causal variants within established loci. To this end, the UK10K project is currently comparing the genomes of 2000 extremely obese children and 4000 population-based individuals.

Functional follow-up in animal models can help pinpoint the causal genes within loci by selectively overexpressing or inactivating positional candidate genes, either at the whole-body or tissue level. Identifying causal genes within established loci may aid sequencing efforts by substantially reducing the region across which sequenced variants need to be examined.

9.5.3 Alternative Study Designs

Large-scale efforts in non-European populations,[16,17] as well as in children and adolescents,[85] may contribute to an increased understanding of obesity genetics. In addition, studying intermediate traits that predispose to energy imbalance, such as physical activity and the attitude toward eating, may provide new insights. Such intermediate traits may increase our understanding of obesity genetics when studied as an outcome or as an exposure in interaction with genetic information.

9.6 CONCLUSION

GWASs have revolutionized the search for obesity-susceptibility genes. While the candidate gene approach has only recently started to identify genes in which variants are unequivocally associated with obesity-related traits, GWASs have identified at least 50 loci within the past 5 years alone that are robustly associated with such traits. Future studies aiming to identify causal genes and variants within these loci are required before their relevance for obesity etiology can be established.

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10 Epigenetic Mechanisms in Obesity

Robert A. Waterland

CONTENTS

10.1 INTRODUCTION

Just as susceptibility to obesity is affected by genetics, it can also be affected by epigenetic mechanisms. The nascent field of epigenetics and obesity has generated considerable excitement, not only because environmental influences on epigenetics could partially explain the increasing prevalence of obesity in recent decades but also because, unlike genetic causes of obesity, epigenetic marks are inherently malleable, affording potential opportunities for therapeutic intervention. The overall hypothesis of this field is that interindividual epigenetic variation contributes to individual variation in adiposity. This chapter considers the evidence in support of this hypothesis and suggests priorities for future research.

10.2 EPIGENETICS AND HUMAN DISEASE

Epigenetics describes the study of mitotically heritable and stable alterations in gene expression potential that are not caused by changes in DNA sequence.[1] The distinct gene expression profiles, morphologies, and functional characteristics of the hundreds of different cell types in the human body are fundamentally regulated by epigenetic mechanisms established during embryonic, fetal, and early postnatal development. The molecular mechanisms that function synergistically to perpetuate cell type-specific epigenetic states include methylation of cytosines within CpG dinucleotides (i.e., cytosine followed by guanine), various N-terminal modifications (methylation, acetylation, etc.) of the histone proteins that package DNA in the nucleus, autoregulatory DNA-binding proteins, and noncoding RNA.[2–5] Over 25 years ago, Holliday proposed that just as genetic variation can cause cancer, so too might epigenetic variation.[6] This insight has proved correct; the important role of epigenetic dysregulation in cancer is now well established.[7] Indeed, because epigenetic mechanisms can essentially turn genes on or off, any disease with a genetic basis is equally likely to have an epigenetic basis.

Understanding epigenetic mechanisms in human disease, however, is significantly more complex than studying genetic pathogenesis. A major reason is the inherent tissue specificity of epigenetic regulation. As context for the study of epigenetics and human disease—including obesity—it is helpful to consider that genomic regions exhibiting interindividual epigenetic variation can generally be divided into two classes (Table 10.1). At metastable epialleles, found only infrequently in the human genome,[8] epigenetic regulation is established stochastically in the early embryo, then maintained during subsequent cellular differentiation, resulting in interindividual epigenetic variation that is not tissue-specific.[9,10] Analogous to genetic polymorphisms that can be assessed in peripheral blood DNA, epigenetic variation at metastable epialleles is consistent across all cells in the body. Conversely, the vast majority of interindividual epigenetic variation is limited to specific cell types. Given that such cell type-specific differentially methylated regions, for example, are much more common than metastable epialelles (Table 10.1), epigenetic variation at these loci is more likely to be associated with human disease, including obesity. The tissue specificity of epigenetic variation at these loci, however, means that epigenetic marks in peripheral blood DNA will in most cases not be indicative of epigenetic variation in tissues of primary importance to body weight regulation.

The goal of advancing our understanding of epigenetic mechanisms in human obesity (and other diseases) is further complicated by the multiple interactions among environment, genetics, epigenetics, and obesity (Figure 10.1). The effects of environment, moreover, must be considered in a developmental perspective; developmental periods when epigenetic mechanisms are undergoing establishment or maturation constitute critical windows when environment can affect these processes, with lifelong consequences.[11]

TABLE 10.1
Two Classes of Interindividual Epigenetic Variation

	Metastable Epialleles	Cell Type-Specific Differentially Methylated Regions
Tissue specificity	Little/none	Tissue-specific or cell type-specific
Developmental establishment	Early embryo	Fetal and early postnatal
Studying association with disease	Relatively simple	Difficult, especially in humans
Genomic prevalence	Rare	Widespread
Likely role in specific human disease	Occasional	Extensive

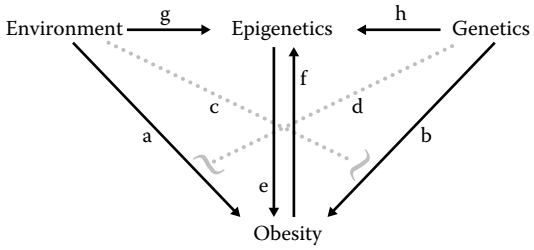

FIGURE 10.1 Epigenetic mechanisms in obesity must be considered in the framework of environmental and genetic influences. Environment and genetics affect the risk of obesity (pathways a and b), and gene–environment interactions (c, d) modify these effects. Environment and genetics can both also affect epigenetic processes (g, h). In particular, during critical developmental periods, transient environmental influences can induce persistent epigenetic alterations. When testing for associations between epigenetic variation and obesity, it must be recognized that interindividual epigenetic variation can be either a cause (e) or effect (f) of obesity.

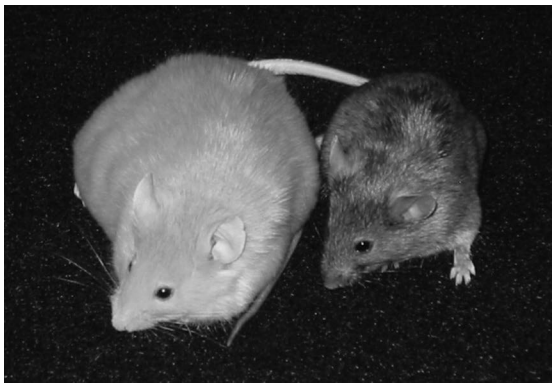

FIGURE 10.2 Genetically identical adult A^{vy}/a sisters with stochastic differences in DNA methylation at A^{vy} provide a compelling illustration that epigenetic dysregulation can cause obesity. (From Waterland RA, *J Pediatr*, 149, S137–42, 2006.)

10.3 EPIGENETIC DYSREGULATION AND OBESITY

These caveats notwithstanding, animal models and clinical studies have provided compelling evidence that epigenetic dysregulation causes obesity. Perhaps, the best characterized example is the murine *agouti* viable yellow (A^{vy}) metastable epiallele. The A^{vy} mutation was caused by the transposition of an intracisternal A particle (a retrotransposon common in the mouse genome) upstream of *agouti*. Normally expressed only in hair follicles, *agouti* encodes a paracrine signaling molecule that regulates the production of a yellow pigment in fur. The intracisternal A particle insertion has been shown both to induce a cryptic promoter that drives ectopic agouti expression and to cause dysregulated establishment of DNA methylation in the early embryo.[12] Consequently, within a single litter of isogenic A^{vy}/a mice, coat colors can range from yellow to brown (and all stages between), correlated with systemic hypomethylation or hypermethylation at A^{vy}, respectively. Because ectopically expressed agouti protein binds antagonistically to the melanocortin 4 receptor in the hypothalamus,[13] yellow A^{vy}/a mice also become hyperphagic and obese (Figure 10.2)

Cloned mice and other animals are often born with normal body size but develop adult-onset obesity.[14] It is thought that aberrant epigenetic reprogramming during somatic cell nuclear transfer results in obesity. Indeed, mice deficient for the histone 3 lysine-specific 9 demethylase Jhdm2a (also known as Kdm3a) developed obesity and metabolic syndrome,[15] indicating a direct link between epigenetic histone modification and obesity. Observational studies in mice have provided indirect evidence of a role for epigenetics in obesity; within an isogenic population of C57BL/6J mice provided ad libitum access to a high-fat diet, a twofold range of body weights and fourfold range of adiposity were observed.[16] Such variation among genetically identical mice in a controlled environment could be attributable to epigenetic mechanisms. Consistent with this conjecture, in a three-generation study in A^{vy}/a mice, a methyl donor supplement known to increase DNA methylation during development completely prevented the obesity-promoting effect of maternal obesity.[17]

Prader–Willi syndrome, a human neurodevelopmental disease characterized by hyperphagic obesity (among other symptoms), provides a clear demonstration that epigenetic dysregulation can cause human obesity. Although usually caused by a genomic deletion in chromosome 15, a subset of sporadic Prader–Willi cases results instead from inappropriate epigenetic silencing of the same chromosomal region.[18] A parent-of-origin effect was reported at a variable number of tandem repeat (VNTR) polymorphism upstream of the human insulin (*INS*) gene. Children who inherited the class 1 VNTR from their father (but not from their mother) had a twofold higher risk of early-onset obesity,[19] suggesting epigenetic silencing of the obesogenic allele when inherited from the mother (i.e., epigenetic protection from obesity). A recent case

report[20] described two monozygotic twin girls discordant for rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (a rare pediatric disorder). From the ages of 8–12 years, the isogenic twins followed dramatically different body weight trajectories, highlighting the possibility of epigenetic differences.

10.4 EPIGENETIC ANALYSIS OF "OBESITY GENES"

Given the clear potential for epigenetic dysregulation to cause obesity, numerous studies have characterized the epigenetic regulation of known "obesity genes." Of potential candidates,[21] the human gene encoding leptin (*LEP*) has been studied most extensively. An early in vitro study showed that the *LEP* promoter, heavily methylated in human preadipocytes, undergoes extensive demethylation as the cells differentiate toward adipocytes.[22] Because promoter DNA methylation is generally associated with transcriptional silencing, this study provided compelling evidence that epigenetic mechanisms at *LEP* are critical to the transcriptional regulation of this adipocyte-specific hormone. Subsequent studies confirmed that the *LEP* promoter is relatively hypomethylated in primary human adipocytes compared to peripheral blood lymphocytes or T cells[23] and in human adipose tissue compared to peripheral blood lymphocytes.[24] White adipose tissue comprises both adipocytes and stromal vascular cells; thus, it is somewhat surprising that apparently no studies have yet compared DNA methylation at *LEP* (or, indeed, other loci) between primary adipocyte and stromal vascular DNA. If, as expected based on the available data, the *LEP* promoter is methylated in stromal vascular and relatively unmethylated in adipocyte DNA, this cell-type specificity presents a major potential confound in studies of *LEP* methylation in obesity. Notably, in one of the few studies to avoid this potential confound, Milagro et al.[25] found slightly elevated methylation at the *Lep* promoter in DNA from isolated adipocytes of rats who were overweight because of a high-fat diet.

Extensive human and animal model data indicate that environmental influences during critical periods of development can dramatically alter lifelong obesity susceptibility.[26–28] Epigenetic changes at *Lep* and other candidate genes have been investigated as a potential mechanism to explain such "programming" of obesity. Jousse et al.[29] reported that mouse offspring of mothers fed a low-protein diet during pregnancy and lactation (LP) are lighter and leaner in adulthood. Finding significantly lower methylation at the *Lep* promoter in white adipose tissue DNA of the adult offspring of low-protein-fed mothers, the authors concluded that the early "nutritional stress resulted in the removal of methyls at CpGs located in the promoter of leptin." A more likely explanation, however, is suggested when one considers the cellular heterogeneity of white adipose tissue, as described earlier in this section. Because LP mice are leaner and have smaller adipocytes compared to controls, adipocyte DNA is "overrepresented" in LP white adipose tissue DNA. Relative hypomethylation of the *Lep* promoter in adipocytes relative to stromal vascular DNA would naturally result in lower *Lep* promoter methylation in white adipose tissue DNA of the LP mice. A subsequent study[30] reported alterations in specific histone modifications at the *Lep* and adiponectin (*Adipoq*) promoters in white adipose tissue in adult offspring of mouse dams fed a high-fat diet during pregnancy and lactation; the authors postulated that the early exposure to a high-fat diet might cause persistent epigenetic modifications. However, the epigenetic analyses were conducted on DNA from white adipose tissue instead of isolated adipocytes; thus, the excess adiposity of the high-fat offspring makes it likely that, again, the reported epigenetic differences simply reflect altered cellular composition of the white adipose tissue.

Pro-opiomelanocortin (POMC), a precursor of the alpha-MSH signaling molecule produced in the arcuate nucleus of the hypothalamus, plays a central role in regulation of food intake. Mutations in *POMC* have been associated with human obesity.[21] A recent study examined whether epigenetic variation at *POMC* might also predispose to human obesity. Kuehnen et al.[31] examined two CpG islands in *POMC*, one at the 5′ end and one overlapping the last exon. (CpG islands are clusters of high CpG density and are often associated with genes.) Unlike the 5′ island, the 3′ island was extensively methylated in peripheral blood DNA and was shown to contain a transition zone in which methylation dropped abruptly from nearly 100% to 0%. Interestingly, in obese adolescents, this methylation border was significantly extended toward the 3′ end of the gene, allowing methylation to overlap a P300 enhancer binding site; in vitro studies demonstrated that methylation in this small region inhibited *P300* binding and reduced *POMC* expression in peripheral blood. Although the general methylation pattern in DNA from postmortem human arcuate nucleus was shown to be similar to that in peripheral blood DNA, the authors were unable to obtain data on matched peripheral blood and hypothalamic DNA from the same individuals. Future studies will therefore be required to determine whether the interindividual epigenetic variation detectable at *POMC* in peripheral blood represents a systemic epigenetic signature affecting hypothalamic body weight regulation or whether, for example, the methylation differences found in peripheral blood of obese versus lean individuals are a consequence rather than a cause of obesity (Figure 10.1). This same question of causality is relevant to a recent study that reported subtle correlations between obesity and methylation at the solute carrier family 6, member 4 (*SLC6A4*) promoter (encoding serotonin transporter) in peripheral blood DNA of monozygotic twins.[32]

10.5 EPIGENETIC ANALYSIS OF ADIPOSE TISSUE AND HYPOTHALAMUS

Because of the inherent tissue specificity of most epigenetic regulation, understanding epigenetic mechanisms in obesity will require a focus on specific cell and tissue types with major roles in body weight regulation. Adipose tissue and hypothalamus have been studied most extensively in this regard,

and most epigenetic studies in adipose tissue have focused on the *LEP* gene, as described in Section 10.4. In one study that took a different approach,[33] the role of histone demethylation in adipocyte differentiation was explored in vitro. Knocking down the histone 3 lysine 4/lysine 9 demethylase Lsd1 (by small interfering RNA) markedly decreased differentiation of mouse preadipocytes to adipocytes, indicating that histone methylation at adipogenic genes plays a critical role in adipocyte differentiation. A subsequent in vitro study[34] used a genome-scale method to profile changes in DNA methylation as human preadipocytes differentiated to adipocytes. Several thousand genomic loci undergoing methylation change were identified, and several were validated by methylation-specific PCR. Many of the associated genes were involved in developmental processes and signaling pathways, providing compelling evidence that DNA methylation plays an important role in adipocyte development.

Several recent studies have focused on the hypothalamus to identify potential epigenetic mechanisms underlying developmental programming of obesity. In a classic model of early postnatal overnutrition, rodents are fostered shortly after birth to small litters of three to four pups. Compared to control rodents suckled in normal-size litters, small-litter offspring are heavier and fatter at weaning and remain so throughout life.[35] Plagemann et al.[36] studied DNA methylation at the neuropeptide Y (*Npy*) and *Pomc* promoters in the hypothalamus of postnatal day 21 (P21) small-litter and control rats. The *Npy* promoter was essentially unmethylated in both groups. In the *Pomc* promoter, however, methylation ranged from 1% to 20%, and 1 of the 20 CpG sites assayed was significantly more methylated in small-litter versus control rats. Given the considerable site-to-site variation, the physiological significance of this site-specific effect is unclear. Moreover, as the persistence of this effect was not evaluated, it is unknown whether this difference constitutes a stable epigenetic alteration. The same group subsequently reported higher methylation in the insulin receptor (*Insr*) promoter in hypothalamic DNA of P21 small-litter versus control rats.[37] The average CpG methylation in this region, however, was <1%, making it difficult to evaluate the physiological significance of the reported differences.

Effects of early *undernutrition* on epigenetic development in the hypothalamus have also been evaluated. Coupe et al.[38] studied the offspring of rat mothers fed a low-protein diet during pregnancy and lactation. At P12, they identified seven CpG sites on the 5′ edge of the *Pomc* promoter CpG island (200-bp upstream of the transcription start site) that were consistently hypomethylated in offspring of low-protein versus control dams. It was not reported whether this change persisted to adulthood. A persistent effect of maternal undernutrition on hypothalamic epigenetic regulation was recently reported, however, in a sheep model.[39] After a period of undernutrition around the time of mating, ewes were fed ad libitum for the remainder of pregnancy, and fetal tissues were collected at 131 days of gestation (just short of full term). Offspring of previously undernourished ewes showed relative hypomethylation and alterations in histone modifications at the *Pomc* promoter in hypothalamic DNA but no change in hypothalamic *Pomc* expression. At the glucocorticoid receptor (*GR*, also known as *NR3C1*, nuclear receptor subfamily 3, group C, member 1) promoter, lower DNA methylation and altered histone modifications in the hypothalamus were accompanied by increased *GR* expression.[39]

Whereas epigenetic analysis of adipose tissue is complicated by the presence of adipocyte and stromal vascular DNA, interpretation of epigenetic changes in whole hypothalamus is even more complicated. The hypothalamus comprises several different regions—or nuclei—with very different functions and gene expression patterns, and within each of these hypothalamic nuclei are diverse cell types.[40] Using microdissection in combination with clonal bisulfite sequencing, Hoivik et al.[41] recently identified specific gene regions that are hypomethylated in the ventromedial relative to the paraventricular nucleus of the mouse hypothalamus. Such data clearly indicate the need to study epigenetic variation not in whole hypothalamus but in specific hypothalamic nuclei. Although not directly related to obesity, recent studies have shown the utility of that approach. For example, social stress in mice appeared to reduce DNA methylation at specific CpG sites in the promoter of the corticotropin releasing hormone (*Crf*, also known as *Crh*) gene in the paraventricular nucleus,[42] and intrauterine position in female rats persistently affected estrogen receptor alpha (*Esr1*) expression and promoter DNA methylation in the ventromedial hypothalamus.[43]

10.6 EPIGENETIC MARKS IN PERIPHERAL BLOOD AS BIOMARKERS OR PREDICTORS OF OBESITY

Despite the dearth of knowledge about how epigenetic variation in peripheral blood DNA relates to that in tissues of greatest relevance to obesity, several recent studies have sought to identify locus-specific DNA methylation marks in human peripheral blood DNA that either predict or correlate with obesity. Feinberg et al.[44] used a genome-scale DNA methylation profiling technique to identify epigenetic variants in peripheral blood that are both stable (over 11 years) and associated with obesity. However, their assay was based on DNA digestion with the methylation-sensitive endonuclease McrBC; thus, a large proportion of the interindividual variation they detected is likely attributable to single-nucleotide polymorphisms affecting McrBC sites, rather than DNA methylation variants.[8] Indeed, single-nucleotide polymorphisms at some of the loci they identified were previously reported to associate with BMI.[44] In a prospective study, Godfrey et al.[45] sought to identify DNA methylation variants in cord blood (at birth) that predicted adiposity in childhood. They measured DNA methylation at multiple CpG sites of five candidate genes using Sequenom bisulfite sequencing. Cord blood DNA methylation at one CpG site 2-kb upstream of the retinoid X receptor alpha (*RXRA*) gene was found to correlate positively with fat mass at age 9, and this result was confirmed in a second independent cohort (age 6). A subsequent

study using an Illumina methylation microarray approach in 178 individuals, however, failed to detect methylation marks in cord blood that associate with fat mass at age 9.[46] In a study of obese and overweight men, Milagro et al.[47] used a commercial DNA methylation array in an attempt to identify epigenetic marks in peripheral blood mononuclear cells that predict response to a weight loss intervention. Although several associations were identified, the extremely small sample size (six "high responders" vs. six "low responders") makes it difficult to assess their significance.

10.7 WAY FORWARD

While we know epigenetic dysregulation can cause obesity,[13,14,18] the extent to which epigenetic mechanisms have contributed to the worldwide obesity epidemic remains unknown. The literature reviewed here—most published just in the past few years—both provides useful insights and points to obvious gaps in our knowledge. For example, decades of work into the genetics of obesity have identified many obesity genes.[21] If any of these loci behave like metastable epialleles, systemic epigenetic variation detectable in peripheral blood DNA could provide relatively simple tests of an epigenetic basis for common human obesity. The human *POMC* intragenic CpG island[31] is a promising potential candidate metastable epiallele, but more studies are needed. There is also some suggestion that the human *LEP* promoter exhibits systemic interindividual variation in DNA methylation.[48]

Given that most obesity-associated epigenetic variation, however, will occur only in specific tissues (Table 10.1), improved methods for probing specific cell and tissue types must be developed. White adipose tissue clearly plays an important role in body weight regulation and can be sampled with minimal invasiveness, making it an attractive tissue to study. More work is needed, however, to characterize the epigenetic differences between adipocytes and stromal vascular cells. If, as expected, these differences are extensive, future studies attempting to draw inferences about epigenetic dysregulation in adipocytes must examine DNA from isolated adipocytes rather than white adipose tissue. Likewise, a key priority is to obtain a more detailed understanding of epigenetic mechanisms in hypothalamic development and function. Not only will different hypothalamic nuclei (arcuate, paraventricular, etc.) need to be considered separately, but also the diverse neuronal subtypes within each of these are likely to be epigenetically specialized. Adding yet another level of complexity, the hypothalamus (like the brain in general) comprises roughly equal proportions of neurons and glia, which are epigenetically distinct.[49,50]

Whereas previous studies in this field have focused on adipose tissue and hypothalamus, epigenetic variation in many other tissues (e.g., other brain regions, skeletal muscle, and liver) could play important roles in body weight regulation. Such studies will require using postmortem human tissues or appropriate animal models; for example, primate-specific epigenetic variation[31] may warrant studies in nonhuman primates. In every case, it will be important to keep in mind that epigenetic mechanisms are just one of several interacting developmental processes that determine physiological set points. For example, meaningful insights into developmental epigenetics in the hypothalamus are unlikely to be obtained unless such processes are considered in the context of hypothalamic neuroanatomic development, which establishes the circuitry so critical to lifelong integrative regulation of energy balance.[51]

Despite the daunting nature of these research challenges, it is crucially important to obtain this knowledge. The design of successful approaches to prevent and treat human obesity may very well depend upon our ability to understand and eventually manipulate epigenetic mechanisms affecting body weight regulation.

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11 Fetal and Early Postnatal Life Determinants of Adiposity

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CONTENTS

11.1 INTRODUCTION

Until recently, much of the medical and public health research on the causes of and risk factors for obesity and its related diseases, including type 2 diabetes mellitus (T2DM) and cardiovascular disease, was focused on two areas: the fixed genetic determinants of risk on the one hand and environmental and lifestyle factors such as excessive caloric intake and inadequate energy expenditure on the other. However, the expectations surrounding the explanatory role of genomic variation have become somewhat deflated following the rather modest effect sizes of gene variants discovered from genome-wide association studies of metabolic diseases. For example, while fat mass and obesity-associated (*FTO*) gene polymorphisms have an impact on satiety and affect predisposition to obesity, the association accounts for less than 0.5% of overall variance in body mass index (BMI).[1] Meanwhile, public health strategies predominantly focusing on diet and exercise have been relatively ineffective in stemming the relentless rise in obesity rates worldwide.[2]

There are also substantial differences in susceptibility to obesity-related disease at both the individual and population levels, as evidenced by the markedly higher prevalence of T2DM found among U.K. residents of South Asian ancestry compared to those of Caucasian ancestry across the whole range of waist:hip ratios, despite their sharing a similar contemporary environment.[3] Even under strictly controlled overfeeding conditions, considerable variation in weight gain and patterns of fat deposition has been seen between individuals.[4]

Disentangling the complex etiology of obesity and its related diseases is informed by an understanding of *why*, rather than simply *how*, disease develops. To this end, there is growing recognition of the importance of incorporating evolutionary perspectives into the physiological and mechanistic frameworks known to underlie adiposity.[5] Humans are likely to have evolved with a propensity toward maintaining a positive energy balance, so as to cope with episodes of transient undernutrition. Past nutritional environments were very different from present environments, with less caloric availability.[6] Indeed, the current environments of the developed, and increasingly of the developing, world can be envisaged as evolutionarily novel. The speed at which environmental change leading to modern-day obesogenic environments and sedentary lifestyles has occurred has likely exceeded our evolved adaptive capacities, hence increasing our vulnerability to obesity. We have termed this an evolutionary "mismatch."[6] But beyond this mismatch—which is a reflection of both our evolved genotype and the environment we live in—we need to understand what other factors may play a role in generating individual and population-based variations in the propensity to obesity when living within an obesogenic environment.

Over the past 25 years or so, a growing line of thought, driven by increasing amounts of epidemiological, clinical, and experimental research in humans and animals, has led to the incorporation of developmental factors into the discourse on the origins of obesity. This hitherto largely overlooked third dimension to the traditional genetics/environment dyad has shown that events spanning from before conception through to infancy can influence an individual's susceptibility to obesity and related diseases in later life, in addition to accounting for some of the variation in disease risk within and between populations.

In this chapter, we discuss how fetal and early postnatal influences may impact on an individual's subsequent

weight, risk of adiposity, and other traits related to obesity. We examine the evidence for epigenetic mechanisms underpinning such plastic responses, and we draw on evolutionary developmental biology (evo-devo) principles to illustrate our arguments.

11.2 DEVELOPMENTAL PLASTICITY

Developmental plasticity refers to a set of adaptive processes employed by an organism that enables it to cope with variable environments by fine-tuning its developmental trajectory.[7] This response, which has evolved through classical Darwinian selection as a result of its fitness-promoting effects, is typically elicited by environmental exposures ranging from the normative to exceptional, but the presence and nature of the plastic response depend on past exposures to the environmental cues in the ancestral lineage. Depending on the severity of the inducing exposure, and hence the latency with which phenotypic consequences are evinced, such plastic responses may be loosely categorized as immediate or predictive adaptive responses (PARs).

Broadly, immediate adaptive responses are due to more severe challenges, and they provide short-term advantages that are generally accompanied by long-term costs. This situation is termed a "trade-off," where a change in one trait benefits the organism—generally by increasing fitness—but concomitantly incurs a cost in another trait. For example, uterine infection may accelerate parturition to improve the immediate chance of survival, but this may lead to a growth-restricted neonate with a poorer outlook in terms of both morbidity and mortality.

More subtle developmental exposures may trigger PARs, in which the induced phenotype and consequent advantages gained are generally apparent only later in life.[8] As an example, nutritional cues from the mother during pregnancy, and perhaps her body composition at the time of conception, provide the fetus with a means of predicting its nutritional environment in later life. Suboptimal nutrition prompts predictions of nutritional scarcity, and through the processes of developmental plasticity, the offspring grows up with an integrated phenotype that favors metabolic prudence characterized by increased appetite, sedentariness, insulin resistance, fat deposition, and reduced skeletal muscle mass. This has been well demonstrated in experimental studies.[9,10] In this way, provided the prediction is accurate, the individual is better matched to its environment in later life. Reproductive tempo also appears to be sensitive to prenatal and postnatal nutrition, with accelerations in the onset of puberty seen in both rats undernourished in utero and human girls born small[11,12]; a major determinant of (Darwinian) fitness in humans is survival to reproductive age,[13] and thus, this potentially represents an optimizing life course strategy.

Multiple instances of PARs can be found among a range of species in various ecological contexts, such as the formation of a protective helmet in *Daphnia* offspring upon maternal exposure to predators.[14] There is also now growing evidence for the operation of PARs in humans: Forrester et al. recently demonstrated that among survivors of severe childhood malnutrition, those with a lower birth weight were more likely to develop a less fatal form of malnutrition known as marasmus, while those with a higher birth weight were more prone to kwashiorkor, for which mortality is higher because of impaired mobilization of protein and fat stores.[15] This suggests that a fitness effect of increased survival during childhood famine can be related to birth size and that potentially marasmic individuals develop with a metabolically thrifty physiology that is more adaptive to postnatal undernutrition.

It is important to emphasize that developmental plasticity operates in all pregnancies, hence the lack of a consistent genotype–phenotype relationship observed in many species, including the human. Subtle changes in the experience of the embryo or fetus, such as the nature of maternal nutrition during pregnancy,[16] can induce changes in the developmental trajectory. The operation of plasticity across the normal range of developmental exposures suggests that it essentially affects all individuals.

Developmental plasticity operates at least in part through epigenetic processes, as reviewed in Chapter 10 of this volume and elsewhere.[17] The most commonly studied epigenetic mechanisms are changes in DNA methylation at specific sites, especially in promoter regions of genes; environmentally mediated changes in the epigenetic state of genes have been demonstrated in both imprinted[18] and non-imprinted genes.[17,19]

11.3 DEVELOPMENTAL DETERMINANTS OF ADIPOSITY

In the 1970s and 1980s, reports hinting at the importance of developmental factors in influencing an individual's susceptibility to disease emerged. For example, Aerts and Van Assche showed that the pharmacological induction of diabetes in the pregnant rat led to offspring with dysregulated insulin response, glucose tolerance, and pancreatic β-cell function in adulthood,[20] and similar outcomes were also observed after surgical induction of growth restriction in utero.[21] In a study of a birth cohort, Higgins and colleagues reported that maternal influences affected blood pressure in young people[22]; meanwhile, Forsdahl raised speculations that poor socioeconomic status in early life was a risk factor for high cholesterol levels later and hence for cardiovascular disease.[23]

Despite these earlier observations, the idea that there could be intrauterine influences on the risk of disease in later life did not gain substantial support until systematic analyses in a large, well-defined U.K. cohort by Barker's team in the late 1980s. These researchers found that low birth weight—a proxy measure of poor fetal nutrition—was associated with higher risk of heart disease–related mortality in middle-aged men and women.[24] While the initial focus was on low birth weight, this relationship was in fact observed in a graded manner across the entire range of birth weights.[25,26]

Since then, evidence for the concept, now a burgeoning field known as the developmental origins of health and disease (DOHaD), has been continually strengthened by

TABLE 11.1
Major Developmental Contributors to Risk of Obesity and Related Diseases in Later Life

Early-Life Determinant	Potential Pathway(s)
Prenatal Factors	
Maternal preconceptional body composition[28]	Mismatch
Maternal constraint[56–61]	Mismatch
• Parity—being first-born	
• Maternal short stature	
• Multiple birth	
Maternal undernutrition/unbalanced nutrition[9,10,16,36,37,40,41,47,48]	Mismatch
Maternal obesity, excessive gestational weight gain, gestational diabetes mellitus[63,65–67,71]	Fetal hyperinsulinemia, increased fat cell number—epigenetic processes?
Exposure to endocrine disruptors[29]	Interference with adipogenesis?
Paternal obesity/unbalanced nutrition[92,94]	Epigenetic marks transmitted through sperm?
Neonatal Factors	
Prematurity[30,31]	Premature induction of metabolic pathways?
Low birth weight[42,43]	Mismatch
Postnatal Factors	
Postnatal nutrition[85,86]	Effects on appetite control, food preferences, number of fat cells—epigenetic processes?
• Formula versus breast-feeding	
• Maternal lactational diet	
• Infant overfeeding	
Parental cultural effects in infancy[88,32]	Cultural inheritance—learned acquisition of eating behaviors and food preferences; altered satiety control
• Parental obesity	
• Weaning style	
Nutritional transition[50–53]	Mismatch

further epidemiological, clinical, and experimental research. Development is now known to play a role in determining susceptibility to a range of pathologies in later life, including those of mental health and cognition, the musculoskeletal and respiratory systems, reproduction, cell proliferation (some forms of cancer), the cardiovascular system, and metabolic control reflected in obesity, insulin resistance, and T2DM.[27] The phenomenological and theoretical framework for DOHaD has become increasingly supported at the molecular level by human and animal studies demonstrating that epigenetic alterations are induced by developmental environmental exposures (reviewed in Ref. 17).

There are multiple developmental factors known to confer increased risk of obesity and its related chronic diseases in later life (Table 11.1). Although manifesting in a similar phenotype, they are likely to differ in their specific mechanistic processes and may have either adaptive or nonadaptive origins.

11.3.1 Developmental Mismatch

The potential adaptive value of PARs is subject to several caveats. First, the maternal-to-fetal signals need to be transduced accurately, as interference caused by pathological factors such as placental insufficiency may result in incorrect predictions. Second, signals need to be a faithful reflection of the actual environment. Inaccuracy may arise from poor maternal diet, including undernutrition or overnutrition with imbalances in macronutrient and/or micronutrient consumption, in spite of the accessibility of adequate nutrition. It may also result from physiological factors such as maternal constraint, unbalanced body composition, stress, excessive physical exercise, or heavy workloads. We note again that the influence of both maternal nutrition and maternal constraint includes a normative range of fetal experiences and potentially applies to most pregnancies. Finally, the nature of the environment can change between generations or within a life course, for example, with migration or socioeconomic transition, and this can lead to mismatch and increased risk of disease in later life.[8]

Developmental (as opposed to evolutionary) mismatch leading to obesity and other noncommunicable diseases arises when there is a discordance between the predictions made in early life of the prevailing conditions and the actual environment encountered. Thus, the offspring of (say) an undernourished mother, having experienced some degree of impaired fetal growth, preemptively adopts an energy-preserving phenotype that leaves it ill-equipped in terms of

metabolic physiology to cope with an obesogenic postnatal environment. Essentially, the altered developmental trajectory can be viewed as a response that has potential adaptive advantages in early postnatal life but later can have adverse health effects.

This raises the question of why PARs have evolved if the advantages are contingent on the fulfillment of many criteria that may well be unmet, especially in long-lived species such as humans. Why have they not been subjected to the eliminatory processes of natural selection, given the potentially adverse impact in the event of mismatch? A core tenet of evolutionary medicine is that natural selection acts to maintain or promote fitness up to and through the reproductive age of the organism. Hence, inaccurate predictions do not incur a fitness cost as long as reproductive success is not compromised. Beyond that, health and longevity become generally irrelevant in fitness terms, and there is little selective pressure to devote resources to their maintenance.[33] This becomes a liability in long-lived species such as humans because the adverse impacts of inaccurate PARs become manifest in later life. For example, a study by Moore et al. showed that rural Gambians had similar mortality rates in early life irrespective of seasonally dependent nutritional availability at birth, and higher mortality among those born during the hungry season was seen only after the age of peak reproduction.[34] The evolutionary retention of PARs suggests that humans have faced varied environmental conditions—and hence varied diets—in different locales over their evolutionary history. With respect to obesity, it is likely that incorrectly predicting a nutritionally scarce postnatal environment has a minimal fitness cost compared to incorrect predictions of a nutrient-replete environment (see the earlier example of marasmus and kwashiorkor in Section 11.2); thus, there may well be a bias toward predictions of the former.[35] Furthermore, adult adiposity does not generally adversely affect fertility unless it is extreme.

11.3.2 Maternal Undernutrition

Evidence for the adverse metabolic outcomes of maternal malnutrition in humans is provided by studies on the effects of early-life exposure to famine. Extensive epidemiological data are available on a historical cohort of Dutch individuals whose mothers were exposed to the wartime famine of 1944–45. Those whose mothers were affected during early pregnancy were more likely to display symptoms of the metabolic syndrome in adulthood, such as obesity and coronary heart disease, as well as biochemical abnormalities including glucose intolerance and lipid dysregulation, compared to unexposed individuals.[36,37] The effects were dependent on the trimester of gestation in which famine was experienced, which is in accord with the concept that there are critical developmental windows during which traits predisposing to adiposity and cardiovascular disease risk are established. Epigenetic analyses in these individuals nearly 60 years later suggested that famine exposure leaves a persistent molecular imprint in the form of differential methylation of several genes involved in growth and metabolic disease; observed differences were sexually dimorphic and dependent on gestational timing.[38] Hypomethylation at the promoter of insulin-like growth factor 2 (*IGF2*), a maternally imprinted gene implicated in growth and development, has also been observed in those exposed during the periconceptional period relative to unexposed siblings, although the effect size was small.[39] In other more recently established cohorts, individuals exposed in utero and during infancy to the Nigerian civil war famine of 1968–70 were at increased risk of hypertension, impaired glucose tolerance, and overweight approximately four decades later.[40] Similarly, adult women exposed to the 1959–61 China famine during gestation or early childhood were at heightened risk of metabolic syndrome,[41] although epigenetic alterations in individuals from the latter two cohorts have yet to be reported.

While famine studies involve extreme situations, other unselected, general population cohort studies have shown that lower birth weight is associated with increased abdominal obesity in adulthood,[42,43] suggesting that early-life experiences need not be extreme for the risk of obesity to be elevated.

Animal models of globally or protein-restricted maternal diets have afforded a more thorough understanding of the physiological and biochemical effects on offspring health. Rats that were undernourished during gestation but that were fed an adequate postnatal diet developed symptoms of metabolic dysfunction in later life, including obesity, hyperphagia, decreased physical activity, and insulin and leptin resistance.[9,10] In the livers of the offspring, the promoter for the lipid metabolism regulator gene peroxisome proliferator-activated receptor alpha (*Ppara*) was hypermethylated, and gene expression of *Ppara* and the glucocorticoid receptor (known as nuclear receptor subfamily 3, group C, member 1 [*Nr3c1*]) was lowered.[44] Consistent with the mismatch model, this phenotype represents the outcome of an integrated, developmentally plastic response that enables the organism to cope with a predicted scarcity of food but that is clearly maladaptive when the prediction turns out to be inaccurate and food supply is sufficient. Indeed, the extent of the metabolic dysfunction is compounded by a postnatal hypercaloric diet, that is, an environment that presents a greater degree of mismatch.[9] In further support of the predictive model, neonatal administration of the satiety hormone leptin in these rats has been shown to restore a normal adult phenotype and normalize the epigenetic alterations, suggesting the reversal of putative PARs made in early life.[44,45] While the exact biochemical mechanism through which leptin acts is not clear, it appears to play an important role in hypothalamic neurogenesis and the regulation of appetite control,[46] and it may permanently alter the epigenetic modulation of hepatic *Ppara* expression.[47]

Disrupted metabolic function has also been observed in the offspring of rat dams that were fed an isocaloric, low-protein diet. As adults, these offspring became hypertensive and dyslipidemic and demonstrated impaired glucose tolerance. Livers of the offspring were characterized by hypomethylation of the *Nr3c1* and *Ppara* promoters, together with increased

expression of the gene products and histone modifications at the *Nr3c1* promoter that favor its transcription.[48,49] Folic acid supplementation of the maternal diet prevented the onset of metabolic dysregulation and hypomethylation of most of the CpG (dinucleotide wherein cytosine is located 5' to guanine) sites at *Ppara*, although coincident hypermethylation at two CpG sites suggests a nuanced effect of folic acid supplementation on gene regulation.[50]

Recent studies have shown that even subtle changes in maternal nutrition can be associated with specific changes in the infant's epigenetic profile at birth and that these changes are linked to altered markers of metabolic risk. In humans, maternal carbohydrate consumption during the first trimester of pregnancy was inversely correlated with methylation levels at the retinoid X receptor, alpha (*RXRA*) gene promoter in umbilical cord tissue.[16] RXRA forms a heterodimer with PPARA to effect the transcriptional regulatory role of the latter. Most notably, within-cohort and between-cohort analyses demonstrated that *RXRA* methylation was associated with adiposity at age 6 or 9 years and could explain more than one-quarter of the variance in adiposity. As these observations were made in a healthy population in which pregnancies were uneventful, this shows that the developmental induction of metabolic risk, and the associated epigenotype, can occur under outwardly normal conditions and apply to virtually every pregnancy.

The human health implications of the mismatch pathway are manifold. First, and arguably the most likely factor to have the greatest impact in terms of sizes of populations affected, is the economic advancement occurring in many developing countries, including the urbanization of rural areas. This advancement is accompanied by a rapid nutritional transition wherein food is more plentiful and its composition more akin to that of the so-called Western diet—high in calories, glycemic index, and sugar.[51] Consequently, individuals who were exposed to poor early-life circumstances will likely possess an adult phenotype that is incongruent with the mature environment, and they will be at higher risk of obesity and related diseases.

Second, abrupt nutritional transition may be experienced by those who were undernourished in utero but who then relocate to a more prosperous, nutrient-dense region or country. Such scenarios may eventuate from sociological factors such as internal migration from rural areas to cities and voluntary emigration or refugee displacement to more developed countries. There is evidence pointing toward increased rates of obesity and other metabolic diseases among migrants compared to their counterparts in their original region or country of inhabitance.[52–54]

Third, even in countries where food accessibility is generally not of concern, it has been shown that many women of reproductive age—even those considering pregnancy—do not consume an optimal diet.[55] This suggests that there may be great value in employing preventive measures such as nutritional education and appropriate public health recommendations targeted at young women who are reaching or are of reproductive age.

11.3.3 Maternal Constraint

Mismatch may be amplified by physiologically inherent factors. The processes of maternal constraint, whereby maternal factors restrain fetal growth in part by limiting nutrient availability to the fetus,[56] operate in all pregnancies to varying degrees. It is thought to be necessary to restrict birth size to the size of the mother's pelvis rather than to the fetus's genetic growth potential; the absence of maternal constraint would lead to immense challenges for the birth process in which a comparatively large human skull, needed to accommodate a large brain, has to pass through a narrow pelvic canal. A consequence of maternal constraint is a bias toward predictions of undernutrition.

Maternal constraint affects firstborns to a greater extent than their siblings, possibly because vasodilation of the blood vessels supplying the uterus is less efficient in primigravidae and perhaps because, in evolutionary terms, the firstborn was likely to have been conceived while the mother herself was still growing, pelvic size not being maximal until about 4 years after menarche. Accordingly, firstborns tend to be about 100 g lighter at birth than their later-born siblings, and in line with the predictive model, recent studies have found that they have increased adiposity, higher blood pressure, and a poorer metabolic risk profile in early adulthood compared to those who are second or subsequent children.[57–59] This may be a factor of import given global demographic trends toward reduced family size in many Asian and European countries, leading to a larger proportion of firstborn children.

There is a greater extent of maternal constraint in teenage mothers in whom maximal pelvic dimensions have not yet been reached, as well as in mothers of short stature. Uterine size has been found to be smaller in women who were born small for gestational age[60]; maternal constraint in turn results in female offspring with a smaller uterus with the same propensity to produce smaller children. Another factor that greatly increases maternal constraint is twinning, for which a later start to motherhood—an increasingly prevalent occurrence in many countries—is a risk factor. The age-related decline in fertility has led to increased use of assisted reproductive technologies, which also are associated with a higher risk of twinning and higher-order multiple pregnancies.[61] Even in the absence of medical interventions, evidence has shown that the rate of multiple births increases with maternal age because of increased frequency of multifollicular development.[62] Twins are generally born smaller than singletons and are therefore more susceptible to abdominal obesity, T2DM, and other adverse health outcomes associated with lower birth weight. Studies in sheep have uncovered similar epigenetic alterations in key hypothalamic metabolic regulators from fetuses that were twins or moderately undernourished singletons, compared to control singletons.[63]

11.3.4 Maternal Overnutrition and Hyperglycemia

The early epidemiological data linking birth weight to disease risk showed that the risk curve for mortality from cardiovascular disease rebounded toward the other spectrum of higher

birth weights.[25] These large-for-gestational-age and macrosomic babies were likely to include children born to mothers who were obese or had gestational diabetes mellitus (GDM). Indeed, there is now increasing epidemiological evidence indicating that maternal overnutrition—comprising factors such as maternal obesity, excessive gestational weight gain, and GDM—is, paradoxically, also a risk factor for a similar offspring phenotypic outcome to that of maternal undernutrition. For example, in a study by Modi et al., maternal BMI was positively correlated with total and abdominal adiposity and with hepatic lipid content in infancy.[64] Importantly, this relationship was graded and held across the entire range of maternal BMIs. Other studies have found that exposure to a diabetic intrauterine milieu could account for nearly half of T2DM cases in 14- to 15-year-olds,[65] and that GDM was associated with higher BMI in offspring at age 18 years.[66] Pregnancy weight gain exceeding Institute of Medicine guidelines was associated with higher neonatal and early-adult obesity.[67,68]

The transfer of glucose, while transporter-mediated, is not readily saturable, unlike the transfer of other nutrients. Thus, the fetus of a mother with GDM and raised blood glucose will become hyperglycemic and thence hyperinsulinemic.[69] Fetal hyperinsulinemia drives fetal adipogenesis, and fetal adiposity and macrosomia with persistent increased fat cell numbers may make obesity more likely in adulthood. Indeed, infants of diabetic mothers show relative adiposity from about age 4 years, with the differential showing marked increases after 6 years of age.[70]

Again, evolutionary explanations can improve our understanding of the basis of GDM. Moderately increased insulin production induced by mild fetal hyperglycemia has growth- and adiposity-promoting effects that probably enhance fitness, at least in infancy. In fact, humans hold the distinction of having the highest proportion of body fat at birth among mammals, possibly for thermogenesis and to buffer the large brain from nutritional depletion.[71] Given the low probability of living in nutritionally surfeit environs throughout our evolutionary past, we posit that the placenta has evolved to protect the fetus from undernutrition rather than overnutrition. Thus, GDM is likely to be an evolutionary novelty and may simply be a manifestation of an evolutionary mismatch between our evolved biology and the modern-day obesogenic environment.

As is observed in humans,[64] maternal obesity is associated with offspring obesity in animal experiments:[72] altered growth and metabolic sequelae are seen in offspring, which display features such as obesity, insulin and leptin resistance, hypertension, dyslipidemia, and impaired glucose tolerance. Studies in rats have suggested that a high-fructose maternal diet may compromise endocrinological integrity in female offspring.[73] Excessive levels of maternal overnutrition are not necessary for phenotypic changes to be seen, as even mild overnutrition during suckling has been found to promote adiposity, glucose intolerance, and expression of hypothalamic appetite regulators in rats.[74] Rodent offspring in maternal high-fat feeding experiments displayed reductions in kidney mitochondrial DNA and in mitochondrial DNA genome expression,[75] as well as the impairment of hepatic mitochondrial function leading to anabolic lipid metabolism.[76] In the macaque, a maternal high-fat diet stimulated pro-inflammatory responses in the placenta and reduced uteroplacental blood flow.[77] Emerging research suggests that early-life overnutrition may also involve epigenetic perturbation. For example, rats that received high-fat nutrition in utero showed hypomethylation at the hepatic cyclin-dependent kinase inhibitor 1a (*Cdkn1a*) gene, which suggests hepatic dysfunction that is consistent with a fatty liver phenotype.[78] In Japanese macaques born to mothers on a chronic high-fat diet, the energy- and appetite-regulating melanocortin system was disrupted, and site-specific changes in hepatic histone H3 acetylation were detected.[79,80]

In contrast to maternal undernutrition, intrauterine overnutrition to the extent induced in these studies is likely beyond evolutionary norms and is more likely to be nonadaptive. Because the exposure is an evolutionary novelty, PARs would not be appropriately established during development, and providing a "matched" high-fat postnatal environment would not ameliorate the nature of the phenotype.[81] Rather, as a consequence of these exposures, fat cell number is enhanced, making the individual more likely to accumulate fat in a postnatal high-nutrition environment.

The dramatic increases in rates of overweight, obesity, and GDM in pregnant women over the past decade have alarming implications on public health. For instance, in the United Kingdom, maternal obesity doubled from 1990 to 2002–04, such that nearly half of all expectant mothers were overweight or obese.[82] The prevalence of GDM in many Asian countries has increased too: in China, prevalence rose 2.8-fold, from 2.4% to 6.8% in the decade up to 2008,[83] while prevalence stands at 21% in Singapore. In addition to the heightened risk of obstetric complications in these women, the adverse impact on offspring health means that the maternal phenotype is in danger of becoming perpetuated through the generations in a vicious cycle of "diabesity." Modeling studies have suggested that GDM could explain up to 30% of incidences of T2DM in Saskatchewan First Nations people.[84]

11.3.5 Postnatal Nutrition

The period in the life course during which developmental influences can modulate disease risk is not limited to the periconceptional and fetal period but appears to extend to the early postnatal period and even infancy. Postnatal nutrition, received indirectly through the maternal lactational diet or directly through infant feeding, can modulate the risk of obesity later in life. It is notable that the fatty acid content of human milk has changed dramatically over the past two decades, presumably reflecting maternal dietary changes.[85] Earlier weaning from breast milk has been associated with greater risk of overweight in adolescence,[86] and the nature of the maternal diet during breastfeeding, as well as the foods onto which infants are weaned, can modulate subsequent food preferences and appetite control.[87] Yet a multicountry

European study found that awareness among first-time mothers of the importance of early-life nutrition on lifelong health is low.[88] Even the weaning style may influence food preferences and body weight: compared to infants who self-feed, those who were parentally spoon-fed preferred sweet foods and had a higher rate of obesity in early childhood.[89]

11.3.6 Paternal Contributions and the Intergenerational Transmission of Obesity Risk

Although the majority of studies examining the DOHaD phenomenon focus on maternal contributions to offspring risk of disease, there is increasing experimental data that paternal nutritional state or adiposity may also be important determinants. In addition to the obvious public health implications for fathers-to-be, these studies have significant ramifications for our understanding of the transgenerational transmission of obesity and other disease risk. Several indirect pathways of non-Mendelian mechanisms of disease risk inheritance have been defined, including maternal effects, grandmaternal effects, and maternal care (reviewed in Ref. 17). However, little evidence is available on direct germ line–mediated epigenetic inheritance, that is, the meiotic transmission of epigenetic marks through the gametes and survival of these marks past early embryogenesis. Studies that focus on the transmission of developmentally induced phenotypes through the paternal line as opposed to the maternal line are able to rule out the indirect mechanisms of inheritance, as the sole input from fathers in these experimental studies is sperm.

There are some epidemiological reports of nongenetic disease risk inheritance in humans. A historical Swedish cohort has shown that good access to food during the paternal grandfather's slow-growth period was associated with a fourfold risk of death from T2DM in the grandchild,[90] and that food supply of the paternal, but not maternal, grandparent was correlated with mortality risk of the same-sex grandchild.[91] In the Dutch famine cohort, famine exposure in utero was associated with increased neonatal adiposity in the offspring's children.[92]

Recently, a number of murine studies have helped shed further light on this. Male mice that were fed a protein-restricted diet sired offspring that showed numerous alterations in the expression of genes regulating lipid and cholesterol biosynthesis in the liver, and hypermethylation at a putative enhancer region for *Ppara* identified this locus as a possible upstream regulator of the hepatic gene expression response.[93] Consuming a high-fat diet led to impaired reproductive health in male mice that was transmitted to their grand offspring (F2 generation).[94] In rats, a high-fat paternal diet led to a phenotype akin to diabetes in female offspring, with impairments in glucose tolerance, insulin secretion, and β-cell replication.[95] In a maternal high-fat diet mouse model, phenotype alterations in body weight and length were seen in females up to the F3 generation only through the paternal line.[96] In support of germ line–mediated epigenetic inheritance, molecular studies have picked up epigenomic alterations in the spermatids of high-fat-diet-induced obese fathers[97] and have suggested that developmentally important histone modifications can survive the widespread epigenetic reprogramming during spermiogenesis.[98]

11.4 IMPLICATIONS FOR INTERVENTIONAL STRATEGIES

The rampant increase in global rates of obesity and related metabolic diseases raises grave questions about the utility of current strategies that primarily target adult lifestyle factors. The downstream health, social, and economic consequences present a significant burden to developing countries in particular. It would therefore seem negligent not to capitalize on the recent insights into the unequivocal importance of early-life developmental factors in determining disease risk when devising interventional approaches to prevent or reverse developmental trajectories leading to obesity.

Multiple animal studies have provided conceptual proof that the phenotypic effects of a poor start to life can be reversed, provided interventions are performed sufficiently early in the life course when they are most likely to be efficacious (Figure 11.1). The ability of neonatal leptin administration

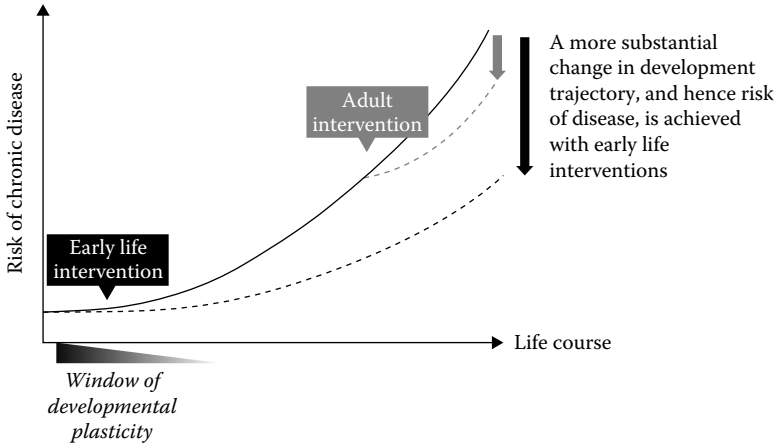

FIGURE 11.1 Early versus later life interventions on the mitigation of the risk of obesity and related diseases. (Modified from Godfrey KM et al., *Trends Endocrinol Metab*, 21:199–205, 2010.)

to reverse the developmentally induced metabolic trajectory in rats undernourished in utero[45] has been replicated in a growth-restricted pig model,[99] and direct nutritional intervention has been shown to be viable in corticosteroid-exposed rat offspring otherwise destined to become hypertensive and hyperleptinemic.[100] Prevention of T2DM onset in the growth-restricted newborn rat has been achieved by an incretin analogue through the normalization of epigenetic alterations associated with pancreatic β-cell function.[101]

Developmental epigenomic analysis, such as that undertaken by Godfrey et al.,[16] has much to offer both in our fundamental understanding of early-life influences of obesity and metabolic disease risk and in the clinical potential for epigenetic profiling to predict those who are most at risk of disease onset in later life and those who are candidates for intervention. There are methodological issues that need to be overcome,[102] but the outlook is promising as new prospective longitudinal studies continue to be undertaken and our mechanistic understanding of the developmental origins of obesity and its related diseases deepens.

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12 Animal Models of Obesity
Perspectives on Evolution of Strategies for Their Development and Analysis of Their Phenotypes

Heike Münzberg, Tara M. Henagan, and Thomas W. Gettys

CONTENTS

12.1 INTRODUCTION

The World Health Organization recently estimated that 1.4 billion people in the world are overweight and over 500 million of them are obese.[1] Epidemiological data indicate that obesity is associated with premature death through increased risk from chronic disease.[2–4] Obesity is the product of a chronic positive energy balance, and the resulting accumulation of excess adipose tissue is strongly linked to disordered lipid metabolism, development of insulin resistance, and a cluster of comorbidities called the metabolic syndrome. Obesity is viewed as the seminal event in disease progression, but the underlying mechanisms that link development of obesity to metabolic disease are less well understood. This is partly because of the chronic nature of the progressive deterioration in responsiveness of multiple, highly integrated organ systems to endocrine signals, which function to compartmentalize substrate utilization and maintain energy balance. However, given the growing impact of obesity on public health and the recognition that obesity is a precipitating event in the development of essentially all forms of metabolic disease, coordinated efforts of scientists from around the world have been devoted to understanding the genes, molecules, and systems biology involved in energy homeostasis.

A case could be made that the molecular era of obesity research began in 1949 with the chance occurrence of the mutation producing the *ob/ob* mouse and the astute recognition of its phenotype by colony caretakers.[5] However, the subsequent cloning of the *ob* gene in 1994[6] represents the watershed event that transformed the field by providing an initial roadmap for the systematic identification of the molecular components that function within the complex physiology of energy balance. The mechanistic framework of energy balance regulation inferred from the phenotype of the *ob/ob* mouse[6–8] led to the identification of many candidate genes for obesity. Corresponding mutant mouse models have been generated using transgenic techniques, but the remaining great challenge is to ascribe function to each gene in the physiological context of energy homeostasis. Realizing the promise of these advances has required the development of sophisticated metabolic phenotyping approaches to understand the role of specific genes within the complex network of genes involved in regulating energy balance. The primary goal of this chapter is to provide a perspective on the evolution of obesity research, with special emphasis on how the development and implementation of advances in genetic approaches and metabolic phenotyping technology has transformed the field.

12.2 BIOENERGETICS OF POSTWEANING GROWTH, NUTRIENT PARTITIONING, AND OBESITY

Maintenance energy is most simply defined as the daily energy intake required to maintain constant body weight and composition.[9–12] The maintenance energy requirement is summative in the sense that it includes the energy costs of basal metabolism, thermoregulation, activity, and assimilation of food. Thus, energy balance is defined as a state when energy intake and expenditure are equal, and it occurs in practice upon the attainment of physical maturity when the rate of energy intake maintains a constant body weight and composition. In contrast, energy intake in excess of expenditure is required to support the deposition of new tissue during postweaning growth, and the proportion of intake devoted to maintenance is a function of the efficiency of energy use for maintenance. Stated in another way, the proportion of energy intake required for maintenance defines the remaining energy that is available to support new growth. As a consequence, inefficient use of energy for maintenance (e.g., high energy expenditure) effectively limits net energy available to support the deposition of new tissue. It then follows that energy intake, relative to energetic efficiency, is a critical term in the energy balance equation. In a comprehensive review and compilation of results from nutrition experiments, Parks[13] concluded that the establishment of a fairly constant rate of food consumption is characteristic of many, if not most, species. Careful long-term studies in rats, sheep, and cattle showed that stabilization of energy intake occurred shortly after weaning and at a rate that was characteristic of each animal and maintained over a fourfold increase in body weight.[14–20]

The significance of a stable rate of intake is that it defines the nutrient resources available to the animal for growth to maturity. As inferred by Blaxter and colleagues,[14,15,21] the expected mature size and trajectory of approach to it (e.g., mature size) can be accurately predicted if the efficiency of energy use for maintenance is also known when the constant rate of energy intake is established.

Energy intake in excess of expenditure is defined as net energy and is partitioned between fat and protein synthesis in a manner that determines the relative composition of tissue deposition during growth to maturity.[9–11] In the young growing animal, net energy is primarily used to support protein synthesis and growth in length, with the proportion of net energy deposited as fat increasing gradually during the approach to adult size. The result is an incremental increase in adiposity that can be accelerated by any combination of lower energy expenditure and/or higher intake. For example, the rapid development of obesity after weaning in *ob/ob* mice is driven by a combination of hyperphagia, low energy expenditure, and endocrine changes that favor fat deposition.[7,8,22] However, hypertrophy of adipose tissue occurs even when *ob/ob* mice are pair-fed with lean littermates.[22] For example, over a 10-day period at equivalent energy intake immediately after weaning, *ob/ob* mice deposited twice as much fat as their lean littermates.[22] These findings illustrate the contribution of low energy expenditure to the high rate of fat deposition in *ob/ob* mice and more generally how the efficiency of energy use for maintenance can impact overall energy balance and fat deposition. Excessive fat deposition can also occur during growth when energy intake far exceeds the combined requirements for maintenance and protein deposition. Under these circumstances, the excess energy is efficiently deposited as fat, producing a rapid and premature expansion of adipose tissue. Conversely, a chronic positive energy balance after maturity selectively increases adiposity by effectively channeling net energy into fat deposition. Regardless of the mechanism or when it occurs, the accumulation of excess fat in adipose tissue is the defining feature of obesity.

12.3 MOUSE MODELS: PAST, PRESENT, AND FUTURE

In the broadest sense, normal growth can be viewed as the bioenergetic process of tissue assimilation, culminating in a stable body mass and composition that do not predispose the mature animal to metabolic disease. Therefore, although it is axiomatic that obesity can develop only when energy intake chronically exceeds energy expenditure, a better understanding of the complex biology of energy balance regulation is needed to counter the expanding rates of both childhood and adult obesity. This has required the development of experimental approaches that incorporate careful measurement of the components of energy balance (e.g., energy intake, energy expenditure, and body composition) over time with systematic manipulation of the molecular components that provide input to regulation of energy balance. Examples include major advances in our understanding of hypothalamic control of food intake and how central and peripheral signals are integrated within anorexigenic and orexigenic systems that regulate energy intake. Sensing systems that detect and respond to environmental cues (e.g., temperature and diet composition) affect energy balance by engagement of adaptive thermogenic mechanisms that alter energetic efficiency.

12.3.1 Origins and Evolution of Genetic Approaches to Obesity

In the past 20 years, great progress has been made in understanding the anatomical organization of these anorexigenic and orexigenic systems and identifying the molecular components of the corresponding effector molecules and signaling networks. The identification of specific mutations giving rise to the obese/diabetic phenotypes of *ob/ob*[5,6] and *db/db*[23,24] mice, the so-called monogenic mouse models, were critical discoveries in the field, because they provided the first glimpse into the molecular mechanisms that provide integrated control of energy balance and a conceptual framework on which to base systematic explorations of the sensing and signaling networks involved in regulation of energy balance. These mice[5,23] also provided a compelling demonstration of the power of loss of function approaches to study the complex physiology of obesity. Building

on these initial mechanistic insights, the systematic application of this experimental paradigm has led to spectacular progress in our understanding of energy balance within the past 18 years. This progress has been fueled by the broad implementation of loss and gain of function approaches that became possible with the availability of the complete mouse genome. Recent advances in the technology of gene targeting in embryonic stem (ES) cells have been essential elements of this progress.

12.3.2 Polygenetic Mouse Models: Inbred and Outbred Mice

Even though monogenic mouse models have been instrumental in understanding specific pathways that control energy homeostasis, most human obesity is thought to involve the combined effects of an array of gene mutations (polygenic). Indeed, many of the traditional obesity rodent models like the polygenic inbred New Zealand obese mouse, the obesity-prone C57BL/6J mouse strain, or the selectively inbred rat strains that are obesity prone or obesity resistant[25–28] have been instrumental in the study of polygenic obesity. To identify individual genes that contribute to a polygenic obesity phenotype, genome-wide association studies (GWASs) have been used in lean and obese human cohorts that were evaluated for the occurrence (allele frequency) of known single-nucleotide polymorphisms. In humans, GWASs have been quite successful in identifying novel, interesting gene loci that may eventually lead to the identification of individual genes that cause or influence the development of obesity or type 2 diabetes.[29] The enormous genetic variations among humans is beneficial for GWASs and subsequent quantitative trait locus (QTL) analyses to identify the exact location of target genes. However, its adaptation to mouse models has been difficult due to a lack of genetic variations in inbred as well as outbred mouse colonies.[25,30,31] Thus, in 2004 a new project was initiated to generate a new inbred mouse model with the specific goal of mixing and randomizing genomes to obtain unique recombination sites to support QTL analysis.[32] It was named the Collaborative Cross (CC) Project and is being pursued at the Jackson Laboratory, Bar Harbor, Maine.[33] Although CC mice are not yet fully inbred, pre-CC mice were tested and have confirmed their usefulness for QTL mapping studies.[34] In an extension of the CC mouse resource, another mouse model derived from the CC colony, called diversity outbred mice, has been designed to further maximize allelic diversity. These mice are expected to be available for distribution to the research community within the next year.[35]

12.3.3 New Era of Mouse Genetics: The Development of an Online Phenotyping Resource

Work with monogenic models of obesity gave way in the 1980s to mouse models with targeted mutation of genes as the method of choice for studying the role of specific genes in the regulation of energy balance.

Completion of the whole genome sequencing project in 2001 identified approximately 20,000 gene products, but the function of only a small fraction was known at the time. In 2006, the International Knockout Mouse Consortium (IKMC) was launched as a broad-based effort to organize and optimize individual projects from the United States (Knockout Mouse Project [KOMP] and Texas Institute for Genomic Medicine), Canada (North American Conditional Mouse Mutagenesis Project), and Europe (European Conditional Mouse Mutagenesis Program) to systematically generate mutant ES cells for every gene product in the mouse and to make them publicly available to the scientific community from repositories.[36,37] Their initial objective is nearing completion as 16,000 mutant ES cell lines have been generated, and they have begun to generate the corresponding lines of knockout mice for a select group of genes. In 2011, the International Mouse Phenotyping Consortium was launched as the continuation of IKMC, with the goal of conducting a systematic, albeit basic, phenotyping of generated knockout mouse models, merging pioneering projects from the United States (KOMP2) and Europe (European Mouse Disease Clinic). Thus, it is projected that general phenotyping data of all 20,000 gene products will become available by 2020. It is anticipated that this effort will identify important new genes that were previously unappreciated for their roles in energy balance. The overall goal of the project is to support and accelerate progress toward a genetic analysis of all mammalian genes by making the biological resources and associated information available to the scientific community. As of early 2011, more than 12,000 vectors and 9000 conditional targeted alleles had been produced in highly germ line–competent ES cells.[36,38]

12.3.4 Conditional Targeting of Genes

In addition to global deletion and overexpression models, the development of conditional gene manipulation systems (*Cre/loxP*, *Flp/Frt*, and derivatives)[39] has added a valuable new level of sophistication to the way gene expression can be manipulated. This approach permits the targeting of genetic deletion (or reactivation) to a specific tissue, cell type, or neuronal population. The importance and advantages of conditional approaches were demonstrated through several surprising results that challenged the dogma that leptin's main effect was mediated via its interaction with the melanocortin system in the arcuate nucleus (ARC) of the hypothalamus.[40] It was assumed that specific deletion of the long form of the leptin receptor (ObRb) from proopiomelanocortin (POMC) neurons would largely recapitulate the severely obese, hyperphagic phenotype of *db/db* mice. However, these animals showed only a mildly obese phenotype,[41,42] as did mice with agouti-related protein (AgRP)-specific or POMC + AgRP-specific ObRb deletion.[42] Further, ARC-specific rescue of ObRb showed that limiting the action of leptin to ARC accounted for only a fraction of leptin's effect on body weight.[43] Thus, these data expanded interest in other hypothalamic and extra-hypothalamic sites that now have been shown to contribute

to whole-body leptin effects.[44–47] In addition, advances were made in identifying the functions of specific ObRb populations by rescuing ObRb expression in specific brain areas and examining the corresponding physiological responses to leptin. Using this approach, rescue of ObRb within the ARC of ObRb-deficient mice normalized their hyperglycemia and locomotor activity,[43] whereas the specific deletion of ObRb from dopaminergic neurons prevented leptin-dependent anxiolytic actions.[48]

Similarly, it was originally thought that POMC and AgRP neurons mainly act via melanocortin receptor 4 (MC4R) in the paraventricular hypothalamus to mediate their effects on food intake and energy expenditure. The phenotype of global *Mc4r*-null mice supported the importance of MC4R in the control of energy intake and expenditure. However, conditional reactivation of MC4R in the paraventricular nucleus (PVN) established that MC4R signaling there controlled only food intake,[49] whereas energy expenditure was controlled by cholinergic MC4R neurons in the brain stem.[50]

12.3.5 Circumventing Developmental Compensation: The Use of Inducible Systems

A common problem with genetic manipulations is that developmental mechanisms compensate for the absence of the targeted gene. This was clearly demonstrated in studies involving targeted deletion of the orexigenic neuropeptides AgRP and neuropeptide Y,[51,52] which were expected to but did not result in lean, hypophagic mice.[53,54] Compensatory mechanisms were suspected, and follow-up studies examined this possibility using an inducible system in which the diphtheria toxin receptor was conditionally expressed in AgRP neurons. Selective ablation of AgRP neurons with exogenous diphtheria toxin had the expected orexigenic effect in adult mice, whereas neonatal ablation had little effect on energy intake.[55,56]

Additional inducible approaches include the tetracycline on/off (tet-off) system and the estrogen receptor–based system to control gene expression by pharmacological intervention at any developmental stage.[57,58] The tet-off system was recently used to cause acute cessation of leptin expression at any point during development, producing the equivalent of a reversible *ob*/*ob* mouse.[59] This model has been useful in distinguishing leptin-specific phenotypic responses from effects that are secondary to the severe obesity produced by its absence.

12.3.6 Tracing Neuronal Circuits: Conditional Reporter Systems

Conditional expression systems provide the added flexibility of linking endogenous gene expression to the expression of a *Cre*-inducible reporter gene such as green fluorescent protein. This has proved particularly useful for the localization and mapping of receptors (e.g., ObRb and MC4R) that are notoriously difficult to detect with antibodies. An attractive feature of the approach is that it enables functional colocalization studies, such as those that identified the specific ObRb- or MC4R-expressing neurons linked to thermoregulatory circuits involved in the regulation of energy expenditure.[60,61]

Modifications of cre-inducible reporter genes have also been used to generate farnesylated reporter proteins that become anchored to the cell membrane and provide excellent visualization of neuronal processes. Similarly, trans-synaptic tracers can be used as cre-inducible reporter genes to visualize postsynaptic second-order (using anterograde tracers like wheat germ agglutinin) or presynaptic input neurons (using retrograde tracers like tetanus toxin B). Application of these methods has provided an effective way to map projection sites of specific populations of ObRb neurons. For example, the approach was used to challenge the consensus that dopaminergic ObRb neurons innervate the nucleus accumbens directly.[62] Although consistent with the classic mesolimbic dopaminergic reward system,[63] it was found that ventral tegmental ObRb neurons directly innervate the amygdala but not the nucleus accumbens.[64] In conjunction with innovative advances in the design of conditional reporter systems, the application of this approach offers great promise in advancing our understanding of the neural circuitry of energy balance.

12.3.7 Driving Behavior using Pharmacogenetics and Optogenetics

The expanding list of cre-inducible tools now includes the expression of receptors or ion channels that can be selectively activated using pharmacological effectors (via designer receptors exclusively activated by designer drugs) or light activation (e.g., via channelrhodopsins) to control neuronal excitability within defined neuronal populations. This approach was used to show that induction of neuronal activity in AgRP neurons acutely induced feeding behavior.[65,66] Neuronal stimulation typically results in the synaptic release of neurotransmitters and neuropeptides such as AgRP, which should increase food intake by inhibiting MC4R signaling, for example, in the PVN. Surprisingly, Aponte et al.[65] showed that POMC, but not AgRP, neurons required MC4R to regulate feeding, suggesting that other AgRP-independent signaling mechanisms in AgRP neurons (e.g., γ-aminobutyric acid release) provide major effects on food intake, in agreement with the study by Wu et al.[67] A particularly attractive feature of optogenetic approaches is that neuronal circuits can be studied (e.g., by recording from PVN neurons) during light activation of POMC or AgRP neurons.[68] Thus, application of these exciting new technologies is expected to increase our understanding of how neuronal circuits code behavioral changes.

12.4 CHALLENGES IN APPLICATION OF METABOLIC PHENOTYPING TO ANIMAL MODELS OF OBESITY

A guiding principle of investigators in the obesity field has been to target genes within pathways linked to the regulation of energy intake or expenditure. The proof of principle

for a gene's physiological significance is obtained when the corresponding transgenic models either resist or develop obesity, providing prima facie evidence for involvement of the target gene in energy balance. Transgenic mice generated in other scientific disciplines that develop an unanticipated metabolic phenotype have also helped to identify new genes not previously suspected of being involved in energy balance. An overarching goal within the obesity field is to discover and map the complex network of genes involved in the regulation of energy balance. Genetically modified mice with an energy balance phenotype contribute to this broader effort, but their greatest value lies in their potential to provide mechanistic insights into how each gene functions within the overall scheme of energy homeostasis. A significant remaining challenge to realizing this potential is developing and refining the experimental approaches that are needed to detect and identify the source of subtle energy imbalances underlying the mouse phenotypes.

The intake and expenditure components of energy balance are regulated and function in a highly integrated manner. An accurate accounting of the changes in energy intake and/or expenditure that is fully reconciled with observed changes in adiposity is essential to understanding how specific genes function to affect the corresponding in vivo energy balance phenotypes. Using an example from the authors' laboratories, it can be shown that the energy imbalances that account for the moderate obesity of most models are quite small. For example, in a recent 9-week study, the positive energy balance that accounted for a twofold greater fat deposition in experimental mice was 2.4 kJ/day in mice that consumed an average of approximately 55 kJ/day (unpublished data). It is readily apparent that detecting such small differences (e.g., 3.6%) in energy balance and correctly attributing their source between energy intake and expenditure are technically challenging but essential to understanding the basis for the differential fat deposition.

Beginning in 2000 as part of a transinstitute initiative, the National Institutes of Health (NIH) established centers at institutions in the United States devoted to providing state-of-the-art metabolic phenotyping expertise and methodology to the scientific community engaged in the study of mouse models of obesity, diabetes, metabolic disorders, and complications. Currently, the Mouse Metabolic Phenotyping Center Consortium (www.MMPC.org) and the Diabetic Complications Consortium (www.DDC.org) provide a broad range of sophisticated phenotyping services to the mouse research community, with special emphasis on developing new technologies for assessing in vivo metabolism and physiology that are needed to dissect the role of specific genes in energy balance and metabolic disease. This NIH-led initiative to establish much-needed intellectual and technical infrastructure has been paralleled by the development of new instrumentation by private industry to scale the needed analytical platforms to work with mice. Perhaps the most significant advances have been in the development of (1) small-animal nuclear magnetic resonance spectrometry and (2) indirect calorimetry platforms that provide continuous measures of oxygen consumption, carbon dioxide production, voluntary activity, and food consumption.

A stochastic approach to the law of energy conservation that is sufficiently robust to explain the progressive development of obesity will require the development of complex differential equations to model the corresponding bioenergetics of energy flow over time. However, an intuitive prediction derived from an empirical approach to the law is that imbalances between energy input and output will be buffered by ongoing changes in adiposity.[69,70] With the exception of a few monogenic models of obesity,[23,71–74] the obesity phenotype of most genetically modified lines of mice reported to date is modest and reflective of a small but persistent positive energy balance. To understand its basis, the key initial question is whether differences in weight and/or adiposity are attributable, wholly or in part, to differences in energy intake. Group differences in adiposity not attributable to differences in energy intake provide de facto support for the alternative hypothesis of group differences in energy expenditure, and expanded access to small-animal indirect calorimetry has made it the method of choice for measuring energy expenditure. The challenges inherent in this method's application are substantial because the comparisons almost always involve mice that differ in size and composition. One of the immutable laws of calorimetry, beginning with the eighteenth-century work of Lavoisier and Laplace and extending through the subsequent work of Rubner, Brody, and Kleiber, is that energy expenditure is proportional to some function of body size. Thus, energy expenditure must be scaled accordingly to determine whether group differences remain after correcting for size. In the past century, the observed differences in energy expenditure across species were used to devise empirical solutions based on functions that raised body weight to a power less than 1 (see the review by Arch et al.[75]). These functions are not relevant in the current context, where scaling of calorimetry data involves corrections for body weight between mice whose primary difference is fat mass. It is well accepted that such differences are not inconsequential since fat and lean tissue make different mass-specific contributions to overall energy expenditure. Scaling to body weight assumes that all tissues have the same rate of metabolism, whereas scaling to lean mass assumes that adipose tissue is metabolically inert. The respective assumptions are demonstrably incorrect, and the error introduced by either method increases in proportion to the difference in mass of the groups being compared.[75–79] It is clear that such practices compromise the validity of group comparisons and undermine the broader goal of identifying the role and mechanism of specific genes in energy balance.[75–79] In addition to improperly accounting for tissue-specific contributions to energy expenditure, mass-specific scaling also fails to capture information about how other experimental variables contribute to variation in total energy expenditure between animals. An alternative to ratio-based normalization of energy expenditure is provided by analysis of covariance (ANCOVA), which uses least-squares analysis to assess the impact of variation in fixed (e.g., genotype) and

continuous (body composition, intake, and activity) variables in relation to variation in energy expenditure between animals. For example, one of the first uses of ANCOVA in this context was to assess the relative contributions of fat-free mass, sex, age, and family membership to variation in resting metabolic rate in 130 adults.[80] Fat-free mass, sex, and age accounted for 83% of the variation, but when family membership was added to the model 94% of the variability in resting metabolic rate could be explained.[80] In another study with 177 adults, ANCOVA was used to assess the relative contributions of body composition, age, activity, and energy intake to variation in basal, resting, and total 24 hour energy expenditure.[81,82] Although the design of these human studies differs from those typically used in experiments with genetically modified mice, the results illustrate the power of this empirical approach to assess the contributions of mass, composition, activity, and energy intake to basal versus total energy expenditure.

ANCOVA was initially recommended for the analysis of rodent indirect calorimetry data in 2006,[75] and a series of recent papers have described the application of this approach to assess the relative contributions of fat-free mass, fat mass,[78] and plasma leptin[79] to energy expenditure. Additional recent publications describe using ANCOVA in the analysis of indirect calorimetry data within a broader set of considerations and recommendations for optimizing the design and interpretation of metabolic phenotyping experiments.[77,83] Although a consensus has emerged to support ANCOVA as the method of choice for comparing treatment effects on energy expenditure, further refinement of the model is needed to capture all available information in data already being collected by the latest generation of indirect calorimeters. For example, in addition to the repeated measures of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) while mice are in the chambers, simultaneous measures of energy intake and activity are recorded but typically not included in the model for analysis of energy expenditure. The analysis of chamber data in humans shows unsurprisingly that energy intake and activity make a significant contribution (~20%) to variation in 24 hour energy expenditure among individuals,[81] so inclusion of intake and activity data as covariates in the mouse model is clearly warranted and will enhance the power to isolate and account for important components of variation in energy expenditure that have heretofore been retained within the error term used to test for group differences. Exclusion of these covariates from the model has the unfortunate effect of diminishing the power to detect phenotypic differences in energy expenditure. A strength of ANCOVA is that it makes no prior assumptions about the impact of model variables on energy expenditure but determines their relative contributions empirically. Including genotype, measures of body composition, energy intake, and activity in the ANCOVA model will provide a direct test of whether the targeted gene alters the relative impact of each variable on overall energy expenditure. Thus, in addition to testing the primary hypothesis of interest (e.g., genotype) the analysis will provide the added benefit of an objective assessment of the components of energy expenditure being affected, which in fact is the paramount objective of metabolic phenotyping of mouse models of obesity.

12.5 RECOMMENDATIONS AND POTENTIAL SOLUTIONS

The most common experimental and analytical misdemeanors committed during metabolic phenotyping have been enumerated to emphasize the need to devise experimental approaches that enhance the sensitivity and discriminatory capacity of the method to detect changes in energy intake and/or expenditure. As noted in Section 12.4, the daily energy imbalances that can account for significant differences in fat deposition are small, and their detection requires accurate and precise assessments of energy intake and expenditure. Using the earlier example, assume that the basis for the observed twofold difference in fat deposition in the experimental group was a 150 mg/day difference in food consumption (e.g., 2.4 kJ). It is easy to see how periodic measurement of intake for short intervals could easily miss this difference and incorrectly attribute differences in fat deposition to energy expenditure. In this case, since no differences actually exist, careful measurement of energy expenditure by indirect calorimetry should fail to detect group differences, leaving the investigator with an unexplained phenotype. Alternatively, assume that the energy imbalance in our example was entirely due to group differences in energy expenditure. Given the documented shortcomings of commonly used approaches, accounting for the approximately 4% difference between groups by indirect calorimetry would challenge the discriminatory capacity of the technology. The simple message from this real-world example is that an accurate assessment of the metabolic phenotype underlying mild to moderate obesity is likely to require a more comprehensive and rigorous analysis of the components of energy balance over time.

An alternative approach to test for group differences in energy expenditure involves pair-feeding control and experimental groups until they achieve stable body weights and composition. At energy balance, the rate of metabolizable energy intake is equivalent to energy expenditure. A recent study measured energy expenditure in mice at energy balance using indirect calorimetry and confirmed that estimates from each approach were equivalent.[84] In this study, repeated measures of body composition were used to confirm the attainment of energy balance in mice whose weights were stratified using a combination of caloric density and food restriction. In practice, using the energy balance approach to compare energy expenditure between control and experimental mice involves pair-feeding to the group with the lower rate of intake. Unless the targeted gene has a strong orexigenic or anorexigenic effect, the degree of restriction imposed by the pair-feeding regimen will be minor. However, when the pair-feeding regimen does impose a significant reduction in the voluntary rate of intake in one of the groups, the associated reduction in body weight can induce an adaptive increase in metabolic efficiency and

decrease in mass-specific energy expenditure. These compensatory reductions in energy expenditure have been studied extensively in weight-reduced humans,[85–87] in which the threshold for adaptive response is approximately 10% weight loss. A similar compensatory response was observed in food-restricted mice maintained at 20% below their initial body weight.[88] This possibility should be considered in mouse models of obesity with an established hyperphagic component of their phenotype, because engagement of an adaptive increase in metabolic efficiency could easily mask detection of the target gene's effect on energy expenditure.

To illustrate the application of the energy balance method in an experimental setting where these concerns apply, data from a study using loss-of-function mice that are hyperphagic and obese (*Mc4r*$^{-/-}$) or obese without hyperphagia (*Mc3r*$^{-/-}$) are presented. Mice of the respective genotypes were fed ad libitum for 6 weeks after weaning prior to the imposition of pair-feeding for the following 24 weeks to allow establishment of energy balance. The original reports of the metabolic phenotype of *Mc4r*$^{-/-}$ mice attributed the development of significant obesity in these mice to a combination of hyperphagia and reduced energy expenditure,[89,90] whereas *Mc3r*$^{-/-}$ mice became obese through altered nutrient partitioning without any effect on energy intake or expenditure.[91,92] Our energy balance study was conducted in two phases to allow expression of the respective energy balance phenotypes of the groups. Data from the first phase illustrate the fundamental differences in appetite, size, and composition among the genotypes when allowed ad libitum access to food (Figures 12.1 and 12.2, Table 12.1). The temporal changes in weight among the groups after initiation of pair-feeding are shown in Figure 12.1, which also shows that 12 weeks of pair-feeding resulted in similar and stable body weights in all three groups. Over the final 12 weeks, the weights decreased slightly but stabilized at levels that did not differ among the groups (Table 12.1). Thus, if we use stability of body weights to conclude the attainment of

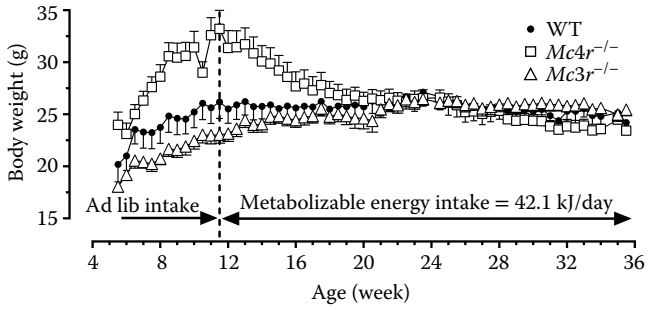

FIGURE 12.1 Mean body weights of wild-type (WT), melanocortin receptor 4-null (*Mc4r*$^{-/-}$), and melanocortin receptor 3-null (*Mc3r*$^{-/-}$) mice (n = 8/group) from 5.5 to 36 weeks of age: mice of each genotype were fed Purina Mouse Diet 5015 ad libitum from 5.5 to 11.5 weeks of age, after which all mice were pair-fed 2.7 g/day of the diet (e.g., 42.1 kJ/day metabolizable energy) for 24 additional weeks. The mouse lines were developed on an outbred Black Swiss/129 background (BSw;129) as described previously[93] and is available from Charles River (Wilmington, Massachusetts).

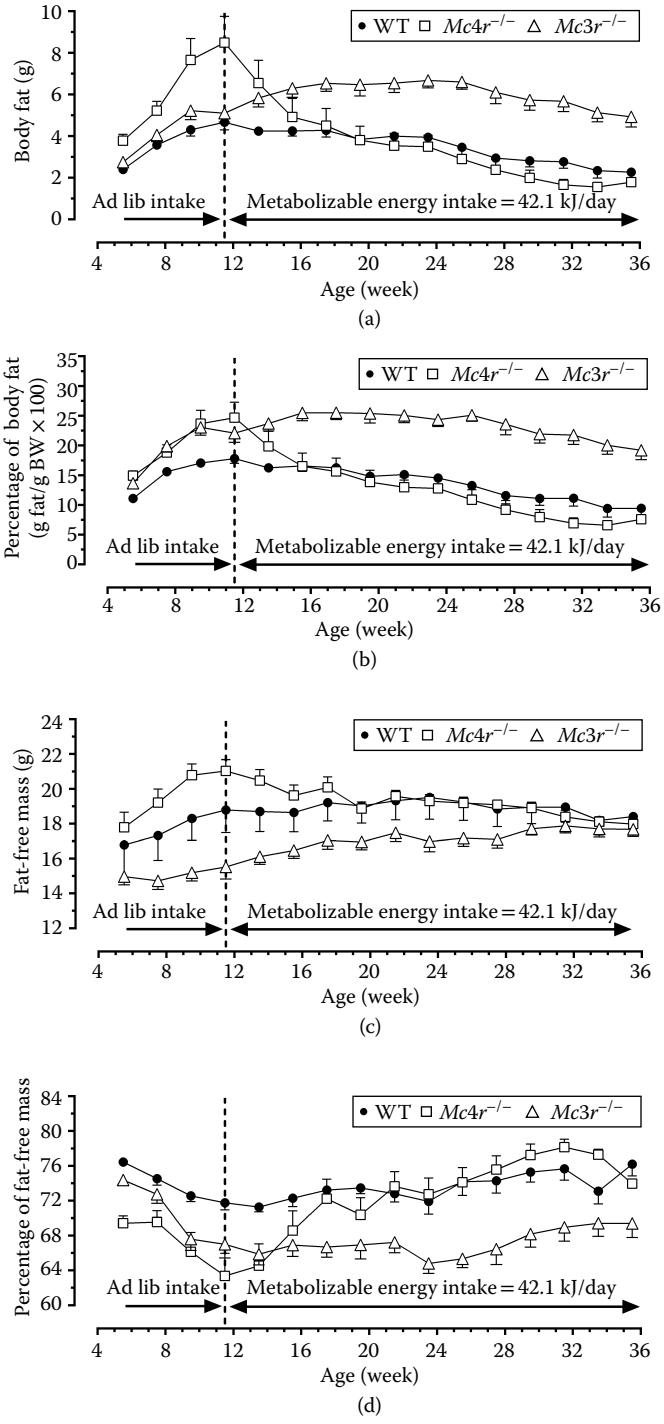

FIGURE 12.2 Mean body composition of wild-type (WT), melanocortin receptor 4-null (*Mc4r*$^{-/-}$), and melanocortin receptor 3-null (*Mc3r*$^{-/-}$) mice (n = 8/group) from 5.5 to 36 weeks of age: mice of each genotype were fed Purina Mouse Diet 5015 ad libitum from 5.5 to 11.5 weeks of age, after which all mice were pair-fed 2.7 g/day of the diet (e.g., 42.1 kJ/day metabolizable energy) for 24 additional weeks. At 5.5 weeks of age and at 2 week intervals thereafter, fat mass (a), fat-free mass (c), and fluid mass were determined in triplicate for each mouse using a Bruker Minispec NMR analyzer (Bruker Optics, Inc., Billerica, Massachusetts). Percentage body fat (b) and percentage fat-free mass (d) were expressed relative to body weight (BW), and means of each variable were compared by analysis of variance ($P < .05$).

TABLE 12.1
Metabolizable Energy Intake, Body Weight, and Body Composition of Wild-Type, *Mc4r*-Null, and *Mc3r*-Null Mice at Initiation of Pair-Feeding and 12 and 24 Weeks Thereafter

Week of Pair-Feeding	Genotype	Metabolizable Energy Intake (kJ/day)	Body Weight (g)	Fat-Free Mass (g)	Fat Mass (g)
0	WT	43.8 ± 1.8^{a}	26.2 ± 1.6^{a}	18.8 ± 1.3^{a}	4.7 ± 0.4^{a}
	Mc4r-null	54.7 ± 2.2^{b}	33.2 ± 1.8^{b}	21.0 ± 0.6^{b}	8.5 ± 1.3^{b}
	Mc3r-null	42.1 ± 1.3^{a}	23.0 ± 0.8^{a}	15.5 ± 0.7^{c}	5.1 ± 0.4^{a}
12	WT	42.1	27.1 ± 1.4^{a}	19.5 ± 1.3^{a}	3.9 ± 0.4^{a}
	Mc4r-null	42.1	26.5 ± 0.8^{a}	19.3 ± 0.4^{a}	3.5 ± 0.5^{a}
	Mc3r-null	42.1	26.5 ± 0.6^{a}	17.0 ± 0.6^{b}	6.7 ± 0.4^{b}
24	WT	42.1	24.2 ± 0.6^{a}	18.4 ± 0.7^{a}	2.3 ± 0.3^{a}
	Mc4r-null	42.1	23.4 ± 0.6^{a}	18.0 ± 0.3^{a}	1.8 ± 0.2^{ab}
	Mc3r-null	42.1	25.5 ± 0.6^{a}	17.7 ± 0.4^{a}	4.9 ± 0.5^{c}

Note: Eight mice of each genotype were fed Purina Mouse Diet 5015 ad libitum for 6 weeks after weaning, after which all mice were pair-fed 2.7 g/day of the diet (e.g., 42.1 kJ/day) for 24 additional weeks. Means from each time point were compared by analysis of variance, and means bearing different superscripts differ from each other at $P < .05$. WT refers to wild type.

energy balance, the energy expenditure in all groups is indistinguishable (e.g., 42.1 kJ/day). Despite the 42% reduction in body weight observed in *Mc4r*$^{-/-}$ mice after initiation of pair-feeding, the expected lower energy expenditure[89,90] and the predicted increase in metabolic efficiency[88] are not evident in the comparison to wild-type (WT) mice at energy balance (Table 12.1). However, examination of the changes in body composition after initiation of pair-feeding illustrates profound differences in partitioning of metabolizable energy between protein and fat deposition, even during the last 12 weeks when body weight did not differ among the groups (Figure 12.2 and Table 12.1). For example, consider first the contrast between WT and *Mc3r*$^{-/-}$ mice, in which the pair-feeding imposed essentially no food restriction on the WT mice and, within experimental error, involved no difference in body weight for the duration of the study (Table 12.1). As reported previously[91–93] and shown in detail in Figure 12.2), the absence of MC3R favors fat deposition at the expense of lean mass. This fundamental difference in nutrient partitioning occurs without any detectable effect on energy expenditure as measured by energy balance. In *Mc4r*$^{-/-}$ mice, fat deposition was also favored over fat-free mass when the mice were fed ad libitum, but imposition of pair-feeding produced a fundamental change in nutrient portioning such that fat-free mass was preserved at the expense of fat (Figure 12.2, Table 12.1). Collectively, this simple but rigorously applied energy balance approach illustrates that the obesity phenotype of ad libitum–fed *Mc4r*$^{-/-}$ mice involves nutrient partitioning but is dependent on hyperphagia, whereas the absence of MC3R favors fat deposition independent of energy intake.

It seems clear that end point measures of ad libitum energy intake, energy expenditure, and body composition are inadequate and capture only a snapshot of the underlying phenotype of these mice. In contrast, the approach described here could be further strengthened by the incorporation of an enhanced ANCOVA approach to indirect calorimetry in animals after they reach energy balance. It seems apparent that the path to unlocking the full potential of the expanding number of sophisticated genetic models of obesity being produced requires a far more rigorous approach to metabolic phenotyping. It also seems clear that the result will provide a far firmer foundation on which to base subsequent experiments to further elucidate the roles of targeted genes.

A last important design consideration is especially relevant to the overall approach of using genetically modified mouse models to model human obesity. With few exceptions,[88,94,95] a fundamental flaw in the experimental design of most metabolic phenotyping experiments is that they are conducted at temperatures below thermoneutrality for the mouse, where a significant proportion of energy expenditure is devoted to thermoregulatory thermogenesis.[83] Housing temperatures also have a significant effect on energy intake in the mouse,[88,96,97] reflecting the progressive increase in energy costs devoted to the maintenance of body temperature at subthermoneutral temperatures. In contrast, the absence of thermoregulatory effects on energy intake and expenditure in mice reared at thermoneutrality is far more representative of the mostly thermoneutral environment in which humans live and develop obesity. As applied to genetically modified mice, it seems apparent that the ability to disentangle thermoregulatory thermogenic costs from the remaining components of energy expenditure will provide far better models of human energy balance. It is also worth noting that the thermal environment has significant effects on voluntary activity, nutrient partitioning, and the integration of lipid metabolism among peripheral tissues.[96,98–100] The extraordinary advances in our capacity to perform genetic manipulations coupled with advances in our ability to monitor in vivo metabolism in real time offer great promise to the acceleration of progress in our fundamental understanding of the networks of genes and molecules that regulate energy balance. Realizing this promise will ultimately be linked to our ability to obtain fully comprehensive metabolic phenotypes of existing and newly developed animal models of obesity.

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13 Animal Models of Obesity
Nonhuman Primates

Barbara C. Hansen

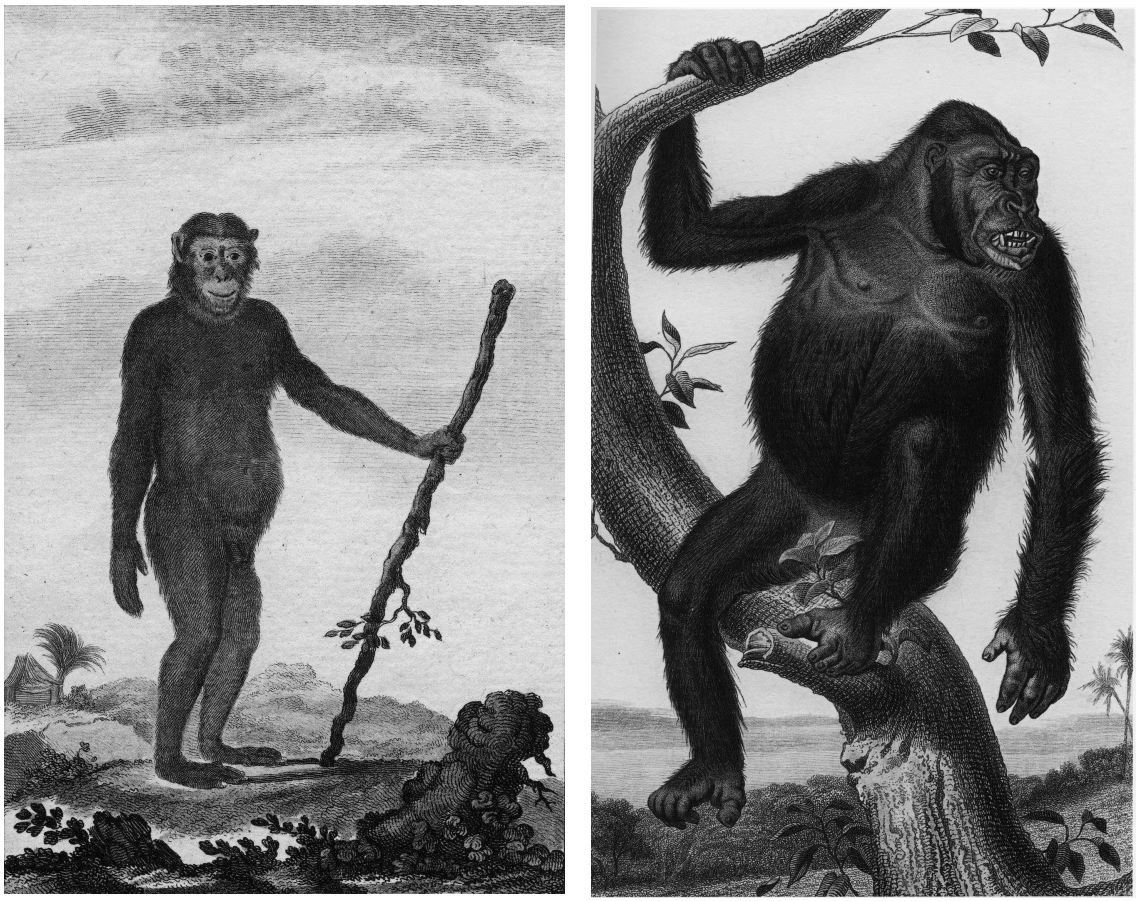
CONTENTS

13.1 SPONTANEOUS OBESITY IN NONHUMAN PRIMATES

13.1.1 Mammalian Species, Including Nonhuman Primates, with Spontaneous Obesity

Obesity has been recognized in nonhuman primates at least as far back as 1830 when an engraving of Jocko was made by A. Bell (Histoire Naturelle, Paris, G.L.L.de Buffon) (Figure 13.1a). In fact, in many orders of mammals beyond mice and rats (Order Rodentia), obesity has been shown to be common, including the Carnivora (e.g., dogs, cats, and bears), the Artiodactyla (pigs, cattle, and deer), and the more exotic orders such as those including whales, dolphins, rhinos, elephants, manatees, and the order Primates. This order includes two suborders, the prosimians (such as lemurs) and simians, also known as Anthropoidea, which includes, for example, monkeys, apes, and humans, a total of ~200 primate species. Within the Primate order, nearly all members of the suborder Anthropoidea have been shown to develop age-associated obesity. Specifically, obesity has been described in all three superfamilies: Ceboidea (New World monkeys, including marmosets, and squirrel monkeys), Cercopithecoidea (Old World monkeys, including 135 species such as baboons and macaques), and Hominoidea (the Hominidae including humans, orangutans, chimpanzees, and gorillas—with specimens of this last superfamily sometimes found to weigh >180 kg [>400 lb] and manifesting significant abdominal obesity per an engraving of a gorilla in A.V.C.D. d'Orbigny's Dictionnaire Universel d'Histoire Naturelle, 1839–1849, Paris, illustrator Travies, engraver, V. Fournier) (Figure 13.1b).

The relationships between these obesity-expressing primate species are diagrammed in Figure 13.2. Within the genus *Macaca*, often referred to as macaques, obesity has been described most frequently in *Macaca mulatta* (rhesus monkeys) as well as in *Macaca fascicularis* (cynomolgus monkeys), *Macaca radiata* (bonnet macaque), and *Macaca nigra* (misnomered the Celebes ape).[1–3] Of note



(a) (b)

FIGURE 13.1 Engravings of obese nonhuman primates. (a) Engraving of Jocko by A. Bell (Histoire naturelle, Paris, G.L.L.de Buffon), 1830, and (b) engraving of a gorilla in A. V. C. D. d'Orbigny's Dictionnaire Universel d'Histoire Naturelle, 1839–1849, Paris, illustrator Travies, engraver, V. Fournier). (From Baulu J, *Singes et Grands Singes: La Decouverte des Primates par les Naturalistes et Leur Representation dans les Gravures et les Dessins des Cinq Derniers Siecles*, Les Editions Fides, Saint-Laurent, Quebec, p. 17, 42, 2005.)

also is the Chlorocebus aethiops sabaeus (vervet, African green monkey), also under study for its obesity and diabetes.[4] Spontaneous, naturally occurring obesity is very common both in free-ranging and in laboratory or zoo-maintained nonhuman primates. In rhesus and cynomolgus as well as in baboons (*Papio hamadryas* and the various subspecies of *Papio*), weight gain and body fat distribution at middle age are predominantly abdominal, with both intra-abdominal and subcutaneous fat accumulation. The pedigreed baboon colony at the Texas Biomedical Research Institute numbering >2000 animals and fed under ad libitum conditions has shown strong familial inheritance patterns for obesity similar to those in humans.[5]

13.1.2 Experimentally Induced Obesity in Primates

In addition to the frequent, naturally occurring, middle-age-onset obesity, experimental induction or exacerbation of obesity has been studied in nonhuman primates. Previous reviews have described the various measures used to produce experimental obesity in primates[6] including the production of hypothalamic lesions to induce weight gain and diabetes-like syndromes, drug and hormonal approaches, and diet manipulations[7,8] or forced overfeeding[9,10] to produce weight gain. These methods have received little use in the past 10 years, probably because as monkeys have been held longer under laboratory conditions, well into middle age, more and more chow-fed, spontaneously obese animals have been identified, thus reducing the need to experimentally create obese primate models. Furthermore, the experimentally induced obese models deviate significantly in both physiology and pathology from the "normal" naturally occurring form(s) of obesity; for example, high-fat feeding induces abnormal lipid profiles,[11] fetal abnormalities,[12] and epigenetic remodeling,[13] while high-fructose diets (with net 30% reduction in fat content and in protein content) have led to disturbances of glucoregulation and fat oxidation.[14] High-dose streptozotocin has been used to produce diabetes in cynomolgus and rhesus, with greater adverse effects in those already obese at administration.[15] Thus, experimentally induced obesity likely differs both in underlying mechanisms and in responses to treatment and requires caution in interpretation. The present review will, therefore, focus on spontaneous obesity in both free-ranging and laboratory-maintained monkeys.

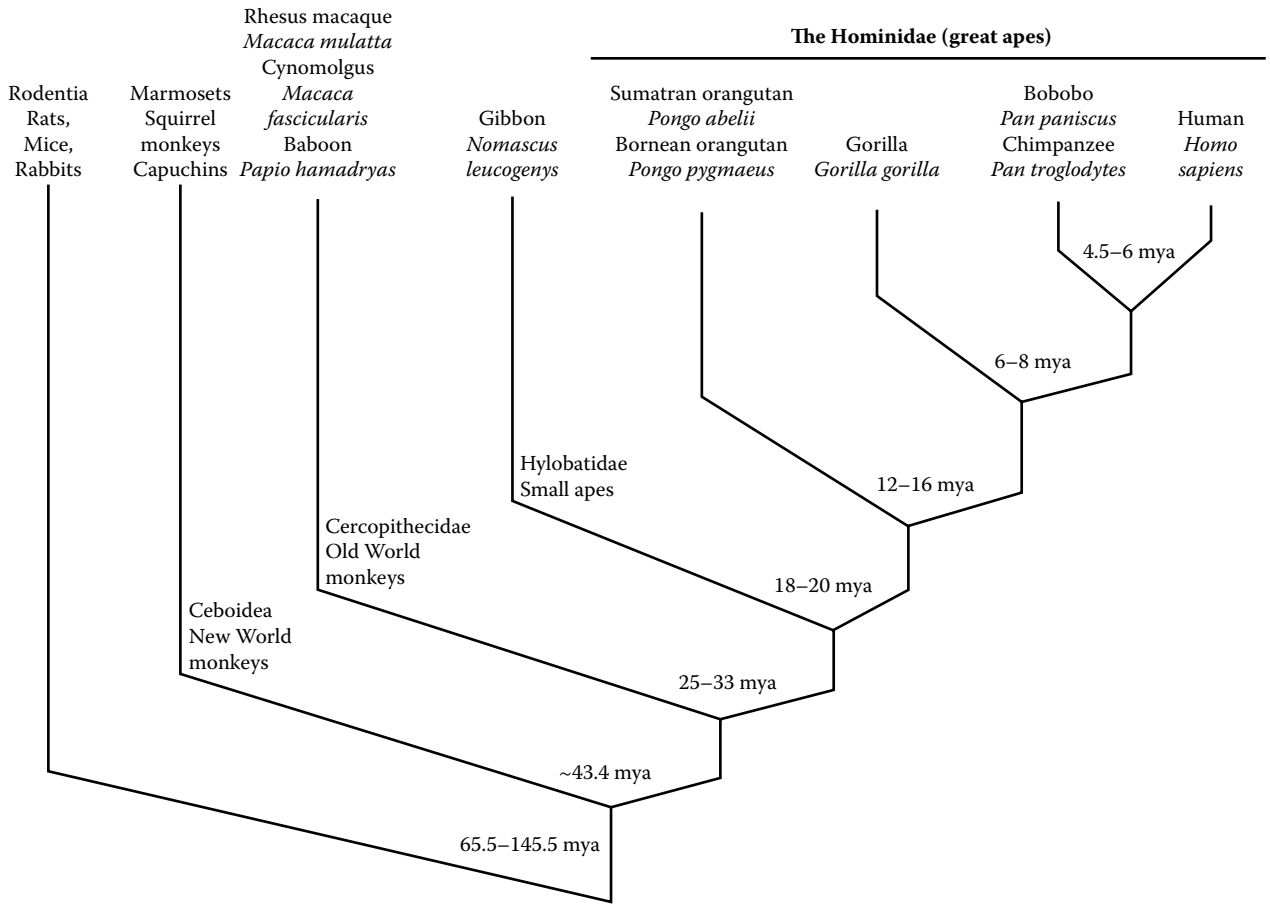


FIGURE 13.2 Diagram of phyla and primate species known to develop spontaneous obesity in middle age. Mya, millions of years ago at divergence. (Redrawn in part from Locke DP et al., *Nature*, 469, 529–33, 2011.)

13.1.3 Spontaneous, Naturally Occurring Obesity in Nonhuman Primates

One of the first surveys aimed at identifying the prevalence of spontaneous obesity in a colony of group-housed monkeys (800 pig-tailed macaques [*Macaca nemestrina*]) examined the body composition of animals found to be heavy for age and sex.[6,16] This obesity occurred in these as well as in rhesus monkeys only in sexually mature animals, generally over the age of 8 years. For reference, sexual maturity is reached in the female rhesus between 3 and 5 years[17] with completion of growth at 6–7 years of age, while in the male rhesus the corresponding ages are 4–6[18] and 8 years. The obese monkeys, identified in a survey of a free-ranging chow-provisioned colony living on the island of Cayo Santiago, ranged in age from 9 to 16 years.[19,20] Peak body weight, on average, is reached around the age of 15 years in *M. mulatta*. The most obese rhesus monkey on record to date (31 kg) is shown in Figure 13.3. Body weight declines several years before overt type 2 diabetes mellitus (T2DM), and this decline is a very early marker of impending diabetes, occurring well before any fasting hyperglycemia.[21]

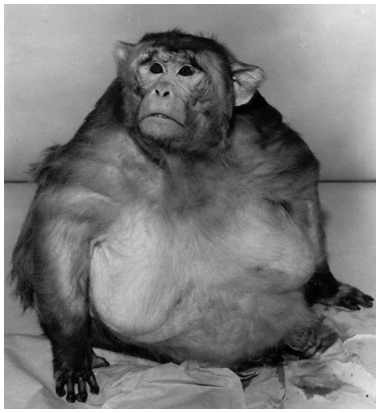


FIGURE 13.3 The most obese rhesus monkey (31 kg) at approximately age 18. The monkey was maintained lifelong on a "healthy" chow diet, supplemented with small treats of fruit several times per week. Activity was not restricted. (Author's personal photo.)

In young adults (under 6 years of age), the risk of or propensity to develop obesity at a later age cannot be determined in nonhuman primates based on any current markers, and thus, other than family history of obesity, as noted for the baboon colony, there are no ways to estimate accurately the risk of obesity. In rhesus, if held under laboratory conditions with a healthy diet provided ad libitum, overweight or obesity will develop in more than 60% of the monkeys when they have reached middle age, especially at ages over 15 years.

Of course, obesity does not develop in an environment where calorie intake is restricted, such as by fixed (non–ad libitum) levels of allocation of chow.[22] Under that calorie-controlled condition, body weight and composition adjust to match the calories available.

13.2 MEASUREMENT OF ADIPOSITY AND DEFINITION OF OBESITY IN MONKEYS

The assessment of obesity in mature adult monkeys can be made by body weight alone, since, in the fully adult animal (above the age of 8 years or about 8 kg), body weight and percent fat are highly correlated (within each sex) ($r = 0.62$, $p < .01$)[23] (Figure 13.4), as are percent fat and abdominal circumference.[24] The body mass index, or Quetelet index (weight/height^2), was adapted for use in monkeys by substitution of the crown-rump length (in cm) for height.[23] This body mass index, termed the Obesity index Rh (for rhesus monkeys), was shown to be highly correlated with percent weight as fat ($r = 0.80$, $p < .01$), mid-girth circumference ($r = 0.82$, $p < .001$), and body weight ($r = 0.80$, $p < .001$), but not with height, and was therefore suggested to be the best simple measurement of body fatness in monkeys. It suffers, however, with having body mass index (BMI) units that are derived from only a portion of height (similar to sitting height) and the resulting numbers are not familiar in human terms. Therefore, a "true BMI" has been calculated using full height (length while lying on the side, measured in two segments: length from the top of the crown to the base of the tail added to length from the hip joint to the heel [plantar surface] with leg extended fully at a 90° angle to the spine) and weight (weight [kg]/height [m^2]).

For nonhuman primates, Table 13.1 summarizes the results of these anthropometric determinations in a large colony of adult rhesus monkeys. Note that if length is measured in three segments (crown to rump, rump to knee, and knee to plantar surface of foot), this measurement suffers from increased interobserver variability and generally greater total lengths compared to "true height" (equivalent to the fully stretched straight length) (Table 13.1).[25] The latter, however, is sometimes difficult to obtain, due to joint rigidities in middle-aged and older animals. Thus, any translation across various height methods to a standardized BMI calculation should be made by applying a specific human conversion factor relative to the selected height method.

The dual-energy x-ray absorptiometry (DXA) method in nonhuman primates is considered to be the "gold standard" for assessing body composition; however, it is not readily available to most primate laboratories. We have examined body composition using both the tritiated water dilution method and

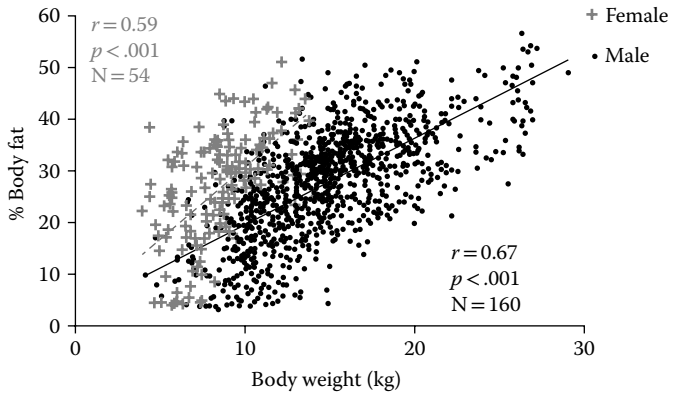


FIGURE 13.4 Relationship between percent body fat versus body weight in 214 adult rhesus monkeys (1358 dual-energy x-ray absorptiometry measurements) with weight range 4–29.1 kg and age range 7.2–29.6 years. The male and female slopes differed significantly indicating that females get fatter per unit weight increase than males, thus requiring sex-specific correction factors for body mass index calculation.

TABLE 13.1
Anthropometric Measures (Rhesus Adults Only)

Variable	Mean	SD	Min	Max
Height indices (cm):				
Crown to base of tail (rump)	51.3	3.6	44.5	61.8
90° angle to spine leg length (from hip joint to heel)	39.4	3.7	34.7	50.6
Additive total height (1 plus 2)	90.7	6.0	80.4	108.5
Abdominal circumference (cm):				
Umbilicus circumference at 90° to spine	61.8	11.5	32.6	98.1

the DXA method, as have Blanc et al.[26] In a thorough comparative methods study, Blanc and colleagues noted that DXA underestimated fat by 7.5% while it overestimated lean mass by 20% relative to the doubly labeled water dilution method, and emphasized the importance of specific machine and software calibration. Colman et al. also compared somatometrics and DXA longitudinally in rhesus.[27] The body composition of female cynomolgus monkeys was examined by DXA against a standard, with the observation that percent body fat of soft tissue mass is a better index of obesity than body weight and/or anthropometry.[28] Chavez et al. have tested various anthropometric measures in baboons compared to DXA assessment and have identified a model that predicts insulin resistance in a colony of living baboons.[29] In our colony, all rhesus monkeys over a body weight of 15 kg had >25% of weight as fat. In obese male rhesus monkeys, body fat can reach 50% of body weight.

Computed tomography has been used to assess abdominal fat distribution, with the observation in cynomolgus of very strong positive correlations between body mass index and intra-abdominal fat, subcutaneous fat, and total abdominal fat (r's > 0.89).[30] Sharma et al.[31] compared magnetic resonance imaging and various anthropometric measures in cynomolgus and found significant heterogeneity in the amounts of intra-abdominal and subcutaneous fat. Body weight correlated best with intra-abdominal fat in these male cynomolgus monkeys.

13.3 DIET, FOOD INTAKE, ACTIVITY, AND ENERGY EXPENDITURE IN NONHUMAN PRIMATE OBESITY

13.3.1 Physical Activity and Energy Expenditure

In spontaneously obese male rhesus monkeys ranging from 12 to 22 kg (percent fat ranging from 23% to 38%), no differences in food intake were observed between the most obese and the least obese groups of the control ad libitum–fed group reported.[32] Obese animals showed reduced physical activity[32]; however, it has not been possible to document reduced activity in advance of the development of obesity.[33] In some studies, obese monkeys have been found to ingest fewer calories per lean body mass than lean monkeys[34]; thus there is, as yet, no evidence for hyperphagia as an important contributor to the development of obesity or its sustaining, a finding first reported many years ago under hypothalamic lesion conditions.[35] Of course, small amounts of deviation in intakes may not be measureable, even under laboratory conditions. It is more likely, however, that small metabolic adjustments are responsible for this weight regulation in obese monkeys, without evidence of hyperphagia.

13.3.2 Diet Composition and Obesity

Although several studies have involved dietary manipulations that were hypothesized to facilitate the development of obesity, where these dietary regimens have been tested in young animals, obesity has not developed.[36] Importantly, the usual dietary regimen of laboratory monkeys, primate chow, would be expected to be optimal in the prevention of obesity, as it is high in fiber, low in fat (17%), and relatively low in caloric density (3.5–4 kcal/g). In colonies where the calorie allocation to each monkey has been strictly controlled, that is, restricted below ad libitum levels, usually to a designated amount per kilogram of body weight, obesity has not developed or is minimal. Under conditions of ad libitum feeding (food continuously available for 8–24 h/day), obesity will eventually develop in, by our estimate, 60% or more of the laboratory-maintained animals, despite the presumed optimal diet composition. Long-term experimental limitation of calories, adjusted in fully adult animals on an individual basis to prevent body weight increase, can, however, prevent the development of this middle-age-onset obesity and can be very effective in preventing diabetes.[37]

Many studies have attempted manipulations of diet composition in monkeys for the purpose of mitigating or preventing obesity, but to date, long-term use of a diet composition that is either supportive of weight loss or effective in preventing weight gain has not been reported. The exception is the report of a very-high-fiber diet (higher than the already high-fiber diet usually provided to primates); however, the negative consequence of this diet, when provided to mothers of infants, is of significant concern. Specifically, the mothers on a high-fiber diet were significantly more rejecting of their infants, with those having the lowest weights being the most rejecting, an unintended consequence of apparent long-term calorie restriction.[38]

13.4 FEATURES COMMON TO MANY PRIMATE MODELS OF OBESITY

13.4.1 Longitudinal Development of Spontaneous Obesity in Rhesus Macaques: Metabolic and Endocrine Disturbances

Obese rhesus monkeys, followed longitudinally, show a gradual, slow decline in glucose tolerance, many years before the development of overt diabetes,[39] and this also has been observed in cynomolgus monkeys.[40–43] In some, but not all, obese nonhuman primates, this deterioration of glucose tolerance takes place at the same time as pancreatic insulin output is increased both basally and under stimulated conditions. Beta-cell hyperresponsiveness to a glucose load has been shown to be a very early and frequent defect in obesity, possibly preceding the development of significant insulin resistance and hyperinsulinemia.[44,45] In obese monkeys, before the development of overt diabetes, de Koning et al.[46] found beginning changes in pancreatic β-cells, with proliferation of β-cell mass, and small deposits of islet-associated polypeptide as islet amyloid, as also noted in cynomolgus.[41] Defects in pancreatic β-cell turnover or reduced β-cell neogenesis were not, however, implicated in either obesity or diabetes in rhesus or in humans.[47] But functional changes in the β-cell seem to be very important in establishing the additional risk above that of obesity in promoting the development of overt T2DM.[45] The insulin resistance is not a requirement for the development of obesity in rodents or primates.

Abdominal obesity in humans, as well as in monkeys, has been shown to be associated with diabetes. Monkeys with central or abdominal obesity could, however, be classified as insulin-sensitive or insulin-resistant (as in humans), and the monkeys showed a strong positive relationship between abdominal circumference and fasting plasma insulin and an inverse relationship with insulin resistance. Yet within the obese group, there was a diversity of degrees of insulin resistance.[24,48]

Among the Texas colony of baboons as well as among the macaques of our colony[24] and others, insulin sensitivity, as determined by the euglycemic hyperinsulinemic clamp, has been closely associated with abdominal obesity.[29] Fasting insulin levels and abdominal circumference together helped to identify among the baboons, those that harbored obesity-associated insulin resistance.[29] Among rhesus, increased abdominal fat mass was necessary for the development of insulin resistance and T2DM, but not all monkeys with such increased mass were insulin resistant. The covariance structure of the variables associated with the development of metabolic syndrome was similar between human beings and nonhuman primates[49] and showed metabolic deceleration with aging.[50] In predicting insulin resistance based on anthropometric indices, fasting insulin, and fasting glucose to identify baboons with obesity and metabolic syndrome, Chavez et al. identified abdominal obesity by circumference as a key feature of their optimal predictive model.[29] Sex hormone–binding globulin has also been implicated in male rhesus with obesity.[51]

Furthermore, the hepatic insulin resistance, as evidenced by the failure of insulin to suppress hepatic glucose production, is not associated with obesity per se, but has been directly related to the subsequent development of overt T2DM in monkeys.[52] Evidence supports the manifestation of insulin resistance in different tissues at different points in the longitudinal progression of obesity toward impaired glucose tolerance (IGT) and subsequently to overt T2DM. The earliest tissue specific evidence for insulin resistance has been measured in muscle,[53] with subsequent insulin resistance developing later in time in adipose tissue,[54] and even later in liver.[52,55]

Reduced hepatic extraction of insulin has also been shown to be involved in the sustaining of hyperinsulinemia.[56] Nevertheless, this reduced extraction does not appear to be primary, occurring only as insulin levels increase above a portal insulin level of 700–1000 pmol/L (117–167 μU/mL) or a peripheral insulin level of >350 pmol/L (58 μU/mL). Thus, at the early stages in the development of both obesity and hyperinsulinemia, there appears to be no defect in hepatic insulin uptake[56] or in hepatic responses to insulin. The liver remains sensitive to insulin action to suppress hepatic glucose production until the occurrence of an increase in fasting glucose levels, apparently a direct indicator of developing hepatic insulin resistance.[52]

13.4.2 Dyslipidemia

In primates, spontaneous obesity has been shown to be associated with an increased frequency of dyslipidemia and varied susceptibility to diet-induced or spontaneous atherosclerosis, and these primates developed atherosclerotic lesions that were similar to humans.[57] There was, however, no significant relationship in this study between abdominal circumference and various lipoprotein fractions. Hannah et al.[58] showed that obese, hyperinsulinemic, normoglycemic monkeys had beginning increases in very-low-density lipoprotein triglycerides, small reductions in high-density lipoprotein cholesterol, and no change in low-density lipoprotein cholesterol. This dyslipidemic profile was significantly exacerbated in those monkeys with T2DM. Using nuclear magnetic resonance techniques to profile the lipids of monkeys ranging from normal to overtly diabetic, Ding et al. and Yin et al. have shown a very humanlike circulating lipid profile, with the dyslipidemia associated with prediabetes and overt diabetes predominating.[59,60] High-fat diets have also been used to alter lipoprotein composition[11,61]; however, they result in abnormal lipid profiles at the lipid fraction level and should be used with caution in assessing the mechanisms underlying dyslipidemia or its treatment.[60,62] Figure 13.5 shows the unique lipid fraction profile of a high-fat/high-cholesterol diet regimen compared to profiles of both monkeys with normal lipids and those with naturally occurring "endogenous" hypercholesterolemia.[11] This naturally occurring obesity-associated dyslipidemia has been the target of multiple pharmaceutical efficacy studies in rhesus, aimed at either the cholesterol[63] or triglyceride components,[62,64–66] as reviewed previously.[6] Bastarrachea et al. have refined the methods for assessing free fatty acids (FFA) and glycerol turnover to improve the in vivo evaluation of drugs affecting adipose tissue metabolism.[67]

13.4.3 Phases in the Progression of Type 2 Diabetes

Many, but not all, obese monkeys go on to develop IGT and then progress to overt T2DM.[6] This longitudinal process was first described by Hamilton and Ciaccia[68] as a period of middle-aged obesity and normal glucose tolerance, associated with hyperinsulinemia, followed by glucose intolerance and frank diabetes. The progressive process was further defined as a series of successive phases leading from normal lean young adult animals to middle-aged or older monkeys with or without obesity.[69] Among those that became obese, some then progressed through successive phases of increasing hyperinsulinemia and insulin resistance, progressive IGT, and finally overt T2DM.[69]

Glucose tolerance, one measure of this progressive process, has been calculated using a number of different formulas, the optimal of which is defined by the slope of the time points 5 and 20 minutes after an intravenous glucose tolerance test using a glucose load of 0.25 g/kg of body weight. This time period was determined to be optimally applicable to all monkeys across the entire range of tolerance from young normal to severely diabetic[19] without the need for different protocols or time intervals for the range of metabolic disturbances. Any other time interval beyond the 5- to 20-minute range for calculation of glucose tolerance suffers from one source of error or another (lean can fall below basal at 30 minutes or beyond, and use of time points before 5 minutes may suffer from

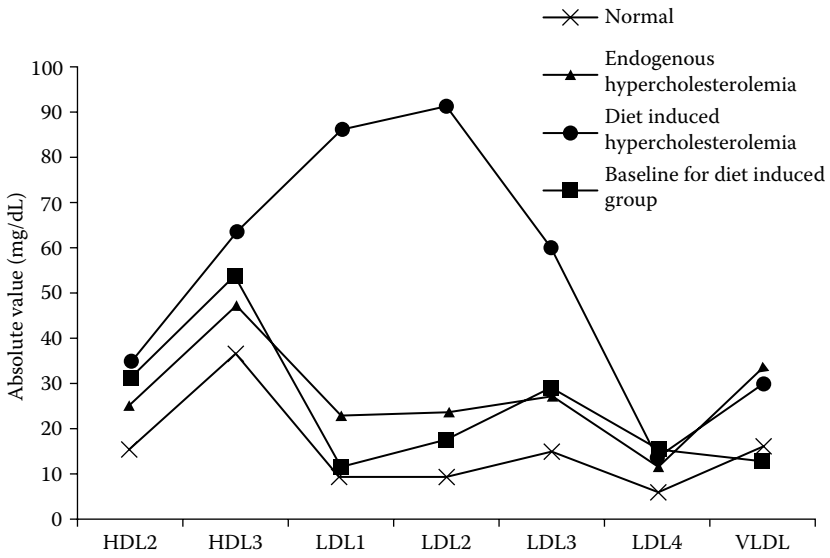


FIGURE 13.5 High-fat diet-induced dyslipidemia produces a very deviant lipid fraction profile compared to the profiles of normolipidemic monkeys (normal), or compared to their own prediet (baseline) profile or to the profile of other monkeys with naturally occurring dyslipidemia (endogenous hypercholesterolemia on a low-cholesterol diet). (Redrawn from Shamekh R et al., *Metabolism*, 60, 1165–77, 2011.)

incomplete mixing of glucose in the circulation, thus resulting in spuriously high or spuriously low glucose levels).[70] To this has been added an additional method for calculation of glucose disappearance rate that improves the predictive power of the intravenous glucose tolerance test for overt diabetes (the Multiple Kglucose program).[70,71] The log of the same time points (5–20 minutes) may also be used.[71]

Surrogate indices of insulin sensitivity or insulin resistance, including quantitative insulin sensitivity check index (QUICKI), homeostatic model assessment (HOMA), Log HOMA, 1/HOMA, and 1/fasting insulin, have been compared to the "gold standard" for insulin resistance, the euglycemic hyperinsulinemic clamp. In summary, simple surrogate indices of insulin sensitivity or its reciprocal, insulin sensitivity based on fasting glucose and fasting insulin levels, show a linear relationship with the clamp-derived insulin sensitivity, comparable to humans, and substantially better than in rodents. The physiological and metabolic similarities between humans and nonhuman primates presumably account for this difference from rodents. Most surrogates showed only modest linear correlations to the clamp estimate of sensitivity[72] and thus are optimally used only when larger-scale studies preclude the costs and expertise required for valid clamp implementation and evaluation. Kemnitz et al.[3,73] showed that during pregnancy, both a deterioration of glucose tolerance and an increase in fasting plasma insulin levels occur in those rhesus monkeys in the highest preconception tertile of adiposity. Wagner et al. also showed a similar effect in cynomolgus monkeys,[74] as was reported by McTighe for chimpanzees.[75]

Another method for assessing insulin action and glucose metabolism, the graded glucose infusion,[76] using stepwise increments of glucose (4, 8, 16 mg/kg/min) to assess glucose rise and insulin output in response to the glucose, clearly shows impairments when the β-cell is functionally disturbed, but is less sensitive for early detection of altered (increased) responsivity of the β-cell.[77] Further complicating the role of obesity in the development and onset of diabetes are our recent findings in which the longitudinal weight trajectory is characterized by a peak body weight usually 1–3 years before the diagnosis of diabetes, with weight loss occurring for several years before basal hyperglycemia.[21,77]

13.4.4 Pancreatic Functional Disturbances

Although frequently islet pathology has been cited as the proximate cause of the deterioration from obesity to overt diabetes, overt pathology of the pancreas has not been identified in the phases preceding diabetes.[46,78] Both human and primate β-cells are long lived and there is little adaptive change in the adult β-cell population.[47] In fact, as noted earlier in Section 13.4.1, β-cell hyperresponsiveness is one of the earliest changes taking place during the long trajectory from obesity to overt diabetes.[44,45] Nevertheless, with the onset of diabetes, it is necessary to treat nonhuman primates and the first line of therapy is often aimed at enhancing β-cell secretion.[79] In experimentally induced diabetes with streptozotocin toxicity to the β cells, glucose rises only when about half of the β cells have been destroyed.[80]

13.4.5 Complications of Obesity, Metabolic Syndrome, and Type 2 Diabetes

With a high frequency estimated to be >50%, obese monkeys eventually develop overt T2DM, with a median age of diagnosis of >18 years.[6] Those with significant hyperglycemia and longstanding diabetes progress to all of the complications of obesity and diabetes known to man. Although the overt manifestations of these complications are delayed for years following diagnosis of diabetes, the obese, prediabetic monkeys have been shown to already be developing early pathologic changes including disturbances in vascular flow-mediated dilation[81]

and early diabetic nephropathy.[82] The urinary metabolism similarly shows early changes that may be biomarkers of this nephropathy.[83]

13.5 GENETICS OF OBESITY IN PRIMATES

13.5.1 Gene–Environment Interactions

Nonhuman primates provide excellent models for examining gene–gene and gene–environment interactions and for seeking the mechanisms underlying the development of aging-associated nondiet-induced obesity and possible mechanisms for associated pathophysiologies such as insulin resistance.[84] Both the induction and the remission of obesity require cellular events involving changes in overall energy balance. As in humans, several studies have documented a familial association in the development of obesity in primates, as noted earlier for baboons in Section 13.1.1. A mother and daughter pair was identified in the 1977 survey of *M. nemestrina* mentioned earlier in Section 13.1.3,[16] and Schwartz et al.[20,85] noted several primary familial relationships among the obese animals of the Cayo Santiago colony. The Japanese macaque, *M. fuscata*, showed evidence of increased obesity in some maternal lineages.[86] Environmental factors, principally ready access to nutritionally adequate food, also influence the incidence of obesity, which has been reported to range from 7% among the free-ranging Cayo Santiago rhesus troops (age range up to 16 years) to 50% or more in individually housed animals over an age range up to 40 years. On average, in our colony, maximum body weight is reached between 15 and 20 years of age, and this age-related phenomenon must be taken into account when seeking the genes for obesity.[87]

Further support for a genetic (as compared to an environmental or dietary) basis of nonhuman primate obesity comes by inference from studies of groups of *M. mulatta* held under identical and constant environmental conditions, in which some animals have become significantly obese, while others, ingesting the same diet, have remained lean throughout their lives.[88]

Nevertheless, the genetic bases for obesity and for T2DM remain unclear, although many putative susceptibility variants have been proposed. An initial genome-wide association study (GWAS) was performed using the Affymetrix 6.0 gene chip arrays to genotype the rhesus monkey.[87] The successful call rate on all chip arrays averaged 91%, with high heterozygosity (42%). Thus, genotyping of the rhesus monkeys using the human platform was shown to be very applicable. Principal component analysis successfully classified the monkeys into control or prediabetic/diabetic/insulin resistant. Five single-nucleotide polymorphisms (SNPs) passed the multiple-comparison P-level threshold for significance: cerebellin-2 (CBLN2), TTLL7, WDR40C, ATP2B3, and RAB39B. Special attention was given to 9 of the 18 SNPs previously associated by GWAS with T2DM in humans. One candidate gene, the CBLN2 SNP, was significantly associated with insulin resistance in rhesus and in Finnish/Swedish T2DM patients. RNA expression of CBLN2 was significantly reduced in type 2 diabetic monkeys, and it is a mechanism that is plausibly related to diabetes. CBLN2, which is expressed in the pancreas, causes lower insulin levels. This demonstrates the successful translation of the human genome array to rhesus.[87]

13.5.2 Candidate Genes for Obesity

No single-gene-induced cases of obesity have been reported in nonhuman primates. Examination of the genetics of obesity in nonhuman primates has focused on a wide range of candidate genes, some specific to adipose tissue, and others potentially involved in insulin action and insulin sensitivity, as reviewed previously for rhesus and baboons.[89] Several candidate genes have received special attention in nonhuman primates, specifically leptin or the *ob* gene, adiponectin, the β-3 receptor, the peroxisome proliferator–activated receptors (PPARs), insulin and its insulin receptor, and galectin-12 as previously reviewed.[6] The galectins are involved in the regulation of a variety of metabolic processes; however, their role in obesity is unclear despite their known elevation during calorie restriction.[6]

13.6 PEROXISOME PROLIFERATOR–ACTIVATED NUCLEAR RECEPTORS AND THEIR AGONISTS (PPAR AGONISTS)

Because of the significant clinical interest, and extensive research on the PPAR agonists, research in nonhuman primates continues. Previous studies were reviewed,[6] so only updates are considered here. They are of three subtypes, PPARα, PPARγ, and PPARδ, and they are the products of different genes on different chromosomes. They have significant effects on body weight (some increasing and some decreasing weight/adiposity), insulin sensitivity, and dyslipidemia.

We have previously reviewed a wide range of studies of all of the PPAR subtypes as examined in nonhuman primates.[6] While neither these PPAR receptors nor their agonists have been found to be causally involved in obesity per se, the strong association of obesity with insulin insensitivity and dyslipidemia has made the PPAR agonists particularly of interest for addressing the pathophysiology associated with obesity. Most recently, several applications of PPAR agonists have been reported in nonhuman primates.[62,80,90–92] The most recently developed and examined PPAR agonists have also shown efficacy to reduce body weight/adiposity (not increase it, as was an earlier concern with PPAR agonists) and to improve insulin sensitivity in nonhuman primates.[55,90,93]

13.7 INSULIN AND THE INSULIN RECEPTOR

Defects in the insulin molecule, the insulin receptor, and/or their sequence variants were earlier considered to be possible candidates for the underlying causes of insulin resistance and obesity. This was of special interest for possible involvement in nonhuman primates as the circulating levels of insulin are approximately fivefold higher in rhesus than in humans. The insulin molecule of the monkey was shown to be identical

in structure to the human insulin molecule, and the proinsulin (C-peptide) differs in only one amino acid.[94] The monkey insulin receptor was cloned and sequenced and found to have 99% amino acid identity to that of human.[95] The two identified nonconservative amino acid changes in rhesus were examined by site-directed mutagenesis of the human insulin receptor and found to have no effect on insulin receptor affinity or autophosphorylation, thus indicating that these were not responsible for the heightened apparent insulin resistance of monkeys relative to humans.[96] Therefore, whether lean or obese, there is as of now still no explanation for the higher circulating insulin levels in nonhuman primates compared to human levels. Nevertheless, the insulin signaling pathway remains of interest, and continuing studies extending those reviewed previously[6] are ongoing.

13.8 OTHER CANDIDATE GENES AND TARGETS FOR ANTIOBESITY ACTIVITY

Nonhuman primates are being used in the development of many new antiobesity compounds. The glucagon-like peptide-1 (GLP-1)-related targets, including several long-acting agents, have been examined in monkeys. Newer, much longer-acting GLP-1 agonists are effective in improving beta-cell function; however, weight loss has usually, although not always, been modest. Combinations of GLP-1 receptor agonists with other target specific molecules, as well as extended action molecules, are currently offering potential for enhanced antiobesity efficacy, possibly with reduced side effects or risks.

Adipotide, a ligand-directed peptidomimetic targeting apoptosis within the blood vessels of white adipose tissue, has been reported to produce rapid weight loss and improved insulin sensitivity in obese monkeys and improvement in renal proximal tubule function, thus suggesting a new potential class of drugs for the treatment of obesity.[97]

13.9 PREVENTION OF OBESITY IN NONHUMAN PRIMATES HAVING A HIGH PROPENSITY TO DEVELOP OBESITY

Prevention of obesity by calorie restriction reduces calorie expenditure and prevents T2DM. Energy expenditure per kilogram of lean body mass was significantly reduced by a degree of calorie restriction sufficient only to prevent the development of obesity.[32] Obesity is well recognized to be closely associated with the development of T2DM in humans and nonhuman primates. A long-term study sought to prevent the development of adult-onset obesity in a group of monkeys through a calorie titration regimen in which calories were adjusted weekly on an individual animal basis to prevent the development of obesity or weight gain. Thus, under this obesity prevention protocol, any gain of weight in fully adult monkeys was met with a reduction in the individually allocated calories, and conversely, weight loss was the trigger for increasing the calories allowed to each adult animal.[32]

Primary prevention of obesity in adult rhesus monkeys has been shown to powerfully and completely prevent the development of T2DM.[37,98] Prevention of obesity by restraint of calories neither increased nor decreased physical activity relative to similar-weight animals.[32] Nevertheless, the onset of overt diabetes was fully prevented. Recent reports on long-term follow-up of patients who were treated with bariatric surgery are reporting similar results[99,100]–confirming the extraordinary power of calorie restriction to prevent the development and/or progression of diabetes.

Chronic long-term restriction of calories to prevent the development of obesity appears to have major effects on several metabolic pathways of insulin action.[101,102] The development of insulin resistance has been shown to be mitigated,[98] and plasma insulin levels were maintained at normal levels by calorie restriction.[103] Basal glycogen synthase activity was greatly increased above the levels of normal lean young monkeys, and the normal effect of insulin to activate glycogen synthase was absent in the calorie-restricted monkeys.[104] The change in glycogen synthase activity was inversely related to the change in glycogen phosphorylase activity. Calorie restriction also increases the expression of genes involved in energy metabolism and downregulates the expression of many proinflammatory genes. The rate of progression of sarcopenia is also slowed by calorie restriction in rhesus.[101,105] Nevertheless, despite prevention of the development of obesity, calorie restriction appeared to unmask some early defects potentially associated with the propensity to ultimately develop obesity.[106] At this time, the effects of calorie restriction in nonhuman primates to extend maximal life span are controversial. One group has recently reported failure of long-term calorie restriction to extend average life span,[22] while two other groups (including ours) disagree.[105,107] The difference in results may depend heavily on the degree of calorie restriction of both the experimental groups and the control groups; the former noted research group having only small differences in body weight due to partial restriction of the "control" group, while the other two groups allowed their controls full ad libitum access to food leading in many of the controls to overweight, obesity, and T2DM.[101,105,107]

In summary, nonhuman primates provide a uniquely humanlike animal model for the study of the factors leading to varying degrees of obesity and further to the identification of mechanisms contributing to the complications of obesity. Most importantly, the spontaneous, naturally occurring (nondiet-induced) obesity in nonhuman primates frequently, but not universally, progresses to overt T2DM, a disease indistinguishable from the obesity-associated adult-onset diabetes of humans. The ability to hold the environment and the diet constant over many years and to assess metabolic changes under highly consistent conditions allows longitudinal studies of the sequence of appearance of various molecular and physiological defects. Importantly, these constancies allow for the careful examination of the consequences of obesity prevention both for metabolism and for affecting the outcomes of obesity. The translational value of findings from

obese nonhuman primates for application to humans, whether derived from the natural progression of the disease or from therapeutic interventions, is unmatched by any other species.

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14 CNS Regulation of Energy Balance

Hans-Rudolf Berthoud and Barry E. Levin

CONTENTS

14.1 INTRODUCTION

Energy homeostasis is the balance between energy intake and energy output. When intake exceeds output, energy is stored, primarily in the form of adipose tissue. When output exceeds intake, these energy stores are drawn upon to provide energy to support the ongoing metabolic needs of the organism. Although one cannot separate the brain from the body in terms of this regulatory system, it seems very likely that the brain is the conductor of the complex orchestra that oversees this complex process. Regulation of such homeostasis requires a constant dialogue among the external and internal environments and the brain (Figure 14.1).

Many have questioned whether there is true regulation of energy balance and whether there is some set point or "settling" point that determines the level of defended body weight and adiposity.[1,2] Several observations suggest that, depending on the genetic background of the individual, these parameters are regulated, but that such regulation most often favors upward but not downward movement of carcass adiposity. In the developed world, obesity is a growing problem and, once a new higher weight is reached, it rarely can be lowered permanently without invasive surgery.[3] Such unidirectional upward resetting of the defended body weight suggests that there might be some degree of plasticity in the system. Such plasticity is characteristic of the brain where formation of new neural circuits and/or connections is required for the formation of long-term learning and memory.[4] Neural plasticity can occur throughout life, but is most marked during gestation and the first few years of life when brain development is at its peak.[5] Thus, maternal undernutrition, obesity and/or diabetes, as well as many other early life environmental factors can have their major impact on the development of obesity during this period, particularly in individuals who have a genetic predisposition to become obese.[5]

To regulate energy homeostasis, the brain must be able to monitor the metabolic status of the body. To do this, it has evolved specialized neurons that can monitor a host of metabolic, hormonal and neural signals from the body. These "metabolic sensing neurons" are widely distributed throughout the brain in an interconnected network. Together with the metabolic support and signaling provided by surrounding glial elements, they form a metabolic sensing unit, which is the ultimate integrator-effector underlying neural control of energy balance[6] (Figure 14.2). Unlike the majority of neurons that utilize substrates such as glucose only to fuel their ongoing metabolic needs, metabolic sensing neurons possess specialized transporters, receptors, and/or biochemical pathways that allow them to monitor and respond to changes in ambient substrate levels by altering their activity, transmitter, and peptide release and gene transcription. So-called glucosensing neurons were the first to be identified.[7,8] When brain glucose levels rise, glucose-excited neurons increase their activity while glucose-inhibited neurons reduce theirs.[6,9] Within the ventromedial nucleus (VMN) of the hypothalamus, as well as other areas such as the arcuate (ARC) nucleus, nucleus tractus solitarius (NTS), and substantia nigra, the majority of glucose-excited neurons function much like pancreatic beta-cells.[6,9] They utilize glucokinase, the pancreatic form of hexokinase, as a gatekeeper and the ATP-sensitive K^+ channel as an effector for altering neuronal activity.[6,9] Many glucose-inhibited neurons also utilize glucokinase as the primary regulator of glucosensing but utilize different downstream pathways to regulate neuronal activity.[6,9] Other mechanisms regulating glucose-excited and glucose-inhibited neurons have also been described[6,9] (Figure 14.3).

Many glucosensing neurons also respond by increasing or decreasing their activity in the presence of long chain fatty acids. A majority of these fatty acid–sensing neurons utilize the fatty acid translocase/CD36 (FAT/CD36) that functions as a receptor to activate intracellular calcium stores and neural activity, processes that do not require metabolism of fatty acids[6,10] (Figure 14.3). Finally, although no specific effect of amino acids on mediating neuronal

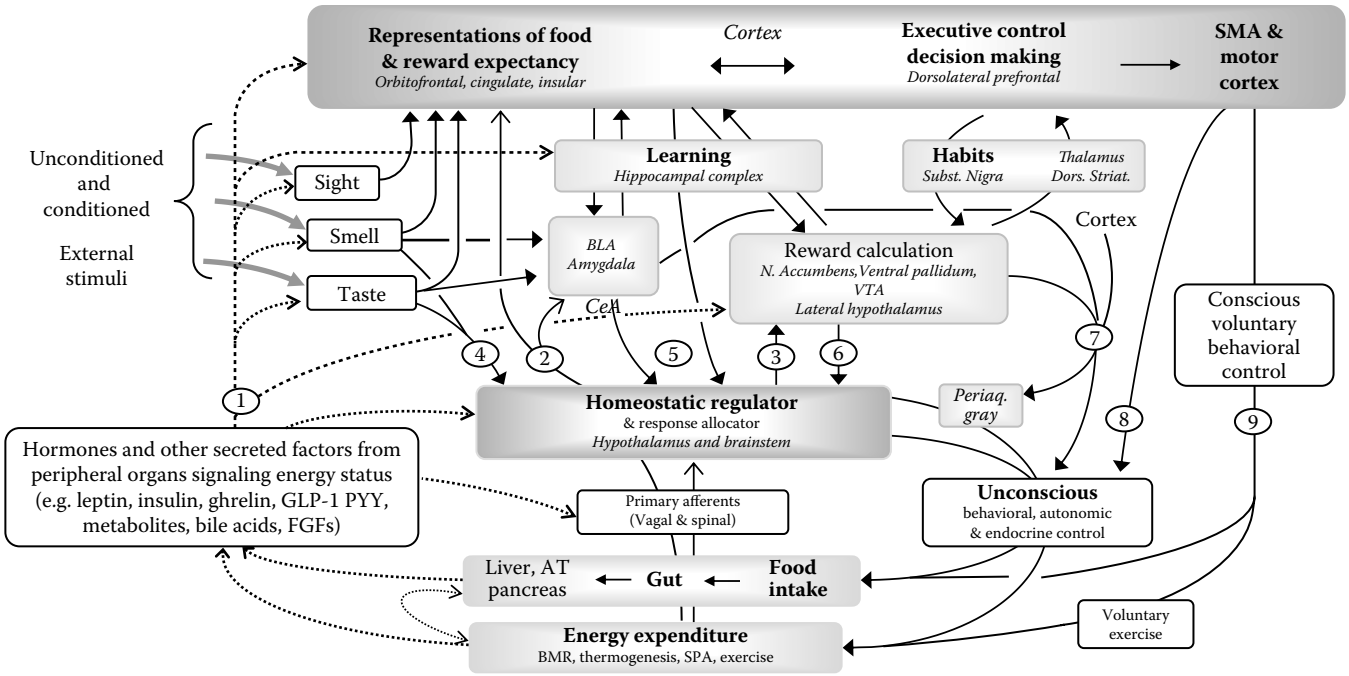

FIGURE 14.1 Major neural systems and pathways involved in the control of ingestive behavior and energy balance regulation with emphasis on interactions between the classical homeostatic energy regulatory system in the hypothalamus and brainstem (lower half) and cognitive/emotional brain systems (upper half). Bottom-up modulation of cognitive and emotional processes by metabolic signals and their derivatives is accomplished by (1) circulating hormones and metabolic substrates acting not only on the hypothalamus and brainstem but also on external sensory processing pathways as well as on components of the corticolimbic system; (2) a stream of vagal and spinal sensory information from within the body to all levels of the neuraxis, including the cortex; and (3) neural signals generated by the integrative hypothalamic metabolic sensor and distributed to areas involved in reward-based decision making. Together, these ascending modulatory influences determine the level of incentive salience directed to specific nutrients. Top-down modulation of food intake and energy expenditure by cognitive and emotional/reward systems is accomplished by (4) direct external (taste and smell) sensory input to the hypothalamic metabolic sensor and response allocator; (5) input from the amygdala and cortex; and (6) reward processing systems to mainly the lateral hypothalamus, responsible for conditioned external signals to elicit food intake; (7) inputs from cortex, amygdala, and basal ganglia to midbrain extrapyramidal motor pathways (emotional motor system); (8) unconscious determinants of actions originating from motor cortex; and (9) pyramidal motor system for voluntary behavioral control. (Adapted from Berthoud HR et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol*. 300, R1266–77, 2011.)

activity has been demonstrated directly, there is evidence that amino acids are sensed in some brain areas and this sensing can alter food intake[11–13] (Figure 14.3). Importantly, many of these same metabolic sensing neurons also respond to hormones from the periphery such as leptin, insulin, and ghrelin, which act on their receptors to interact with the actions of glucose and other metabolic substrates to alter the summated change in membrane potential and neuronal activity[6,9] (Figure 14.3).

Although much is now known about the mechanisms by which metabolic sensing neurons respond to signals from the periphery, there is still some question about how and under what conditions these neurons function to regulate the various aspects of energy homeostasis under physiological conditions.[14,15] Mayer suggested that "hypothalamic glucoreceptor cells regulate food intake by sensing fluctuations in glucose (oxidation)" as, "… mediated by generation of an electrical potential via passage of a K^+ ion into the cell."[16,17] In fact, while we have gained a reasonably good idea of why we stop eating, the issue of what drives us to eat and what role metabolic sensing neurons might play in this drive remains less clear.[18] Metabolic depletion is the best understood of the mechanisms that drive us to eat. During acute hypoglycemia, a situation virtually never seen in nature, glucosensing neurons in the ventromedial hypothalamus (ARC + VMN) are involved in both the drive to eat (hunger) and the counterregulatory neurohumoral responses that the body mounts to raise blood glucose levels.[14,19] But, during fasting, there is a more gradual decline of glucose utilization accompanied by a shift from carbohydrate to fatty acid metabolism and a dramatic decline in plasma levels of leptin and insulin.[20] In fact, it is likely that the withdrawal of these two powerful centrally acting catabolic signals, as well as the rise of the orexigenic hormone ghrelin, is the primary stimuli for the onset of hunger, increased arousal, foraging, and ingestion of food required to replete lost energy stores. In addition, such metabolic depletion also increases the incentive salience of food in almost any form and this phenomenon adds to the powerful forces that drive the individual to seek and ingest food.[21]

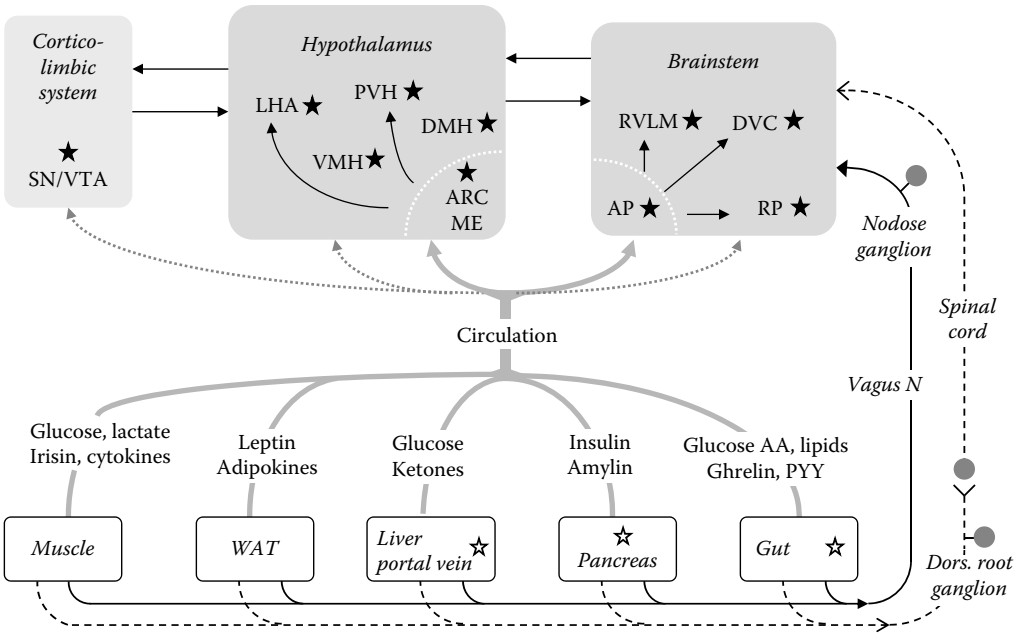

FIGURE 14.2 Metabolic sensing network. Metabolic sensors (open stars in organs) are located in the portal vein and intestines and provide neural inputs through vagal and sympathetic afferents that terminate in the nucleus of the solitary tract (NTS). The NTS contains metabolic sensing neurons (black stars in brain), which respond to metabolic substrates, hormones, cytokines and adipokines, and other blood-borne elements that are either transported across the blood-brain barrier or enter directly through blood vessels in the area postrema, which lack tight junctions that comprise the blood-brain barrier. After integrating all of these incoming signals, NTS neurons send local efferents to hindbrain nuclei involved in autonomic regulation (caudal ventrolateral medulla and rostral ventrolateral medulla, dorsal vagal complex, raphe pallidus and obscurus), and rostrally (directly or indirectly) to the metabolic sensing neurons in the hypothalamic arcuate (ARC), ventromedial nucleus (VMN), and dorsomedial nucleus and the lateral hypothalamic area (LHA), as well as the limbic areas such as the amygdala. The paraventricular hypothalamic nucleus receives inputs from the ARC and VMN and, together with the LHA, represents a major efferent area for neuroendocrine and autonomic function. Metabolic sensing neurons in midbrain reward areas (substantia nigra, ventral tegmental area) provide efferents to the dorsal and ventral striatum and medial prefrontal cortex. The collective output of these receptive areas results in the neuroendocrine, autonomic, motor, and behavioral outputs required for the regulation of energy homeostasis. AAT, amino acid transporter; AMPK, AMP-activated protein kinase; CaMK, calcium-calmodulin-dependent protein kinase; cAMP, cyclic AMP; CPT1, carnitine palmitoyltransferase 1; FATP, fatty acid transport protein; GHR, growth hormone receptor; GLUT3, glucose transporter 3; IR, insulin receptor; MCT2, monocarboxylate transporter 2; mTOR, mammalian target of rapamycin; NMDAR, NMDA receptor; ObRb, leptin receptor-b; OXR1, orexin 1 receptor; PI3K, phosphoinositol-3 kinase; PKA, protein kinase A; PKC, protein kinase C; SGLT, sodium-glucose co-transporter; SOCC, store-operated calcium channel; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription 3; GK = Glucokinase; LCAcyl-CoA = long-chain fatty acid acyl-coenzyme; AMP = adenosine monophosphate; FOXO = forkhead box transcription factor; ERK 1/2 = extracellular signal-regulated kinase 1 and 2; S6K = ribosomal S6 kinase.

The other powerful drive to eat in some individuals can be termed "the anticipation of depletion." This is a complex concept that may underlie many of the psychological and circadian patterns of food intake, particularly in humans. For example, while some degree of metabolic depletion might occur after an overnight fast, and thus explain why we eat breakfast, it is highly unlikely that such depletion occurs between breakfast and lunch or lunch and dinner. More likely, we respond to both external (social, light:dark change) and internal (food entrained rhythms) cues to decide when to eat these other meals. In addition, there are a host of metabolic, hormonal, and neural adaptations that occur in parts of the brain that regulate metabolism, motivation, and learning in response to the sum of all these signals. This chapter deals with these functions separately although it is important to realize that they are inextricably bound together in the functioning organism (Figure 14.1).

14.2 METABOLIC ASPECTS OF NEURAL REGULATION ENERGY HOMEOSTASIS

Arguably, the most important brain areas mediating the metabolic aspects of energy homeostasis lie in the medulla and hypothalamus, which act as primary sites for integration of the neural, substrate, and hormonal information that enter the brain. In these areas, metabolic sensing neurons comprise 10%–15% of the total population of resident neurons. After integrating all these incoming signals, they pass on that information to secondary centers from which efferents arise to control autonomic, hormonal, metabolic, behavioral, and motor responses (Figure 14.4). The hindbrain is phylogenetically among the most ancient areas of the mammalian brain. It represents the first way station for incoming autonomic neural inputs from the periphery and is fully capable of regulating a host of physiological and behavioral functions in the

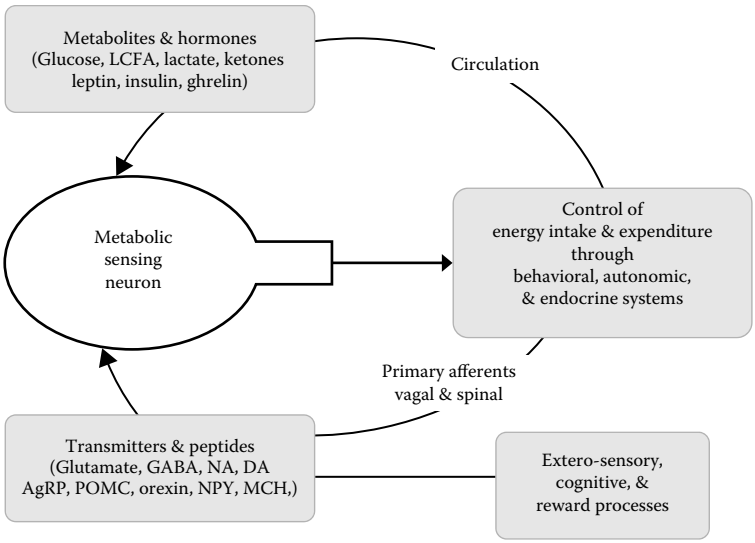

FIGURE 14.3 Metabolic sensing neurons alter their membrane potential, activity, neuropeptide and transmitter release and gene transcription in response to metabolic substrates (glucose, long chain fatty acids [LCFA], lactate, and ketone bodies) and hormones (leptin, insulin, and ghrelin), as well as neural inputs from intrinsic networks; areas involved in reward, motivation, and memory; and receptors that sense the external (taste, smell, and sight) and internal (hepatic portal, and gut) environments. The collective output from the distributed network connecting these metabolic sensing neurons regulates neuroendocrine, autonomic, motor, and behavioral outputs. These outputs provide the feedback signals that allow these neurons to monitor the internal and external environment as a means of regulating energy homeostasis.

absence of forebrain function.[22] The NTS is a long column of neurons that runs from the caudal medulla, rostrally into the pons. It is the primary hindbrain site upon which afferent neural signals carried by the vagus and sympathetic fibers that innervate organ systems involved in energy homeostasis and respiratory and cardiovascular functions converge. Among these are inputs from metabolic sensors in the intestines, hepatic portal vein, and carotid body, which detect glucose, other nutrients, peptide and hormone levels in the blood and organs, as well as afferents from stretch receptors in the stomach.[6,23] Taste receptor afferents from the tongue and oropharnyx terminate in the rostral extension of the NTS in the pons.[24] Many of these NTS neurons are also metabolic sensors and so represent the first site of integration of neural, hormonal, and nutrient signals from the periphery. These integrated signals are then passed both locally within the brainstem and upward to the hypothalamus and other forebrain areas (Figure 14.4).

The hypothalamus is a second-order integrator and primary effector of neuroendocrine output. Within the hypothalamus, the paraventricular (PVN), ARC, VMN, and dorsomedial (DMN) nuclei lie medially along the walls of the third ventricle. Most of these nuclei contain metabolic sensing neurons that receive either direct or indirect neural inputs from the NTS (Figure 14.4). Some also receive inputs from reward, limbic and neocortical, areas as well as being interconnected with each other.[25] Two sets of ARC neurons have critical roles in the metabolic regulation of energy homeostasis (Figure 14.5). Proopiomelanocortin (POMC) neurons release α-melanocyte-stimulating hormone (α-MSH) that binds to melanocortin-3 and melanocortin-4 receptors (MC3/4R) on PVN and lateral hypothalamic area (LHA) neurons to produce a potent catabolic effect, cessation of feeding, and stimulation of thermogenesis. Adjacent to these POMC neurons lie those that co-express neuropeptide Y (NPY) and agouti-related peptide (AgRP). They also project to the PVN and LHA. NPY released from these neurons produces a net anabolic effect with potent simulation of foraging and ingestion of food.[25] On the contrary, AgRP is a functional antagonist at the MC3/4R so that when ARC NPY/AgRP neurons release their peptides onto target neurons, it produces a potent orexigenic effect, blocks the catabolic effects of the melanocortin system, and also inhibits neighboring POMC neurons directly. Both the NPY/AgRP and POMC neurons are metabolic sensors whose activity is altered by glucose, long chain fatty acids, leptin, and insulin.[6]

Although the excitatory and inhibitory responses to the neural and metabolic substrates from the periphery vary markedly depending on a host of factors, insulin and leptin uniformly inhibit NPY/AgRP production and release and stimulate α-MSH production and release. Thus, under homeostatic conditions, increases in adiposity are associated with increased plasma leptin and insulin levels that provide negative feedback to inhibit food intake and stimulate energy expenditure. While leptin and insulin levels in the blood provide a fairly accurate hormonal representation of the amount of carcass adiposity under steady-state conditions, fasting markedly and rapidly reduces levels of both. This withdrawal of these inhibitory hormones leads to a marked anabolic drive because of disinhibition of NPY/AgRP neurons and inhibition of POMC neuronal output.

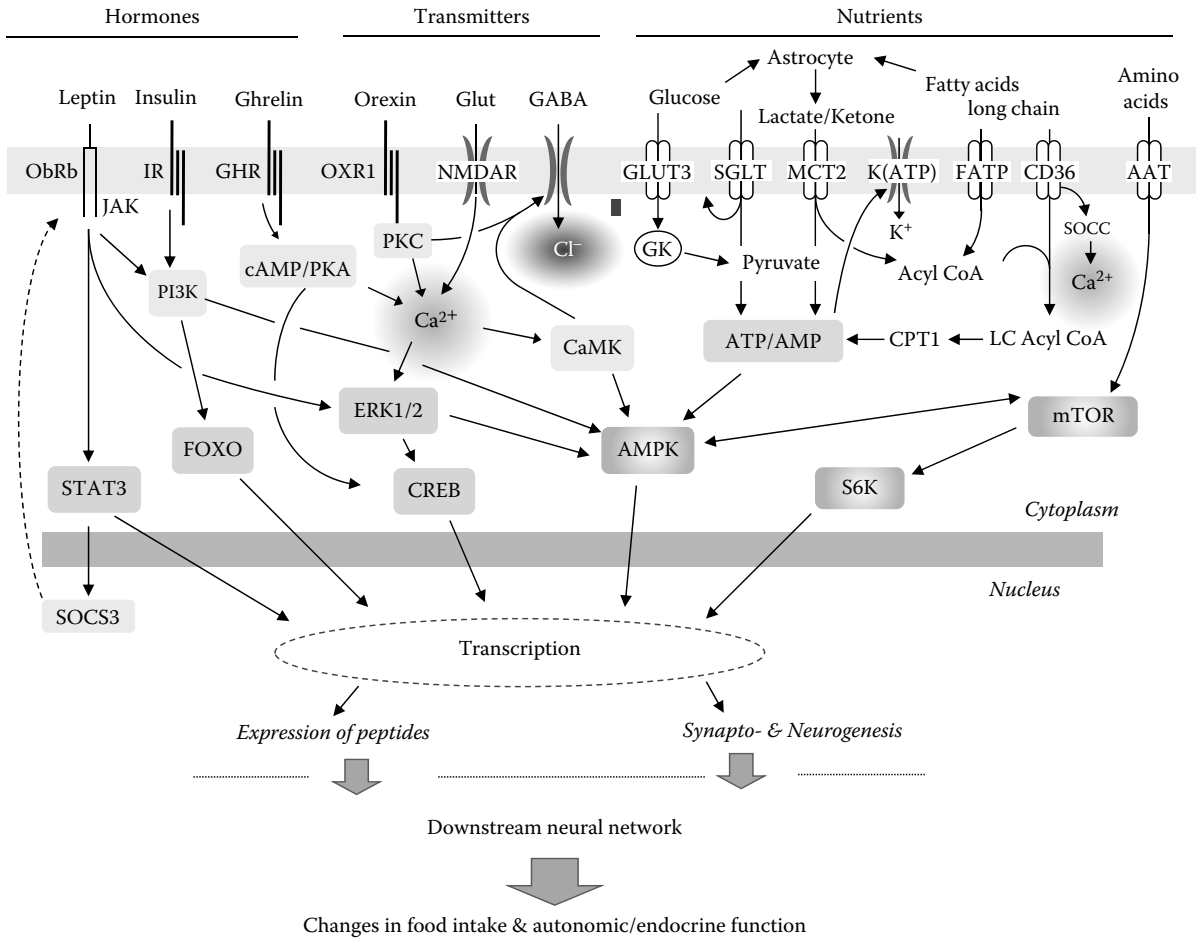

FIGURE 14.4 Molecular mechanisms of integration of various signals by "metabolic sensing neurons" in the mediobasal hypothalamus. Hormones (insulin, leptin, and ghrelin) and metabolic substrates (glucose, long chain fatty acids, lactate, and ketone bodies) interact with receptors, ion channels, and transporters to alter membrane potential and neuronal activity by changes in intracellular energy substrates (ATP, AMP, LCFA, and acyl CoA), activation of downstream signaling pathways (STAT3, PI3K, extracellular signal-regulated kinase (ERK), AMPK, and mTOR), or by direct generation of an electrogenic potential (SGLT). Other downstream effects of metabolic sensing are activation/repression of gene transcription and release of neurotransmitters or neuropeptides. AAT, amino acid transporter; AgRP, agouti-related peptide; AMPK, AMP-activated protein kinase; CaMK, calcium-calmodulin-dependent protein kinase; cAMP, cyclic AMP; CD36, FAT/CD36, fatty acid translocator/CD36 receptor; CPT1, carnitine palmitoyltranferase-1; CREB, cAMP responsive element binding protein; FATP, fatty acid transport protein; GHR, growth hormone receptor; GLUT3, glucose transporter 3; IR, insulin receptor; LC-acyl CoA, long chain fatty acid acyl CoA; MCH, melanin concentrating hormone; MCT2, monocarboxylate transporter 2; mTOR, mammalian target of rapamycin; NMDAR, NMDA receptor; NPY, neuropeptide Y; ObRb, leptin receptor-b; OXR1, orexin receptor 1; PKC, protein kinase C; PI3K, phosphoinositol-3 kinase; POMC, proopiomelanocortin; SOCC, store-operated calcium channel; SGLT, sodium-glucose co-transporter; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription 3. See text and Refs. 7–15, 20, 27–29, 51–53, 55 for details of signaling pathways and mechanisms.

The VMN and DMN also play important roles in the regulation of energy homeostasis although, because their resident neurons are not as fully phenotyped as are ARC NPY/AgRP and POMC neurons, we know less about their relative roles in this process. However, VMN neurons have been extensively studied for their properties of metabolic sensing[6] and are clearly involved in the regulation of energy homeostasis by leptin.[26–28] Similarly, neurons in the DMN express leptin receptors and are involved in various regulatory aspects of energy homeostasis.[29,30]

Neurons in the ARC and VMN project directly or indirectly to targets in the PVN and LHA. PVN neurons that are critical for the neurohumoral control of energy homeostasis include those that express corticotropin-releasing hormone, thyrotropin-releasing hormone, oxytocin, and vasopressin. These neurons project to pituitary hormone–releasing cells and to autonomic outflow areas in the hindbrain and spinal cord. The LHA is a major exception to the general rule of medial location of areas involved in the metabolic regulation of energy homeostasis. This brain area is quite large and heterogeneous in both function and structure. Its neurons receive inputs from the ARC, VMN, DMN, as well as multiple brain areas involved in reward, emotions, and cognitive functions. Subpopulations of LHA neurons are metabolic sensors that

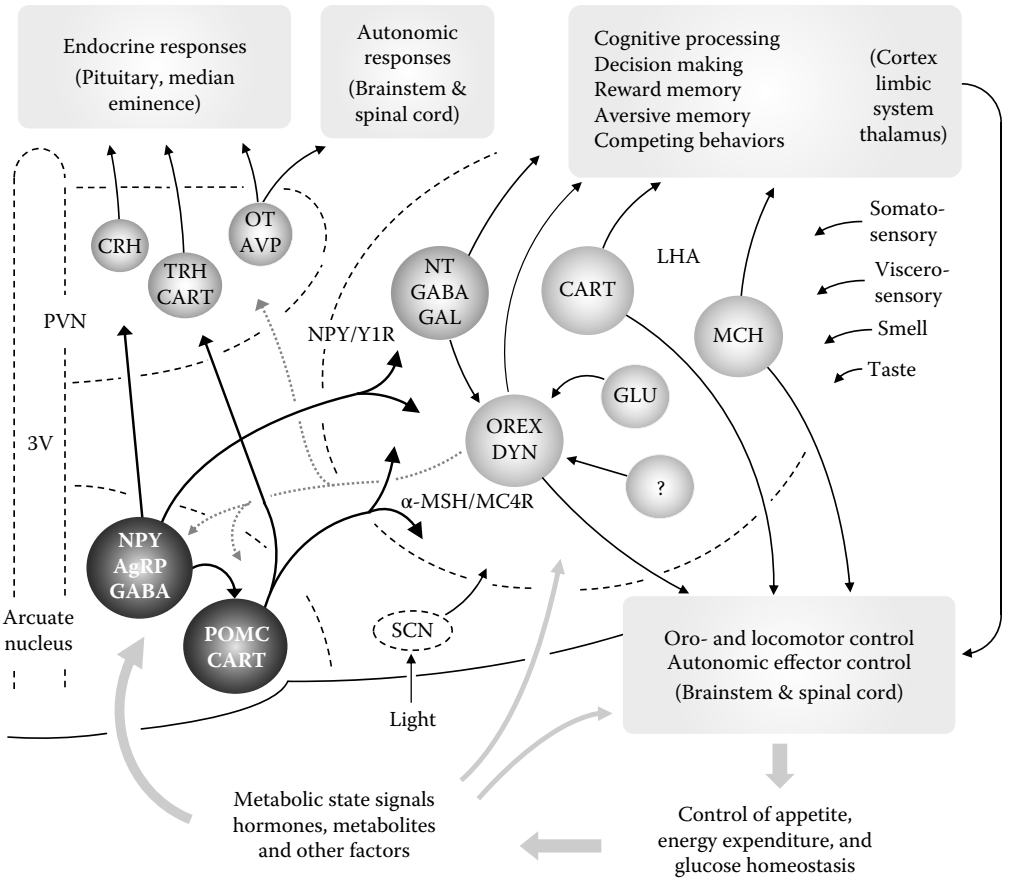

FIGURE 14.5 Hypothalamic peptidergic circuitry related to feeding and energy balance. The highly simplified diagram shows the two known neuron populations (NPY/AgRP and POMC/CART) in the arcuate nucleus sensitive to signals of fuel availability and their projections to other key neuron populations orchestrating the adaptive behavioral, autonomic, and endocrine responses. Neurotransmitters, modulators, and receptors: AgRP, agouti-related protein; AVP, arginine vasopressin; α-MSH, α-melanocyte-stimulating hormone; CART, cocaine and amphetamine-regulated transcript; CRH, corticotrophin-releasing hormone; DYN, dynorphin; GABA, gamma-aminobutyric acid; GAL, galanin; GLU, glutamate; MCH, melanin concentrating hormone; MC4R, melanocortin-receptor 4; NPY, neuropeptide Y; NT, neurotensin; TRH, thyrotropin-releasing hormone; OT, oxytocin; OREX, orexin/hypocretin; POMC, proopiomelanocortin; Y1R, NPY-receptor-1. Brain areas: LHA, lateral hypothalamic area; PVN, paraventricular nucleus of the hypothalamus; SCN, suprachiasmatic nucleus; 3V, third ventricle.

integrate neural, hormonal, and substrate inputs.[6] Together with PVN neurons, they act as third-order neurons that send their efferents throughout the central nervous system for neuroendocrine, autonomic and metabolic regulation, as well as behavioral and motor aspects of energy homeostasis. Orexin (hypocretin) neurons are a prime example of such neurons. They project widely throughout the neuraxis and have important reciprocal connections with ARC metabolic sensing neurons. Those orexin neurons in the medial LHA and DMN project to autonomic outflow areas whereas those in the lateral LHA are involved in arousal, reward, and other behavioral functions.[31]

14.3 COGNITIVE CONTROLS OF FOOD INTAKE

Eating can be initiated by cues in the environment, even in the absence of metabolic need or hunger.[32,33] In humans, such conditioned food intake can be triggered by visual and olfactory cues as well as other conditioned cues that recall memorial representations of prior experience with food. Key neural systems responsible are the hippocampal complex and associated cortical areas involved in spatial orientation and explicit memory functions, the striatum, which is primarily involved in habit and skills learning, and the amygdala, which is involved in emotional learning (Figures 14.1, 14.5, and 14.6). Although humans have the ability to make conscious, voluntary decisions and choices, many of our actions have a subconscious component that escapes voluntary control.[34] This is why we eat palatable foods such as chocolate in the absence of any metabolic need, even if we recognize the negative consequences of such actions. The right prefrontal cortex appears to play a critical role in behavioral restraint and moral self-control by keeping reward-generating mechanisms in check.[35] The prefrontal cortex receives external and internal sensory information as well as emotional and cognitive information from the limbic system and it is intimately connected to cortical areas involved in motor planning and execution. It is thus ideally positioned to translate

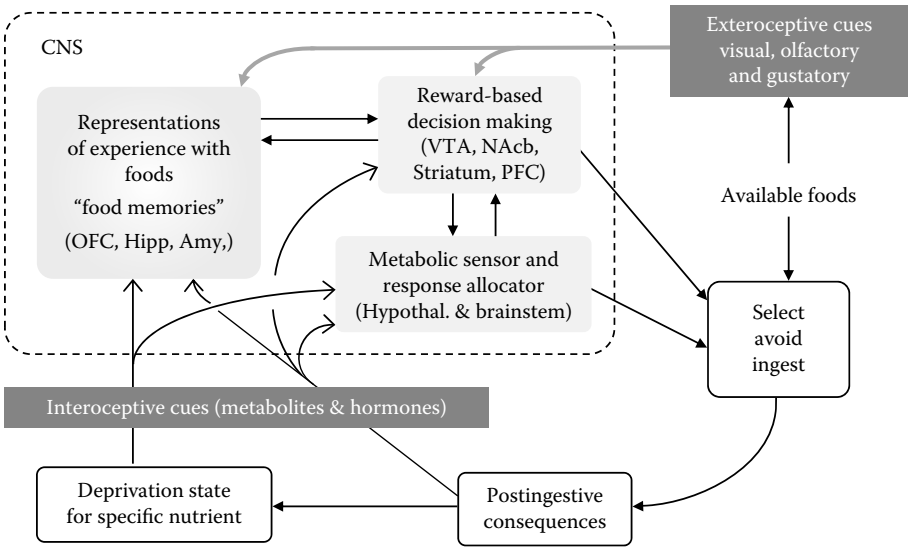

FIGURE 14.6 Schematic flow diagram showing possible neural processing of external and internal food cues leading to nutrient-specific appetites. Representations of experience with a particular food (food memories) take into account (1) exteroceptive cues including taste, available before ingestion of significant amounts; (2) postingestive consequences elicited by ingesting the food (digestion, absorption, and metabolism); and (3) the prevailing deprivation state for the particular nutrient at the time of replenishment. The hypothalamic metabolic sensor may be involved in generating a general hunger signal (incentive), and the corticolimbic, reward-based decision-making circuitry may confer the behavioral specificity for the selection process. Amy, amygdala; Hipp, hippocampal complex; NAcb, nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontral cortex; VTA, ventral tegmental area.

all available homeostatic and environmental information to produce adaptive behavioral responses, that is, the formation of choices and decisions.[36,37] Modern neuroimaging studies also support the importance of a balanced control by distinct areas of the prefrontal cortex in the control of food intake in humans. Successful dieters who have significantly higher levels of dietary restraint than nondieters show increased neural activity in the right dorsolateral prefrontal cortex in response to food consumption.[38] In contrast, obese subjects show less activation of the left dorsolateral prefrontal cortex in response to food.[39] Individuals suffering from the Prader–Willi syndrome have severe disturbances in appetite control resulting in hyperphagia and obesity and show increased activity in the ventromedial prefrontal cortex when viewing pictures of food after glucose consumption.[40] This finding is consistent with a role of the ventromedial prefrontal cortex in the mediation of food intake driven by conditioned (learned) motivational cues in sated rats.[41]

14.4 EMOTIONAL CONTROLS OF FOOD INTAKE

Rewarding aspects of food-related experiences are processed by a complex neural system that includes the nucleus accumbens and ventral pallidum in the ventral striatum, the midbrain ventral tegmental area whose dopamine neurons project back to the nucleus accumbens and prefrontal cortex, the hippocampus, and amygdala (Figure 14.1). Besides neural circuits in the hindbrain, the nucleus accumbens and ventral pallidum in the limbic forebrain are key components of the distributed neural network mediating "liking" of palatable foods where mu-opioid and cannabinoid receptors play a crucial role.[42] To consciously experience and give subjective ratings of pleasure from palatable foods (liking), humans appear to also use areas in the prefrontal and cingulate cortex.[43] Although "liking" a food is typically followed by "wanting" and eating it, "wanting" has a distinct underlying neural substrate involving the mesolimbic dopamine system. With projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex, the mesolimbic dopamine system is the most crucial component of the implicit or subconscious "wanting" system.[44] Manipulation of this dopamine system powerfully influences "wanting" but not "liking" of foods.[45–47] The LHA is also involved in "wanting" as electrical stimulation of this area induces rats to vigorously self-stimulate and eat ("want") food, even though it does not make them "like" the food more.[48] Wanting also has a conscious component that likely depends on areas of the orbitofrontal, cingulate, and insular cortex, as well as the dorsolateral prefrontal cortex, an area known to play an important role in decision making and executive control.

14.5 CROSS TALK BETWEEN HOMEOSTATIC AND NONHOMEOSTATIC CONTROLS

It has become increasingly clear that metabolic signals act not only on hypothalamic homeostatic circuits but also on sensory and corticolimbic systems to affect ingestive behavior (Figure 14.1). That food deprivation or restriction increases the reinforcement value of a food reward has been known since the discovery of hypothalamic self-stimulation by the late Bart Hoebel,[49] but the mechanisms for such bottom-up

modulation were missing. Recent studies in rodents[50–54] and neuroimaging studies in humans[55] show that a number of nutrition-sensitive circulating hormones such as leptin, insulin, glucgon-like peptide-1 (GLP-1), and ghrelin modulate critical nodes within the mesolimbic dopamine and associated corticolimbic systems. The process of fasting-induced heightening of motivation has been termed "incentive salience attribution."[21] Importantly, prior experience with a specific nutrient stimulus is not necessary for making it more attractive under deprivation conditions.[56] For example, in salt-depleted rats, increased "wanting" of salt is accompanied by cue-induced firing of ventral pallidal neurons even before the intense, and normally disliked, saltiness had ever been tasted and "liked." This suggests that a cue's incentive salience can be recomputed adaptively.[56]

Top-down processes include neural signals that influence either peripheral metabolism or the brain systems important in regulating energy state. The recent obesity epidemic makes clear that metabolic homeostatic regulatory processes can be overridden by other influences. In rats, overfeeding a high-fat, high-sugar diet produces an anorexigenic ARC peptide expression profile (increased POMC, decreased NPY) that should reduce energy intake. Despite this, the animals overeat and become obese suggesting that the rewarding properties of the diet can easily override the neurons involved in metabolic regulation to produce hyperphagia and obesity.[57] Similarly, when obesity-prone rats are offered a choice between a relatively high-fat, high-sucrose diet and a highly palatable liquid diet, they eat most of their calories as liquid diet and become severely hyperphagic and become massively obese, despite a marked rise in plasma leptin and insulin levels that should inhibit such weight gain.[58]

Although the role of voluntary and involuntary actions in this overriding process has been debated, we still do not understand its basic neurological pathways and processes. First, it has long been known that the LHA receives functional gustatory and olfactory input that is most likely independent of the cerebral cortex.[59,60] As many of the neurons responding to gustatory stimuli are glucose sensitive and may express orexin, they may be involved in integrating external availability with internal needs as discussed in Section 14.2. Second, the prominent projections from cortex, amygdala, and hippocampus to the hypothalamus[61] (see Dhillon et al.[26] for a review) are likely to play an important role in cognitive suppression of metabolic satiation signals (Figure 14.1). For example, intact projections from the amygdala and prefrontal cortex to the LHA are essential to elicit feeding in sated rats previously conditioned to associate a light or tone with food presentation while hungry.[33,41] Third, the hypothalamus receives direct input from the nucleus accumbens shell,[62] which plays a role in opioid-induced reward-driven food intake through activation of orexin neurons with projections to the ventral tegmental area.[63] This pathway may also be partly responsible for the development of diet-induced obesity in rats through chronic elevation of mu-opioid receptor signaling in the nucleus accumbens,[64,65] as well as for the extinction of alcohol reward seeking.[66]

14.6 CENTRAL MECHANISMS THAT PREDISPOSE TO OBESITY, RESIST WEIGHT LOSS, AND PROMOTE WEIGHT REGAIN

In addition to the factors detailed in the preceding discussion that lead to eating beyond need in societies where an excess of highly palatable, energy-dense foods are readily available, there are at least three other important factors that predispose individuals to become obese. First, in lower animals and many humans, obesity is associated with increased blood levels of both insulin and leptin. Normally, this would feedback to inhibit further intake and increase energy expenditure. However, in some individuals, a state of central "resistance" to the catabolic effects of leptin and insulin occurs. While there is some dispute about the use of this term, the fact is that, despite very high plasma levels, the inhibitory effects of leptin and insulin are markedly attenuated in many obese individuals. A number of mechanisms for such resistance have been proposed, including the potential inflammatory effects of high-fat intake,[67] reduced transport of leptin and insulin across the blood–brain barrier, and downregulation of central leptin and insulin signaling pathways.[68] Whatever the mechanisms, in many obesity-prone individuals, there is a constant upward resetting of the defended body weight in the face of continued excess caloric intake such that whatever level of adiposity an individual reaches when caloric restriction is instituted, there is a powerful drive to regain that level when caloric restriction is lifted.[69]

Second, the propensity to become obese has a strong genetic component that may underlie as much of 70% of human obesity.[70,71] In fact, most genes associated with obesity are expressed in the brain and affect food intake.[72–74] While there are rare single gene mutations that underlie some human obesity, such as individuals who fail to make leptin or have no MC4R,[75] a large proportion of human obesity has a polygenic mode of inheritance.[70] Similarly, there are rodent models of obesity-prone and obesity-resistant rats that appear to have a polygenetically inherited form of obesity.[70,71] Third, there is a powerful gene–by–environment interaction that promotes obesity throughout the life of some individuals. This interaction has a major impact during early development. The obesity-prone/obesity-resistant rat model has proven invaluable for demonstrating that both prenatal and postnatal maternal diet, obesity, and diabetes can all play a major role in altering the development of obesity in offspring dependent on genetic predisposition. For example, obesity-resistant rats can be made obese as adults if they are fostered to obese, obesity-prone dams at birth. This phenotypic switch may result from the highly abnormal milk of the obese dam that contains low polyunsaturated and monounsaturated fatty acid and high insulin levels.[76] On the contrary, rearing obesity-prone pups in large litters (which markedly reduces their intake) or providing them with running wheels for just 3 weeks after weaning prevents or inhibits them from becoming obese as adults.[77,78] These altered outcomes in both obesity-resistant and obesity-prone rats are associated with significant changes in hypothalamic leptin signaling and neuropeptide expression,

findings that largely support the conclusion that such changes contribute to the observed changes in phenotypic outcome.[76–78]

While there are likely to be many other causes of obesity, the major problem facing the obese individual is the high failure rate when attempting to obtain and sustain a lowered body weight and fat mass.[3] It is clear that our brains and bodies are hardwired to preserve energy stores in times of food scarcity. This produces a series of metabolic and physiological adaptations during caloric restriction that provide powerful metabolic and motivational drives that contribute to the high recidivism rate in the treatment of obesity. During short-term caloric deficits seen with fasting, plasma leptin and insulin levels fall precipitously to levels that are no longer representative of adipose stores. Their withdrawal stimulates anabolic NPY/AgRP and inhibits catabolic POMC production leading to a marked anabolic drive to seek and ingest food, a reduction in energy expenditure and an increased incentive salience of food in general.[79] This anabolic state persists for years in humans and months in rodents and is only alleviated when the previous level of adiposity is regained.[80–83] Whether one chooses to call this a return to some set point regulating body weight and adiposity or not, it is likely that this persistent anabolic state during prolonged dieting is a major contributor to the high rate of failure in the dietary treatment of obesity.

While the inhibitory effects on intake and stimulation of expenditure caused by increased plasma leptin and insulin levels associated with increased adiposity do provide a homeostatic feedback in many individuals, this system takes days to effectively regulate body weight. It is insensitive in some individuals to a slow accretion of excess calories and adipose tissue. More importantly, these negative feedback signals are easily overridden or subverted by the highly rewarding effects of palatable diets and to various social and environmental conditions.[84] Finally, maintenance of energy stores is essential for reproduction and survival of the individual and species. To assure survival, the brain has developed a highly redundant set of neural systems that serve as backup systems when primary ones are damaged or deleted by genetic manipulations or naturally occurring mutations. This may explain the extreme difficulty encountered by the pharmaceutical industry's many attempts to produce anti-obesity drugs, particularly ones that affect only one of these many redundant systems.

14.7 CONCLUSIONS

In summary, the function of the brain in the regulation of energy homeostasis appears weighted toward preserving energy stores, primarily as adipose, rather than preventing the development of obesity when excess stores are available. However, we still do not understand why some individuals are prone to become obese when excess energy is available, while others are obesity-resistant under such circumstances. Clearly, a better understanding of the complex neural systems that regulate energy homeostasis should provide us with a better opportunity to treat obesity in human beings.

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15 Gastrointestinal Regulation of Energy Balance

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CONTENTS

15.1 INTRODUCTION

In 1841, the German physician Julius Robert von Mayer (1814–1878) enunciated the "first law of thermodynamics," saying that "energy can neither be created nor destroyed." These days, the law of thermodynamics is one of the most fundamental basics of energy metabolism control. When translated to the regulation of body weight, the law means that the energy (calories) consumed must match the body's energy (caloric) demand to sustain a stable body weight over time. Any prolonged deviation from this equilibrium will inevitably result in either weight gain (in case energy intake exceeds energy expenditure) or weight loss (in case energy expenditure exceeds energy intake). Accordingly, to maintain a stable body weight over time, energy intake constantly needs to be adjusted for changing energy demands. Based on the constant changes in this demand, the adjustment of energy intake must be achieved through the (short-term) regulation of caloric intake (e.g., through regulation of the meal size and/or the meal frequency) and must take into account (long-term) information about the energy stored as fat in the body.

The complex process of energy metabolism control is tightly regulated by the cross talk of central and peripheral signaling systems and depends on constant signal integration. Key peripheral organs implicated in this process are the gastrointestinal (GI) tract with its adjacent digestive organs (such as the liver and the pancreas) and the adipose tissue. The aim of this chapter is to discuss the role of the GI tract and its adjacent digestive organs in the control of systemic energy metabolism.

In its classical role, the GI tract is the place of mechanical and enzymatic digestion and nutrient absorption. In line with this function, the GI tract, as the largest endocrine organ of the body, produces various peptides with autocrine, paracrine, and endocrine functions. Accordingly, among the classical peripheral effects mediated by GI peptides are the secretion of gastric acid (gastrin and secretin), the modulation of gut motility (glucagon-like peptide-1 [GLP-1], peptide tyrosine tyrosine [PYY], cholecystokinin [CCK], and motilin), the maintenance of mucosal integrity (GLP-2), and the regulation of gastric emptying (CCK, oxyntomodulin [OXM], GLP-1), pancreatic enzyme activity (CCK and PYY), and glucose homeostasis (GLP-1, gastric inhibitory polypeptide [GIP]) (Table 15.1).

Whereas digestion and nutrient absorption are mediated by GI peptides over mainly peripheral signaling mechanisms, the regulation of hunger and satiety and thus energy intake and expenditure are under the control of central nervous system (CNS)–dependent mechanisms. Central key areas in the regulation of energy homeostasis are the hypothalamus and the brain stem, which are in cross talk with each other and with various central and peripheral organs including the GI tract with its adjacent digestive organs and the adipose tissue. The communication between GI peptides and the brain is achieved through either the circulation or the afferent fibers of the vagus nerve that project to, for example, the nucleus tractus solitarius (NTS) of the brain stem. The connection between the circulation and

TABLE 15.1
Overview about the Most Relevant Gastrointestinal Peptides and Their Effect on Energy Metabolism

GI Hormone	Main Site of Secretion	Effect on Energy Metabolism	Additional Effects
Ghrelin	X/A-like cells in gastric fundus	Food intake ↑ Energy expenditure ↓	Thermogenesis (UCP1 ↓) Lipogenesis ↑
Insulin	Pancreatic β-cells	Food intake ↓	Blood glucose ↓ Glucagon secretion ↓ Gluconeogenesis ↓ Glycogenolysis ↓ Lipolysis ↓
Amylin	Pancreatic β-cells	Food intake ↓	Bile acid secretion ↓ Gastric emptying ↓ Glucagon secretion ↓
FGF21	Liver	Energy expenditure ↑	Insulin sensitivity ↑ Gluconeogenesis ↓ Glucose uptake in adipocytes ↑
CCK	I-cells of the small intestine	Food intake ↓	Pancreatic enzyme secretion ↑ Gallbladder contraction ↑ Gastric emptying ↓
PYY	L-cells of the distal ileum, colon, and rectum	Food intake ↓→	Gastric emptying ↓ Gut motility ↓
Glucagon	Pancreatic α-cells	Food intake ↓ Energy expenditure ↑	Blood glucose ↑ Gluconeogenesis ↑ Glycogenolysis ↑ Lipolysis ↑ Fatty acid oxidation ↑ Thermogenesis ↑
GLP-1	L-cells of the small intestine	Food intake ↓	Blood glucose ↓ Insulin secretion ↑ Glucagon secretion ↓ Gastric emptying ↓
GLP-2	L-cells of the small intestine		Mucosa growth ↑ Gastric emptying ↓ Gastric acid secretion ↓ Intestinal blood flow ↑
Oxyntomodulin	L-cells of the small intestine	Food intake ↓	Gastric emptying ↓ Gastric acid secretion ↓

the brain is achieved through, for example, the median eminence of the hypothalamus or the area postrema (AP) of the brain stem, which are in contact with the circulation because of the lack of a complete blood–brain barrier (Figure 15.1).

The GI tract, as the place of nutrient absorption, produces various short-term regulators of food intake, which are secreted either preprandially in anticipation of a meal, such as ghrelin, or postprandially in response to a meal, such as CCK, PYY, GLP-1, and OXM (Table 15.1). In concert, these peptides signal the GI fuel status to the brain to adjust food intake and satiety, for example, by adjusting the meal size and/or the frequency with which meals are taken.

In contrast to the short-term regulators of food intake, which are mainly secreted in response to or in anticipation of food, long-term adiposity signals (such as leptin or insulin) are constantly (tonically) secreted from peripheral organs such as the adipose tissue (leptin) or the pancreas (insulin) and give information to the brain in proportion to the body's energy stored as fat. Changes in the amount of body fat are thus reflected by changes in circulating adiposity signals, and the brain responds to these changes by changing its sensitivity for short-term satiety signals to defend a specific body weight set point. For example, a decrease of adiposity due to prolonged food restriction is reflected by decreased circulating levels of leptin and insulin that signal the now-decreased fuel status to the brain. The brain responds with a change of sensation for appetite and food intake, which, when food is again available, leads to increased food intake (e.g., over increased meal sizes or meal frequency) until the body weight comes back to normal (the set point).[1] Notably, most individuals consume food in episodes (meals) that are in most cases not dependent on food availability. The initiation of a meal is thereby also influenced by psychological factors (such as mood) and only rarely coincides with nutrient deficiency (e.g., hypoglycemia) of a critical

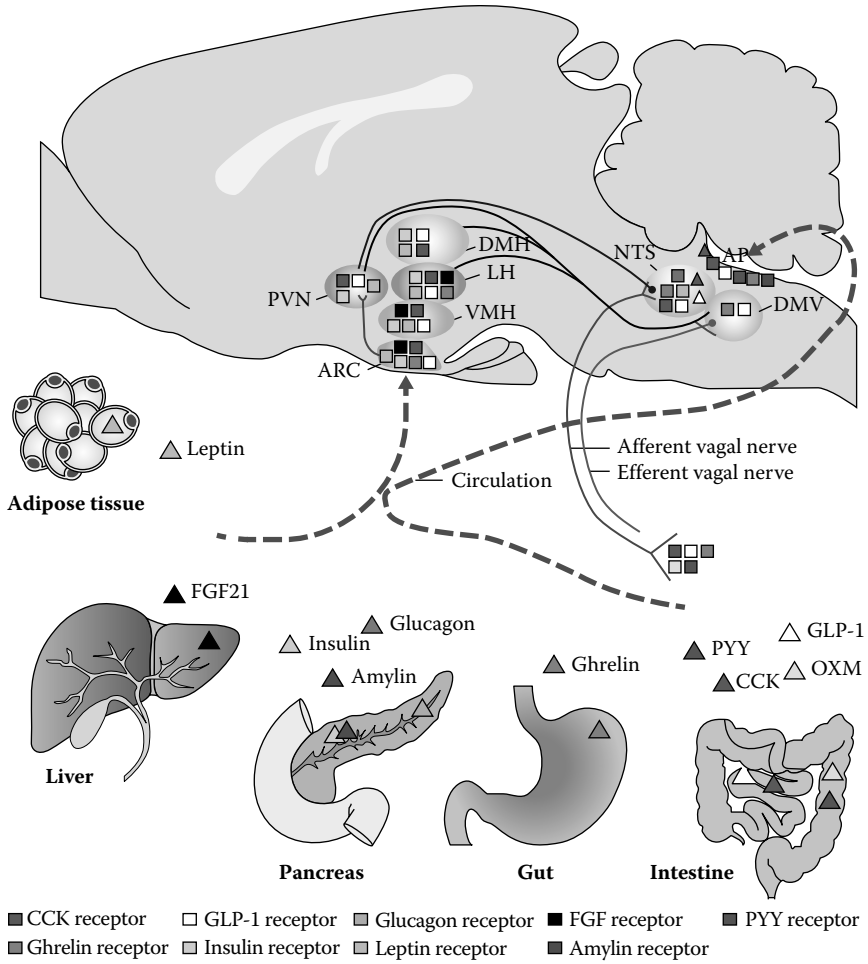

FIGURE 15.1 **(See color insert.)** Schematic of the neuroendocrine regulation of energy metabolism. The gastrointestinal (GI) tract as the largest endocrine organ of the body produces a variety of peptides that are either secreted preprandially in anticipation of or postprandially in response to food intake. In concert, these peptides inform the brain about the GI fuel status. The brain responds to these signals with an activation of signaling cascades that modulate food intake through a regulation of hunger and satiety. ARC, arcuate nucleus; AP, area postrema; CCK, cholecystokinin; DMH, dorsomedial hypothalamus; FGF21, fibroblast growth factor 21; GLP-1, glucagon-like peptide 1; LH, lateral hypothalamus; NTS, nucleus tractus solitarus; OXM, oxyntomodulin; PVN, paraventricular nucleus; PYY, peptide tyrosine tyrosine; VMH, ventromedial hypothalamus.

organ. Meal patterns are further different across species, with humans taking mainly three meals per day, while rodents take many more and feed nocturnally. Accordingly, most GI peptides implicated in energy metabolism regulate energy homeostasis through termination rather than initiation of food intake.[1,2]

15.2 GHRELIN

The GI peptide hormone ghrelin is so far the only known peripheral hormone with the ability to promote body weight gain and adiposity while decreasing energy expenditure and body fat utilization.[3] Ghrelin, which was discovered as an endogenous ligand for the growth hormone secretagogue receptor 1a (Ghsr1a),[4] is synthesized as a 117-amino-acid preprohormone and is posttranslationally cleaved into a 28-amino-acid peptide. Ghrelin is primarily synthesized and secreted by X/A-like cells in the oxyntic glands of the stomach mucosa,[5] but lower levels can also be found in the intestine, pancreas, kidney, lung, ovaries, and the brain. To promote its biological action, ghrelin is acylated on its serine 3 residue by the membrane-bound O-acyltransferase 4, which was later accordingly renamed as ghrelin O-acyl-transferase (GOAT).[6,7] The observation that acyl-ghrelin is absent in mice lacking GOAT indicates that GOAT is the only endogenous enzyme capable of activating ghrelin in vivo.[7]

Ghrelin is secreted from the stomach into the circulation in response to fasting and was thus long believed to serve as a "hunger" hormone that signals the GI fuel status from the periphery to the CNS to stimulate food intake and to adjust energy balance through a decrease in energy expenditure. The role of ghrelin as a hunger hormone was supported by the observation that plasma levels of ghrelin follow a circadian rhythm, with a preprandial rise that peaks directly at meal initiation followed by a postprandial decrease to baseline levels within the first hour after a meal.[8–10] The classical view of ghrelin as a hunger hormone is, however, questioned by more recent studies, which suggest that ghrelin rather acts as a nutrient sensor that prepares the CNS for incoming nutrients. In these studies, in which mice were fed with nonnaturally occurring C7 fatty acids, it was shown that the acyl side

chain necessary for ghrelin activation can come directly from digested nutrients.[11] In line with this observation, transgenic mice overexpressing GOAT/ghrelin show an increased energy expenditure, as compared to wild-type controls, when fed with a diet enriched with medium-chain triglycerides.[11] The role of ghrelin as a nutrient sensor is further supported by the observation that ghrelin, independently from its effect on food intake, promotes lipogenesis in the adipose tissue through control of the hypothalamic melanocortinergic system.

Irrespective of whether ghrelin is a hunger hormone or a nutrient sensor or both, peripheral and central administration of ghrelin stimulates food intake and adiposity through stimulation of hypothalamic orexigenic neuropeptides. In the hypothalamic arcuate (ARC) nucleus, Ghsr1a is coexpressed with the agouti-related peptide (AgRP) and neuropeptide Y (Npy), both anabolic neuropeptides that promote a positive energy balance through stimulating food intake while decreasing energy expenditure.[2] Accordingly, ghrelin-mediated activation of Ghsr1a entails an increased expression and release of Npy and AgRP in the ARC, which in turn leads to the activation of anabolic downstream pathways that finally lead to a stimulation of food intake and to a decrease of energy expenditure.[12,13] Inhibition of AgRP/Npy neurons blunts ghrelin's effect on food intake, thus indicating that the orexigenic effect of ghrelin is mainly mediated over the hypothalamic melanocortinergic system.[14]

In addition to its role on food intake, ghrelin stimulates the expression of fat-storage-promoting enzymes in the white adipose tissue, such as lipoprotein lipase, acetyl-coenzyme A (CoA) carboxylase α, fatty acid synthase, and stearoyl-CoA desaturase-1.[15] In brown adipocytes, ghrelin further dose-dependently lowers the expression of the thermogenesis-related mitochondrial uncoupling proteins 1 and 3, presumably through ghrelin's ability to decrease sympathetic nerve activity.[15] In summary, these data indicate that the endogenous GOAT/ghrelin system plays a fundamental role in the neuroendocrine adaptation to starvation and that modulation of the ghrelin system might be an interesting target for the treatment of individuals with pathologically reduced body weight such as patients with anorexia or cachexia.

15.3 INSULIN

The pancreatic hormone insulin is secreted from the islands of Langerhans in response to nutrient (especially glucose) stimuli. In its classical function, insulin promotes the rapid clearance of glucose from the blood by stimulating the uptake and storage of glucose in peripheral tissues while inhibiting hepatic gluconeogenesis, glycogenolysis, and lipolysis. Albeit best known for its role in glucose homeostasis, insulin was the first hormone reported to control body weight through CNS-dependent mechanisms. In the late 1970s, Woods and Porte proposed that insulin acts as an adiposity signal that informs the brain about the amount of fat stored in the body and that the brain in response to this signal adjusts body weight through an inhibition of food intake.[16,17] The hypothesis by Woods and Porte was based on the observation that plasma levels of insulin are, under both basal and stimulated conditions, directly proportional to the amount of body fat[18] and that insulin, when administered directly into the brain of baboons, reduced food intake and adiposity.[16] Indeed, insulin receptors are expressed in several hypothalamic areas governing energy balance, such as the ARC and the dorsomedial hypothalamus.[19] Accordingly, administration of insulin directly in the brain reduces food intake in various species, including rodents and nonhuman primates.[20] The most common conceptualization about how insulin inhibits food intake is that insulin enters the CNS in proportion to its plasma concentrations[21] where high levels of insulin stimulate the activity of neurons expressing proopiomelanocortin and cocaine- and amphetamine-related transcript while those expressing Npy and AgRP are inhibited.[2]

15.4 AMYLIN

The pancreatic peptide amylin (also known as islet amyloid polypeptide) is a 37-amino-acid peptide cosecreted with insulin from the pancreatic β-cells. Like insulin, plasma concentrations of amylin rapidly increase in response to nutrient (especially glucose) stimuli and subsequently decrease upon fasting. Like the classical adiposity signals leptin and insulin, circulating levels of amylin are increased in obese compared to lean individuals[22,23] and subsequently decrease upon weight loss.[24] In the GI tract, amylin decreases gastric acid secretion, delays gastric emptying, and inhibits glucagon secretion.[25] When administered in either the brain or the periphery, amylin further dose-dependently decreases food intake through a reduction in meal size.[26,27] In line with its role as a meal-terminating factor, blockade of amylin signaling, either through administration of an amylin receptor antagonist[28] or through genetic ablation of amylin,[29] increases food intake, body weight, and adiposity. Several lines of evidence indicate that the effect of amylin on food intake is mediated over the AP, as peripheral administration of amylin increases c-Fos immunoreactivity in this region and as lesions of the AP abolish amylin's effect on food intake and adiposity.[30–34] Accordingly, administration of amylin selectively in the AP decreases food intake through a reduction in meal size whereas an amylin receptor blockade in the AP has the opposite effect.

Based on its effect on body weight and glucose sensitivity, amylin has gained much scientific attention for the treatment of obesity and diabetes. Pramlintide, a synthetic amylin receptor agonist with the trade name of Symlin® (Amylin Pharmaceuticals Inc., San Diego, CA), is one of the few U.S. Food and Drug Administration–approved pharmaceuticals for obesity and diabetes intervention.

The signaling mechanisms of how amylin decreases food intake are not yet fully understood. Recently, coadministration of leptin and amylin was shown to synergistically decrease body weight and adiposity in both obese rodents and humans,[35,36] thus indicating that amylin is able to restore leptin sensitivity. However, whereas the enhanced potency of the amylin–leptin coadministration to promote weight loss is solidly confirmed, other studies show that also cotreatment of

diet-induced obese mice with leptin and exendin-4, a synthetic GLP-1 analog, and with fibroblast growth factor 21 (FGF21) improve leptin sensitivity,[37] thus indicating the improvement of leptin sensitivity is not unique to amylin signaling.

15.5 FIBROBLAST GROWTH FACTOR 21

FGF21 is a 210-amino-acid protein that recently emerged as an important regulator of glucose and energy metabolism. FGF21 is primarily expressed in the liver,[38] from which it is secreted during states of increased fatty acid oxidation, such as during fasting or after feeding a ketogenic diet.[39] Secreted from the liver in response to fasting, FGF21 stimulates hepatic gluconeogenesis, thus helping to maintain normoglycemia in states of increased glucose utilization. FGF21 further promotes the insulin-independent uptake of glucose into the adipocytes by stimulating the expression of the glucose transporter 1.[40] When overexpressed in transgenic mice, FGF21 protects from diet-induced obesity,[40] and when administered to obese rodents or diabetic nonhuman primates, FGF21 decreases body weight, lowers serum triglycerides, and improves glucose tolerance.[40,41] The effect of FGF21 on body weight seems to be mainly mediated through an increase in energy expenditure, as 2-week systemic administration of FGF21 in diet-induced obese and leptin-deficient ob/ob mice decreased body weight without affecting food intake. Instead energy expenditure and core body temperature was increased in mice treated with FGF21.[41]

The mechanisms of how FGF21 exerts its biological action are complex and not yet fully understood. However, FGF21 signaling is mediated through ctivation of FGF receptors upon recruitment of the adaptor molecule βKlotho.[42,43] Downstream targets of FGF21 signaling include the activation of the extracellular signal-regulated kinase 1 and 2 (ERK1/2) and the serine/threonine protein kinase (Akt) signaling pathways.[40] Further studies in diet-induced obese rats indicate that the effect of FGF21 on energy expenditure and insulin sensitivity is centrally mediated.[44] Accordingly, FGF receptor-1 has been identified in the ventromedial hypothalamus and ARC, both areas well known for being implicated in the regulation of systemic energy metabolism.[45] Conversely, peripheral infusion of FGF21 has been suggested to increase energy expenditure through AMP-activated protein kinase (AMPK) action in adipose tissue.[46] The latter study documented an increased activity of AMPK, NAD^+-dependent type III deacetylase sirtuin 1, and peroxisome proliferator–activated receptor-γ coactivator 1α in adipose tissue following FGF21 administration. Furthermore, the effects of FGF21 on energy expenditure were ablated by the deletion of any of the identified signaling nodes. Taken together, it seems that FGF21 acts on both the CNS and peripheral tissue to increase energy expenditure and insulin sensitivity.

15.6 CHOLECYSTOKININ

CCK is primarily secreted by endocrine I-cells of the small intestine in response to food (especially fat) ingestion. CCK-producing cells are further located in the vagal afferent nerve fibers and the brain, albeit with lower density. The classical physiological actions of CCK, which is secreted into the circulation in response to chyme entering the duodenum, include the stimulation of pancreatic enzyme secretion, gallbladder contraction, and the regulation of gastric emptying (Table 15.1). CCK exists in several bioactive forms, and it was the first gut peptide implicated in the regulation of food intake and systemic energy metabolism control.[47] In rats[47] and humans,[48,49] peripheral administration of CCK dose-dependently decreases food intake through a reduction in meal size. This inhibition of food intake is mediated through the CCK1 receptor. Accordingly, CCK does not affect food intake in CCK1 receptor–deficient rodents.[50] Preprandial blockade of CCK1 signaling increases meal size in various species including rats, monkeys, and humans.[51–54] CCK1 receptors are widely expressed in areas implicated in systemic energy metabolism control, such as the afferent and efferent vagal neurons, the NTS, the AP, and the hypothalamus.[55,56] The exact mechanism of how CCK leads to the termination of food intake is not yet fully understood. However, the most common conceptualization about how CCK initiates meal termination is that CCK activates CCK1 receptors on sensory fibers of the vagus nerve, which remit the CCK signal over the NTS to the brain stem from which it is transmitted to the hypothalamus. Once reaching the hypothalamus, the CCK signal then leads to the activation of downstream pathways that finally lead to the termination of food intake.

15.7 PEPTIDE TYROSINE TYROSINE

Peptide tyrosine tyrosine (PYY) is a 36-amino-acid protein that belongs to the Npy family. PYY, which is secreted into the circulation in response to food ingestion, is mainly produced by endocrine L-cells of the distal ileum, colon, and rectum, but can also be found in specific neuronal populations of the CNS.[57] PYY exists in two bioactive forms, $PYY_{1–36}$ and the major circulating form $PYY_{3–36}$. The effect of PYY in the regulation of systems metabolism is conflicting and controversially discussed. Whereas PYY is reported in several studies to inhibit food intake in both rats[58–60] and humans,[61] other studies were not able to replicate these findings.[62–64] Also, reports about energy metabolism in PYY-deficient mice are conflicting. In one study, male and female PYY-deficient mice were reported to have an increased food intake, body weight, and body fat mass when fed with a regular chow diet.[65] In another study, an increased food intake and a modest increase in body fat were only observed in chow-fed female but not male PYY-deficient mice.[66] Other studies found irrespective of the gender no effect on body weight or body composition between chow-fed PYY-deficient mice and controls.[67,68]

15.8 CLEAVAGE PRODUCTS OF PROGLUCAGON

The 160-amino-acid-containing prohormone proglucagon is generated in α-cells of the pancreas, in L-cells of the distal ileum and colon, and at least to some extent in the NTS of the

brain stem. Dependent on the tissue, proglucagon is cleaved by the prohormone convertase (PC) 1 or 2 into either glucagon, GLP-1 or GLP-2, oxyntomodulin, or glicentin (Figures 15.2 and 15.3).

15.8.1 Glucagon

The 29-amino-acid peptide glucagon is exclusively secreted from the pancreatic α-cells in response to decreasing level of blood glucose. The tissue specificity is achieved through post-translational cleavage of the proglucagon peptide by the PC-2. In its classical role, glucagon counteracts the glucose lowering effect of insulin by stimulating hepatic gluconeogenesis, thus helping to maintain normal levels of blood glucose in states of rapid glucose utilization. The secretion of glucagon is mediated through voltage-dependent sodium (Na^+) and calcium (Ca^{2+}) channels[69] in support of ATP-sensitive potassium (K_{ATP}) channels.[70] Depolarization, caused either directly or indirectly by a decrease in blood glucose, leads to an increase in Ca^{2+} influx and subsequently glucagon secretion whereas inhibition of Ca^{2+} influx shuts off glucagon secretion.[71]

Glucagon promotes its biological action through activation of the glucagon receptor (GCGR), a seven-transmembrane G-protein-coupled receptor that is highly expressed in the

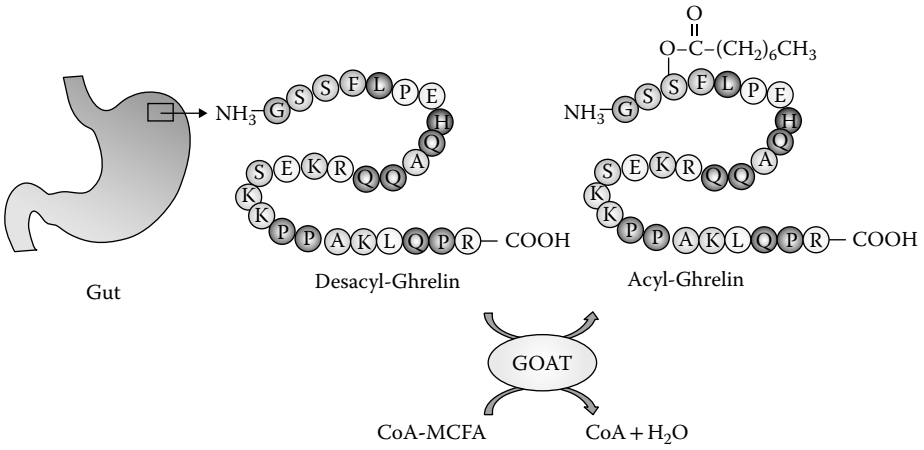

FIGURE 15.2 (See color insert.) Posttranslational activation (acylation) of ghrelin. To promote its biological action, ghrelin is acylated at its serine 3 residue by the ghrelin-O-acyltransferase (GOAT).

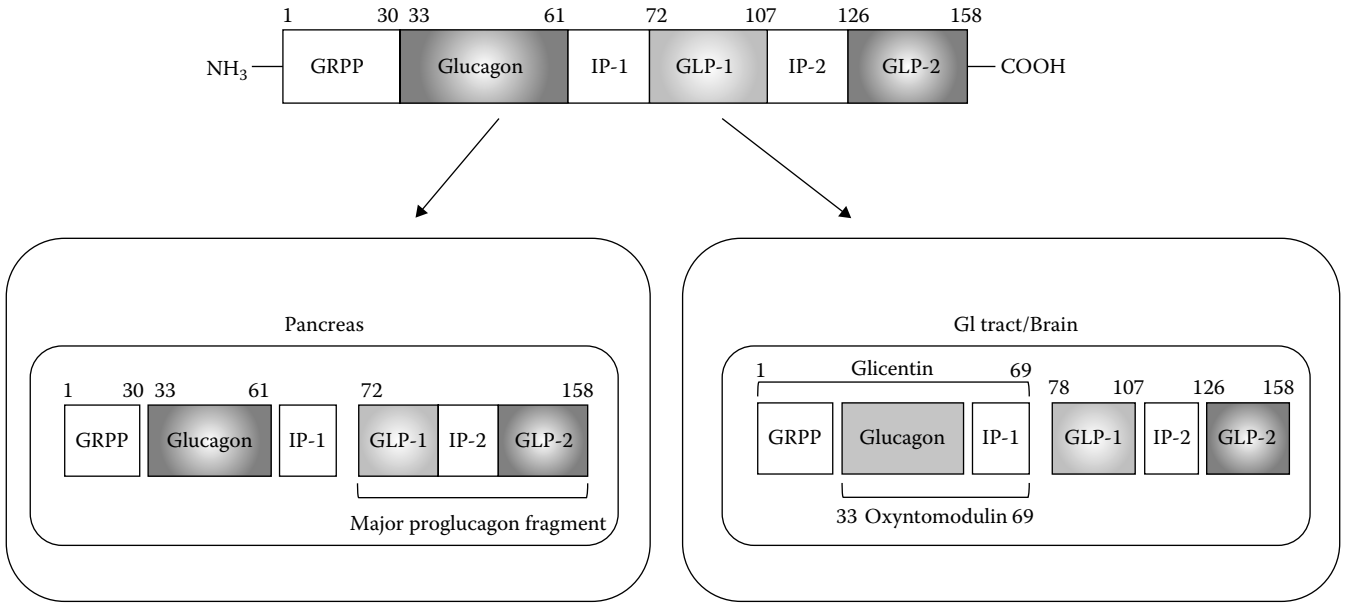

FIGURE 15.3 (See color insert.) Cleavage products of proglucagon. Posttranslational cleavage of proglucagon is mediated by the prohormone convertase 1 or 2. In the pancreas, proglucagon is cleaved into either glicentin-related pankreatic peptide (GRPP, amino acids 1–30), glucagon (amino acids 33–61), or the major proglucagon fragment (amino acids 72–158). In the L-cells of the small intestine and the brain, proglucagon is cleaved into glicentin (amino acids 1–69), glucagon-like peptide 1 (GLP-1, amino acids 72–108), intervening peptide 2 (IP-2, amino acids 111–123), and GLP-2 (amino acids 126–158). Glicentin is then further cleaved into GRPP and oxyntomodulin (amino acids 33–69).

liver and kidney and to a lesser extent in the brain, adipocytes, heart, spleen, lymphoblasts, the adrenal gland, and the GI tract.[72] In the pancreas, GCGRs are predominantly located in the β-cells, where high concentrations of glucagon stimulate the secretion of insulin to prevent hyperglycemia.[73] In line with glucagon's opposing effect to insulin, GCGR knockout mice (*Gcgr*$^{-/-}$) have lower levels of blood glucose[74] and enhanced insulin sensitivity.[75]

In addition to its role in glucose homeostasis, glucagon decreases food intake and promotes body weight loss in various species, including rodents and humans.[76–79] An important site of glucagon's action is thereby the liver, which informs the brain through sensory fibers of the vagus nerve about changes in circulating concentrations of glucagon. The brain responds to increased circulating concentrations of glucagon by inhibiting food intake through a decrease in meal size without affecting meal frequency.[80,81] The identification of the liver as the primary site of glucagon's action on food intake is based on the observation that infusion of glucagon in the hepatic portal vein decreases food intake at concentrations 10 times lower as compared to infusions into the vena cava[80] and that the anorexigenic (food intake inhibiting) effect of glucagon is abrogated by hepatic vagotomy. In line with its role as a meal terminating factor, plasma concentrations of glucagon increase physiologically during meals and preprandial inhibition of glucagon signaling increases the meal size,[81,82] whereas stimulation of glucagon signaling during a meal has the opposite effect.[76]

In addition to its ability to decrease food intake, glucagon participates in the regulation of energy metabolism by stimulating lipolysis and fatty acid oxidation[83–86] while increasing energy expenditure,[87,88] most likely through an increase in sympathetic nervous system (SNS)-mediated activation of brown fat thermogenesis.[89,90]

15.8.2 Glucagon-Like Peptide 1

The GLP-1 is cosecreted with PYY from enteroendocrine L-cells of the small intestine in response to food ingestion.[91] GLP-1 exists as either a 36- or 37-amino-acid peptide and exerts its biological effects through activation of the GLP-1 receptor (GLP-1R). Upon activation, GLP-1R leads to an increase in intracellular cyclic adenosine monophosphate production and subsequent activation of downstream pathways through stimulation of the adenylate cyclase. GLP-1R is predominantly expressed in the brain, pancreas, and GI tract.[92]

In its classical role as an incretin (a peptide that facilitates the release of insulin in the presence of glucose), GLP-1 promotes insulin secretion in a glucose-dependent manner while inhibiting the release of glucagon. In addition to its effect on blood glucose, GLP-1 affects energy metabolism through an inhibition of food intake and through a delay in gastric emptying.[93] In the brainstem and the paraventricular nucleus, peripheral administration of GLP-1 leads to increased c-Fos immunoreactivity,[94] thus indicating that the effect of GLP-1 on food intake is mediated over both the hypothalamus and the brainstem. In line with this observation, intracerebroventricular administration of GLP-1 robustly decreases food intake in rats whereas exendin$_{9–39}$, an inhibitor of GLP-1R signaling, has the opposite effect.[94,95] The effect of GLP-1 on food intake is, however, strikingly ameliorated upon vagotomy, thus indicating that GLP-1 regulates food intake over the vagus–brainstem–hypothalamus pathway.[96]

Because of its effect on food intake and glucose homeostasis, GLP-1 has gained much scientific attention as a target for the treatment of obesity and type 2 diabetes. However, the therapeutic potential of GLP-1 is hampered by its short half-life, which in human beings is 1–2 minutes due to its rapid degradation by the dipeptidyl peptidase IV (DPP-IV).[97] In contrast to native GLP-1, exendin-4, a GLP-1R agonist originally isolated from the venom of the gila monster (*Heloderma suspectum*), exhibits a greatly enhanced half-life due to a relative resistance to DPP-IV degradation.[98] Accordingly, DPP-IV-resistant GLP-1 analogs, such as exenatide (Byetta®, Amylin Pharmaceuticals Inc) and liraglutide (Victoza®, Novo Nordisk, Denmark), are approved by the U.S. Food and Drug Administration and are currently successfully used for the treatment of diabetes.

New ground in diabetes and obesity research was recently broken by the biochemical engineering of a single peptide with agonism at both the glucagon and the GLP-1R, thereby combining the antihyperglycemic effects of GLP-1 with the lipolytic and thermogenic properties of glucagon in a single peptide of improved pharmacokinetic and sustained action as compared to native glucagon and GLP-1. Once-weekly treatment of diet-induced obese mice with this newly designed glucagon/GLP-1 coagonist synergistically normalized body weight and glucose tolerance and decreased liver steatosis within 4 weeks without any adverse effects.[99] Together these data show the principle that new highly active peptides, which simultaneously activate multiple signaling pathways, can be designed to safely and efficiently normalize body weight and blood glucose, thus paving the way for a new area in obesity and diabetes research.

15.8.3 Glucagon-Like Peptide 2

GLP-2 is a 33-amino-acid peptide primarily produced in enteroendocrine L-cells of the small intestine and in various neurons of the CNS. In the intestine, GLP-2 is cosecreted with GLP-1 in response to food ingestion. Unlike GLP-1, however, GLP-2 seems not to be implicated in the regulation of satiety, as peripherally administered GLP-2 does not affect food intake in rats,[100] birds,[101] or humans.[102] Instead, in its major role as an intestinal growth factor, GLP-2 promotes the growth of the intestinal mucosa by stimulating crypt cell proliferation and by inhibiting villous cell apoptosis. In addition to its role in the regulation of mucosal integrity, GLP-2 inhibits gastric emptying and acid secretion while stimulating intestinal blood flow.[103]

15.8.4 Oxyntomodulin

Oxyntomodulin (OXM) is a 37-amino-acid protein containing the full 29-amino-acid sequence of glucagon. OXM is secreted from enteroendocrine L-cells of the small intestine

in response to a meal and exerts its biological effects through activation of both the GLP-1 and the GCGR. When injected in either the brain or the periphery, acute and chronic administration of OXM reduces food intake and promotes weight loss in rodents.[104–106] In line with these findings, 4-week treatment of overweight and obese people with OXM (at doses of 1200 nmol/day) decreased body weight by 2.3 ± 0.4 kg compared to 0.5 ± 0.5 kg in the control group.[107] In another clinical trail, 4-day treatment of overweight and obese people with OXM (at doses of 1200 nmol/day) decreased food intake while increasing energy expenditure, thus supporting the therapeutic potential of OXM in the treatment of obesity. Peripheral administration of OXM increases c-Fos immunoreactivity in the ARC whereas selective inhibition of GLP-1R s in the ARC abolished the effect of OXM on food intake and weight loss. These data indicate that the OXM inhibits food intake over GLP-1R signaling in the hypothalamus.[105]

Like with other GI peptides, the therapeutic potential of OXM to promote weight loss is hampered by its short half-life (in humans 12 ± 1 minutes), which is due to its rapid degradation by the DPP-IV. Accordingly, as with other products of preproglucagon, modified OXM derivates have been generated, which show an increased half-life due to decreased DPP-IV degradation.

In summary, the GI tract and its adjacent digestive organs play a profound role in the regulation and maintenance of energy metabolism. Accordingly, the GI tract, as the largest endocrine organ of the body, produces various neuropeptides that are secreted either in anticipation of or in response to incoming nutrients. In concert, these peptides signal the GI fuel status to the CNS to adjust food intake and energy expenditure. Assessment of the role of GI hormones over the past 50 years has pioneered our understanding of how the GI tract and its digestive organs integrate into the complex network of systemic energy metabolism control, and as a consequence of this pioneering work, many GI hormones have emerged as key peripheral players not only in the regulation of hunger and satiety but also in the control of glucose homeostasis.

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16 Gut Microbiome and Obesity

Patrice D. Cani

CONTENTS

16.1 INTRODUCTION

The role of gut microbes in human physiology was largely underestimated until the past two decades. Once characterized as bystanders in the intestinal tract, the gut microbiota is now being viewed from an ecological perspective by the scientific community, providing the biomedical community with a robust framework for hypothesis formation. From an ecosystems' point of view, ecological studies can help to explain how interactions with the environment may influence species distribution over space and time. From the first observations by Antonie van Leeuwenhoek using the microscope to the use of culture-based methods and the more recent development of high-throughput sequencing and metagenomics technologies, we have moved from descriptive approaches to the assessment of complex functional interactions not only within microbial communities but also within complex ecosystems such as human gut microbiota. The previous paradigm, in which microbes were mainly held responsible for severe diseases and mortality or worldwide epidemics, led medical research to address basic questions such as *how can we fight microbes (pathogens) to avoid diseases*? However, since two Nobel Prizes were awarded in the 1900s to Robert Koch and Ilya Mechnikov, scientists who established the link between microbes and human health, an intricate set of relationships between microbiota and humans has been unraveled. Thus, considerable efforts through international projects are now underway to identify and characterize the collection of microbes that inhabit our gut, and the gut microbiota has been reconsidered in a more positive way.[1,2] The human gut microbiome has been shaped by the continuous coevolutionary history of the host–microbe interaction, and both humans and microbes have been affected by this intimate association. Consequently, the gut microbiota is now considered as a key partner that helps balance important vital functions for the host, including immunity and nutritional status, and participates in the maintenance of health.[3,4]

We and others have uncovered a fascinating potential link between alterations in the gut microbiome and obesity and associated disorders (i.e., insulin resistance, type 2 diabetes, nonalcoholic fatty liver diseases, and metabolic inflammation).[5,6] Changes in the composition of the gut microbiota, as well as specific gut microbial communities, have been associated with obesity and type 2 diabetes in both animal and human studies. This chapter discusses the most recent evidence linking the gut microbiome and obesity, exploring links between gut microbiota composition and specific components or metabolites that may interfere with or initiate metabolic interactions with the host. For instance, it is evident that the gut microbiota provides essential genetic and metabolic attributes, sparing us from the need to evolve on our own. The processes affected by the gut microbiota include epithelial cell proliferation, immune system and barrier function against enteric pathogens, nutrient and drug metabolism, synthesis, and the bioavailability of several vitamins.[7–9]

16.2 GUT MICROBIOTA

Recently conducted investigations have shown that 99% of bacteria are members of five *phyla*: Bacteroidetes (encompassing gram-negative genera, e.g., *Bacteroides*, *Porphyromonas*, and *Prevotella*), Firmicutes (encompassing gram-positive genera,

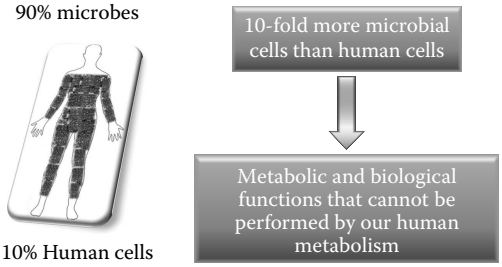

FIGURE 16.1 An extended view of ourselves. At 10^{14} cells, the total number of microbes in the body outnumbers our own human cells by an order of magnitude, thereby supporting the concept that we are 90% microbial cells and 10% human cells.

e.g., *Clostridium*, *Ruminococcus*, *Lactobacillus*, *Butyrivibrio*, *Anaerostipes*, *Roseburia*, and *Faecalibacterium*), Actinobacteria (encompassing gram-negative genera, e.g., *Bifidobacterium*), Proteobacteria (encompassing gram-negative genera, e.g., *Helicobacter* and *Escherichia*), and Verrucomicrobia (encompassing the gram-negative species *Akkermansia muciniphila*).[10–13] Each phylum is subdivided at the class, order, family, genus and species levels. Most gut microbiota data reported to date have focused on changes at the phylum level, but numerous studies have also identified the potential impact of one or several specific species that may play an important role in host metabolism.

The gut microbiota consists of as many as 10–100 trillion microorganisms[14]; therefore, microbial cells outnumber human cells by up to 10-fold. In addition, the microbiome encodes a consortium of genes that exceeds the number in the human genome by a magnitude of 150. It is estimated that each individual houses at least 160 of a consortium of 1000–1150 prevalent bacterial species.[10] Therefore, a valid extended view of ourselves postulates that we are not 100% human, but rather 10% human and 90% microbe (Figure 16.1). Altogether, these data support the astounding concept that the bacteria within the gut contribute to important biological and metabolic functions in humans.

Today, much attention is paid to the role of the gut microbiota in host energy homeostasis and metabolic functions. The gut microbiota is now considered as an environmental factor in the control of body weight and energy homeostasis.[11,15–18] The gut microbiota contributes to homeostasis through several metabolic systems and biological functions, including the control of the extraction of calories from ingested dietary substances and energy storage or expenditure. Unequivocal evidence supporting this rule has come from studies performed in animal models. The first part of this chapter will be devoted to the description of this experimental evidence, and the second part of the chapter will describe selected recent studies performed in human subjects.

16.3 EXPERIMENTAL EVIDENCE OF THE INTERPLAY BETWEEN GUT MICROBIOTA AND ENERGY HOMEOSTASIS

One of the first described mechanisms supporting the role played by the gut microbiota in energy homeostasis was related to the effectiveness of energy harvested by the bacteria, that is, of the energy ingested but not digested by the host. This mechanism describes how microbes optimize the extraction of calories from ingested dietary substances and help store these calories in the host adipose tissue for later use. Among the nutritional compounds that escape digestion in the upper part of the gastrointestinal tract, simple and complex polysaccharides constitute the major source of nutrients for the bacteria (i.e., dietary fiber). It has been known for decades that some of these undigested polysaccharides could be transformed by bacteria into digestible substances such as sugars or short chain fatty acids (SCFA) (acetate, propionate, and butyrate), providing energy substrates for the host. Thus, SCFA, which are considered *indirect nutrients* produced by the gut microbiota, may have a role in the control of energy metabolism. Indeed, SCFA produced by fermentation have been proposed as drivers of the adipose tissue expansion observed in conventionalized (harboring gut microbiota) versus germ-free mice (mice without gut microbiota),[15] as extensively described in the following paragraph. In addition, a transcriptomics analysis of the cecal microbiome revealed a shift in the gut microbiota in favor of carbohydrate fermentation processes in obese mice that were fed a western diet.[19,20] Therefore, SCFA and polysaccharide fermentation in general could be regarded as potentially harmful in the context of obesity. Given that the control of body weight depends on mechanisms that are subtly controlled over time, a small daily excess caloric intake, of as little as 1%–2% of the daily energy needs, can have important long-term consequences on body weight and metabolism.[21] Hence, it has been proposed that all mechanisms modifying the food-derived energy availability could contribute to body weight regulation.

16.3.1 Gut Microbiota and Adipose Tissue Development

Following an elegant series of experiments,[11,15–18] Jeffrey Gordon and colleagues have demonstrated that germ-free mice (raised in the absence of microorganisms) had approximately 40% less total body fat than mice with normal gut microbiota, even though the germ-free mice were eating 30% more energy than the normal mice.[15] Surprisingly, when gut microbiota (cecal content) from normal mice was transplanted into the germ-free mice, the mice exhibited a 60% increase in body fat content and insulin resistance within 2 weeks, without obvious differences in energy expenditure.[15] This experiment was one of the first demonstrations that the composition of the gut microbiota significantly affects the amount of energy extracted from the diet. The two mechanisms proposed by the authors involved an increase in the intestinal glucose absorption and energy extraction from nondigested food and the role played by the SCFA. Later, Samuel et al. demonstrated that in absence of the SCFA receptor (GPR41), $GPR41^{-/-}$ mice colonized with a specific fermentative microbial community (composed of *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii*) resist fat mass gain compared to their wild-type littermates[22] (Figure 16.2).

Backhed et al. found that a 2-week conventionalization of germ-free mice is also accompanied by a twofold increase in hepatic triglyceride content.[15] This increase is mainly driven by hepatic de novo lipogenesis, as suggested by the higher

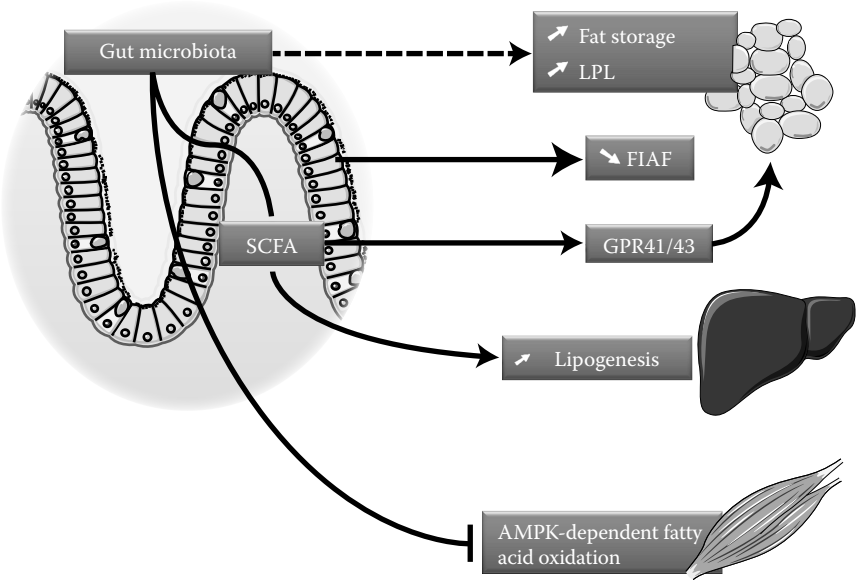

FIGURE 16.2 (**See color insert.**) Mechanisms linking gut microbiota with increased energy storage. Gut microbiota modulates energy storage through various mechanisms, as mostly demonstrated in germ-free mice. Fermentation by the gut microbiota promotes short chain fatty acid (SCFA) production and absorption, thereby increasing the amount of lipogenic substrates available to the host. These SCFAs are involved in hepatic lipogenesis and fat storage through numerous mechanisms, including the suppression of fasting-induced adipose factor (FIAF) in the gut, and eventually indirectly control the activity of the enzyme lipoprotein lipase (LPL). By acting through GPR41 and GPR43, the different SCFAs contribute to fat storage. Finally, AMP-activated protein kinase (AMPK)-dependent fatty acid oxidation is inhibited by the gut microbiota in response to a high-fat diet; however, it should be noted that other unknown direct or indirect mechanisms may exist (dotted line).

expression of several key enzymes such as acetyl-CoA carboxylase and fatty acid synthase or the transcription factors ChREBP (carbohydrate responsive element binding protein) and SREBP-1 (sterol responsive element binding protein).[23] Strikingly, the adipose tissue development observed in the mice harboring gut microbiota was not explained by the modulation of adipogenesis or lipogenesis but by the fasting-induced adipose factor (FIAF) activity in the intestine (Figure 16.2). The authors proposed that the adipocyte hypertrophy due to a general increase in the activity of the enzyme lipoprotein lipase (LPL) could be attributed to factor FIAF (that inhibits LPL activity). This enzyme catalyzes the release of fatty acids from circulating triacylglycerol in lipoproteins that were taken up by muscle and adipose tissue, and blunted FIAF expression in conventionalized germ-free mice could thus participate in the accumulation of triacylglycerol in the adipose tissue. Consistent with this hypothesis, FIAF-deficient mice were resistant to gut microbiota–induced body weight gain.[15] Nevertheless, the FIAF mechanism does not seem to be universally associated with gut microbiota–related fat mass development.[24] Thus, the causal link between FIAF expression and the onset of obesity remains to be demonstrated in other, less specific models.

In parallel to these mechanisms, which were observed in animals that were fed a standard control diet, other metabolic pathways have been explored under western-type diet conditions to further delineate the mechanisms related to the interactions between gut microbiota and energy metabolism. Under these conditions, germ-free mice exhibit protection against high-fat diet-induced obesity and associated metabolic disorders relative to wild-type mice.[17] The major mechanisms seem to be linked to the 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK). More specifically, in the absence of the gut microbiota, the AMPK-driven fatty acid oxidation in the liver and in the skeletal muscle is highly activated, thereby explaining the apparent resistance of germ-free mice to the development of obesity upon high-fat diet feeding, whereas gut microbiota colonization decreased AMPK activity.[17]

More recently, Mestdagh et al. demonstrated that lipolysis is increased and lipogenesis is decreased in the brown adipose tissue of germ-free versus conventionally raised mice, suggesting that the gut microbiota also stimulate lipid metabolism in brown adipose tissue.[25]

In accordance with the potential role played by the G-protein coupled receptors (GPR) and fat mass development, a recent study has shown that GPR43$^{-/-}$ mice are resistant to diet-induced obesity.[26] These data show that specific metabolites produced within the gastrointestinal tract by the gut microbiota (i.e., SCFA) play important roles in metabolism, although they may act in different ways (e.g., as energy substrates or metabolic regulators) (Figure 16.3).

16.3.2 Gut Microbiota Can Transfer an Obesity Phenotype

In a landmark study, Turnbaugh et al.[18] demonstrated that gut microbiota harvested from genetically obese (*ob/ob*) mice can induce obesity when the gut microbiota is transferred into germ-free mice. More precisely, the authors found that the

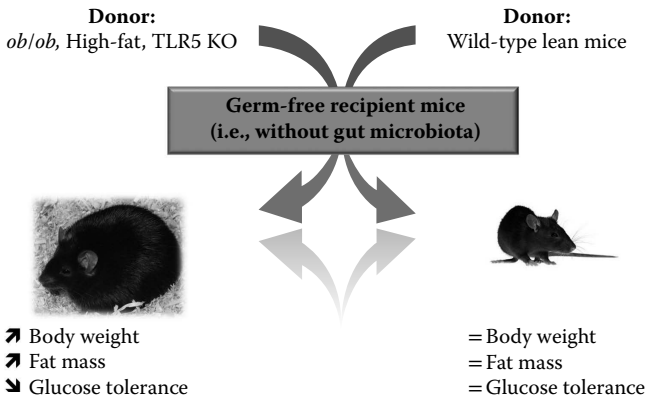

FIGURE 16.3 Gut microbiota transfer the obesity phenotype. Transferring gut microbiota from obese donors (genetically or nutritionally obese animals) to germ-free mice increases body weight gain, fat mass development, and glucose intolerance compared to the transfer of gut microbiota from lean donors. This shows the causal link between the gut microbiota and the onset of obesity and metabolic disorders. It is worth noting that such a direct link has not yet been identified in humans.

transfer of the gut microbiota from obese animals increases the fat mass by 47% within 2 weeks, whereas microbiota transferred from lean wild-type mice increases the fat by only approximately 26% (Figure 16.3). Importantly, the donor microbiota (i.e., from the obese mice) contained higher proportions of Firmicutes than the lean donor microbiota. Accordingly, the proportions of Bacteroidetes were lower in the obese donor and recipient mice than in the lean animals.[18]

Again, the authors proposed a higher capacity to harvest energy from the diet as a mechanism underlying this phenomenon. By using specific metagenomics approaches devoted to the analysis of the different genes present within the gut microbiota, the authors identified an enrichment of enzymes that can degrade indigestible polysaccharides in the gut microbiota of the obese donor and recipient "obese" mice. In addition, specific genes encoding enzymes involved in the synthesis of SCFA (acetate and butyrate) were also enriched in the obese mice.[18] It is worth noting that the *ability* of the gut microbiota to transfer obesity has also been observed in diet-induced obese mice models[20] and in another genetic model of obesity (e.g., Toll-like receptor [TLR] 5 knockout mice)[27] (Figure 16.3).

16.3.3 Are SCFAs the Culprit Metabolites?

Although the original concept that gut microbiota contributes to energy harvesting from the diet through a higher production of SCFA remains highly relevant, several other studies have challenged this theory. For instance, it is unclear whether the higher proportion of SCFAs found in the feces and cecal samples of both obese animals and human subjects directly contributes to the development of fat mass and body weight gain. These data are of questionable value because the major interactions are likely to have occurred within the vicinity of the epithelial intestinal cells and all along the gastrointestinal tract and might not be reflected by the simple measurement of such metabolites in the terminal gut or in the feces.

More importantly, in experiments performed in germ-free mice that were fed a high-fat diet, the energy intake and the fecal energy content were equivalent in the germ-free and conventionalized mice. Thus, these data challenge the hypothesis that SCFAs directly trigger the onset of obesity and metabolic disorders. Finally, we and others have demonstrated that promoting gut microbiota fermentation using specific nondigestible carbohydrates not only increases intestinal SCFA production but more importantly protects against body weight gain, fat mass development, and the severity of diabetes.[28–38] Most of these nondigestible carbohydrates conform to the prebiotic concept that "the selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host."[1] In addition, these prebiotic compounds promote the growth of specific strains that are able to digest the polysaccharides and provide extra energy for the host as they increase the total mass of bacteria in the colon.[39–41]

Therefore, all of these data further support the role of a microbiome-dependent metabolic flux in the regulation of energy storage, which is not solely in favor of fat storage, and these roles should be investigated further.

16.3.4 Potential Mechanisms Linking Gut Microbiota Fermentation and Host Metabolism in the Context of Obesity

As discussed in the preceding paragraph, selectively fermented dietary ingredients (e.g., prebiotics) result in specific changes in the composition and/or activity of the gastrointestinal microbiota (e.g., bifidobacteria and lactobacilli), thus conferring host health benefit(s).[1,42] Therefore, prebiotics are often used as a tool to modulate gut microbiota. One of the key mechanisms involved in the positive physiological impacts associated with gut microbiota fermentation and SCFA production (e.g., improved gut barrier function, reduced metabolic inflammation, and insulin resistance) might be explained by the effects of the gut microbiota on the release of gut peptides, such as glucagon-like peptides 1 and 2 (GLP-1 and GLP-2).[28–31,38,43,44] For instance, we found that prebiotic-induced changes in the gut microbiota promote GLP-1 and GLP-2 synthesis (proglucagon mRNA and GLP-1 and GLP-2 peptides) in the proximal colon.[38] One of the mechanisms explaining the higher endogenous GLP-1 and GLP-2 production is the increased differentiation of the enteroendocrine cells that produce GLP-1 and GLP-2, namely, the L-cells.[38] Fascinatingly, recent studies have shown that L-cells expressed various G-protein-coupled receptors that are activated by a wide variety of endogenous ligands found in the gut lumen.[45] It is worth noting that GPR43 and GPR41 receptors are expressed in L-cells and have been shown to directly control GLP-1 and peptide YY (PYY) secretion.[46,47] On the contrary, leptin has also been proposed to affect GLP-1 secretion.[48] Leptin is involved in the regulation of food intake

and energy homeostasis but is also linked to the regulation of glucose homeostasis and numerous gastrointestinal functions, such as the induction of GLP-1 secretion. In a recent study, we showed, for the first time, that the gut microbiota controls leptin activity. More precisely, we found that changing the gut microbiota composition using prebiotics improves leptin sensitivity in diet-induced obese and type 2 diabetic mice.[38,49] Therefore, this novel link between gut microbiota and endocrine function supports the idea that targeting the gut microbiota could be viewed as a novel therapeutic target to reset leptin sensitivity or other endocrine disorders during obesity.

16.4 GUT MICROBIOTA COMPOSITION UPON OBESITY: EVIDENCE FROM RODENTS TO HUMANS

16.4.1 Animal Models

In 2005, Ley et al. were the first to demonstrate a specific difference in the gut microbial community between genetic obese (*ob/ob*) and lean mice. The microbiota of obese mice contained fewer Bacteroidetes and more Firmicutes than those of their lean +/+ or *ob*/+ littermates.[11] Although these findings might not be causally linked with obesity, the concept that a specific change in gut microbiome content, or dysbiosis, occurs upon obesity was born.

In 2007, we were the first to demonstrate that fat feeding profoundly affects the gut microbial community in mice, resulting in a significant modulation of the dominant microbial populations in the gut microbiota within 4 weeks.[43,50] More specifically, we discovered that fat feeding strongly altered the composition of the gut microbiota by reducing the *Bifidobacterium* spp., *Bacteroides*-related bacteria, and *Eubacterium rectale–Blautia coccoides* group contents.[43,50] A longer period of treatment with a high-fat diet (14 weeks) provoked similar alterations in the gut microbiota, with a significant decrease in Enterobacteriaceae and *Bacteroides* spp.[43] More recently, we confirmed and extended these findings, discovering that this treatment also decreases *Lactobacillus* spp. and *Roseburia* spp.[37] Since these discoveries, several other studies using metagenomic approaches have extensively characterized the composition of the gut microbiota in diet-induced obese mice.[51–55] For instance, Murphy et al. explored the effects of a high-fat diet and genetic obesity on the gut microbiota over time,[52] with higher Firmicutes counts observed in both high-fat fed and *ob/ob* mice. The authors also described a decrease in Proteobacteria and *Bifidobacterium* spp. upon high-fat diet feeding.[52] Turnbaugh et al. demonstrated that diet-induced obesity was linked with a bloom in Mollicutes, a class of bacteria belonging to the Firmicutes phylum, and a proportional decrease in Bacteroidetes phylum.[56] Interestingly, they found specific changes within the Firmicutes phylum following high-fat diet feeding, with a drastic increase in Erysipelotrichi (i.e., *Clostridium innocuum*, *Eubacterium dolichum*, and *Catenibacterium mitsuokai*).[20] The same year, Hildebrandt et al. found that 3 months of fat feeding increases Clostridiales content and decreases Bacteroidales content, also supporting the increase in the proportion of corresponding phyla (increased Firmicutes/Bacteroidetes ratio). In accordance with the lower Bacteroidetes abundance as well as with our previous findings,[43] several specific families (Bacteroidaceae, Prevotellaceae, and Rickenellaceae) were decreased in high-fat-fed mice.[51] Zhang et al. found that Erysipelotrichaceae responded differentially to a high-fat diet and that the family Bifidobacteriaceae (e.g., bifidobacteria) was present in lean control mice but completely absent in diet-induced obese mice.[57] It is worth noting that a decrease in *Bifidobacterium* spp. has been observed in genetic obese rats (*fa/fa* rats),[58] and this genus is virtually absent in obese (*ob/ob*) mice (unpublished observations). Thus, these studies support the presence of a dysbiosis at the phylum and genus levels in both genetic and nutritional obesity. They also highlight the consistent and reproducible changes in the gut microbiota associated with obesity, such as an increase in Firmicutes and/or a decrease in Bacteroidetes and *Bifidobacterium* spp.

16.4.2 Human Studies

One year after their first observations in experimental animals, Ley et al. confirmed that obese human subjects also exhibit a larger proportion of Firmicutes and relatively less Bacteroidetes than lean subjects.[59] Turnbaugh et al. analyzed the gut microbiota of 154 monozygotic or dizygotic twin pairs with concordant lean or obese phenotypes and their mothers. Interestingly, they found a decrease in phylogenic microbial diversity in obese subjects featuring a reduced representation of Bacteroidetes and more Actinobacteria.[19] Although this finding has been recently confirmed,[60] Duncan et al. did not detect any differences in this phylum between obese and non-obese subjects.[61] In contrast, Zhang et al. reported that obese subjects harbored even more Bacteroidetes than normal-weight individuals.[62] In addition to these findings, they also described an enrichment of the Prevotellaceae (belonging to the Bacteroidetes phylum) in the obese subjects.[62] Finally, Schwiertz et al. found that the Firmicutes/Bacteroidetes ratio changed in favor of Bacteroidetes in overweight and obese subjects.[63]

Given that most type 2 diabetes subjects are obese, it is tempting to argue that the study by Larsen and colleagues did not favor such a Bacteroidetes/Firmicutes shift because they also found higher levels of Bacteroidetes in diabetic patients than in control patients.[64] Strikingly, Abdallah Ismail et al. found that the distribution of Bacteroidetes and Firmicutes was significantly increased in the obese group compared to the normal-weight group.[65] In addition, Arumugam et al. reported that the Firmicutes/Bacteroidetes ratio was not significantly different between obese and lean subjects.[66] Finally, Munuka et al. recently demonstrated that the Firmicutes/Bacteroidetes ratio was higher in obese subjects with metabolic disturbances than in so-called healthy obese and lean subjects. However, after adjustment for body weight, the authors did not find any differences in the ratio among the groups. Thus, from those studies, it appears important to question the usefulness of the Firmicutes/Bacteroidetes ratio in studies of metabolic obesity.

Altogether, these findings support the concept that understanding microbial diversity is important because there may be high species diversity within phyla (while the overall Firmicutes/Bacteroidetes ratio remains unchanged or only slightly modified), thereby increasing the need to decipher the role of the gut microbiota at the functional level and at the genus level. Given the lack of evidence that one genus or species is directly associated with obesity, as well as for the sake of clarity, the current literature at this level of detail will not be discussed in the present chapter; it has been reviewed elsewhere.[5,6,67,68] Nevertheless, it is important to mention one recent discovery: three robust clusters referred to as "enterotypes" have been identified in individuals from different countries and a continent.[66] Arumugam et al. found that these enterotypes were identified by variation at the level of one of the three following genera: *Bacteroides*, *Prevotella*, and *Ruminococcus*. It is important to note that these enterotypes were not correlated with host characteristics such as body mass index, age, gender, or nationality. Although this recent finding is interesting, the universality of these data has also been questioned within the literature[69] and by experts.[70]

16.5 GUT MICROBIOTA AND METABOLIC INFLAMMATION ASSOCIATED WITH OBESITY

Along with this increasing worldwide epidemic, obesity is often associated with low-grade chronic inflammation that contributes to the development of insulin resistance, type 2 diabetes, and cardiovascular diseases.[71–73] Therefore, it is critical to identify the link between inflammation and metabolism in the context of obesity and related metabolic disorders. Numerous studies support the hypothesis that this inflammation may stem from the infiltration of macrophages into several organs (e.g., adipose tissue, muscles, and liver), thereby promoting the secretion of pro-inflammatory factors.[74–77] However, the precise role of these macrophages and the sources and types of triggering factors activating the immune system in this specific context remain a matter of debate.[78,79] The relationships between the activation of innate and adaptive immunity and altered glucose metabolism (i.e., insulin resistance and glucose intolerance) have already been corroborated by clinical evidence describing impaired glucose homeostasis, insulin secretion, and defects in signaling pathways associated with infection and sepsis.[80] However, the major pathogenic mechanism linking inflammation with changes in liver and adipose tissue metabolism remains to be determined. A plethora of inflammatory factors (e.g., interleukin [IL]-1, tumor necrosis factor-α, monocyte chemoattractant protein-1 [MCP-1], inducible nitric oxide synthase [iNOS], and IL-6) are causally related to the development of impaired insulin activity or insulin resistance and the multiple molecular interactions between immunity and insulin signaling. Thus, we have sought to identify a potential integrating factor that elucidates the relationship among these mechanisms and have investigated microbe-related factors in the etiology of obesity and associated disorders.

16.6 METABOLIC ENDOTOXEMIA AS A CAUSAL FACTOR?

We discovered that gut microbiota–derived lipopolysaccharides (LPS) are involved in the early development of inflammation and metabolic disease[50] (Figure 16.4). LPS are cell wall components of gram-negative bacteria; they are among the most potent inducers of inflammation and are also likely the most studied. We found that, in pathological situations (genetic or nutritional-induced obesity and type 2 diabetes), the gut microbiota "sends" specific pathogen-associated molecular patterns in the form of LPS to the host.[43,44,50,81] More precisely, we observed that dietary fat ingestion not only increases systemic exposure to potentially pro-inflammatory free fatty acids and their derivatives but also facilitates the development of metabolic endotoxemia (i.e., a very small increase in plasma LPS levels compared to endotoxic shock)[43,50] (Figure 16.4). This metabolic endotoxemia also

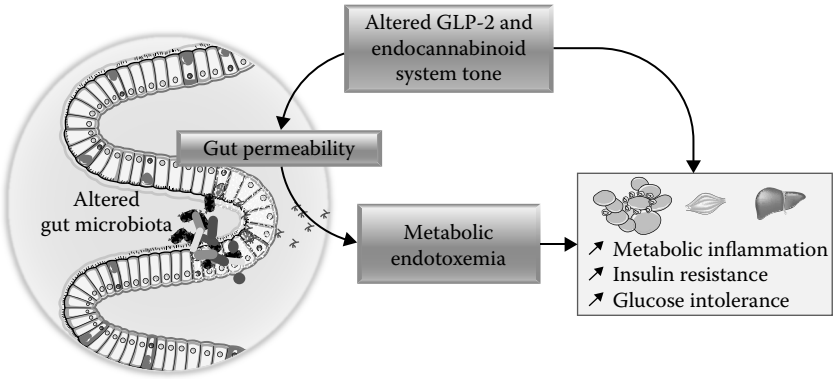

FIGURE 16.4 (**See color insert.**) Metabolic endotoxemia links gut microbiota with metabolic disorders associated with obesity. Both genetic and nutritional obesity are associated with dysbiosis, increased gut permeability, and metabolic endotoxemia. This increased level of lipopolysaccharide production triggers metabolic inflammation, insulin resistance, and type 2 diabetes. Both glucagon-like peptide (GLP)-2 and the endocannabinoid system play a major role in the control of gut barrier function and therefore in the onset of metabolic endotoxemia upon obesity.

occur in genetically obese animals that were fed a normal chow diet, thereby supporting the idea that this phenomenon is not only dependent on fat ingestion. LPS are linked to the innate immune system through their complex interactions with specific proteins that bind to TLR4 (CD14/TLR4 complex). Because LPS can affect inflammation throughout the body and interfere with both metabolism and the function of the immune system, this novel concept provides new insight into the role of gut microbiota–derived products and metabolism. Among the mechanisms explaining the development of metabolic endotoxemia upon obesity, we found that gut microbiota links gut permeability (Figure 16.4) to low-grade inflammation and insulin resistance through GLP-2 and endocannabinoid system–dependent mechanisms, which have been reviewed elsewhere.[38,50,81,82]

In parallel to the link between LPS and inflammation in obesity, recent data indicate that low-grade inflammation and insulin resistance are also controlled by TLR2.[83] More recently, it has been proposed that another receptor from the TLR family, TLR5, plays a crucial role in the development of obesity and associated disorders.[27] Thus, these data further support the hypothesis that other microorganisms and/or derived compounds may play a crucial role in the onset of metabolic disorders associated with obesity. Importantly, numerous studies have confirmed that metabolic endotoxemia occurs in humans.[84–92] In addition, this link has been confirmed in type 2 diabetic patients, and metabolic endotoxemia is viewed as a marker of incident type 2 diabetes.[92]

16.7 CONCLUSION

The changes in the gut microbiota observed in obese individuals create different metabolic and genetic signatures, both from the gut microbes themselves and from the host (e.g., mRNA expression and protein levels), which can often be detected in the bodily fluids (e.g., urine and blood) of the host. These changes reflect the production of several potential bioactive compounds and/or metabolites that are directly affected by the gut microbiota.[93–95] Thus, there is no doubt that understanding the microbiome and thus the functional metabolome will be helpful in the future to identify biomarkers to evaluate the interactions among the gut microbiota, host, and nutrients. Accordingly, to assess the relevance of the gut microbiota in obesity, it will be crucial to understanding how gut microbes interact with the host and participate in the metabolic response according to the dietary pattern and pathophysiological state.

Although the description of nutritional/therapeutic approaches is outside of the scope of this chapter, it should be noted that a growing body of evidence supports the interest in prebiotic or probiotic approaches to selectively changes the composition of the gut microbiota in favor of one or more specific genera and even specific strains, thereby positively impacting obesity and related diseases. All of these key issues will be crucial for the future development of treatments devoted to curing dysbiosis-linked pathologies.

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17 Sympathetic Nervous System and Endocrine Determinants of Energy Balance

Hamid R. Farshchi and Ian A. Macdonald

CONTENTS

17.1 INTRODUCTION

Obesity can be viewed as a disorder of energy balance in which energy stores in the body, especially the adipose tissue, are increased due to increased energy intake and/or reduced energy expenditure (EE).

It is known that a number of sympathetic nervous system (SNS) and endocrine factors can affect energy balance, through effects on energy intake and/or EE. Some hormones may also have effects on fat distribution. The SNS, as an important component of the autonomic nervous system, plays a major role in the maintenance of body homeostasis, including energy balance, and the most common endocrine influences on energy balance are thyroid, glucocorticoid, insulin, and leptin hormones. This short chapter provides an overview of the evidence showing a role for the SNS and major hormones in energy balance, which may lead to obesity.

17.2 SYMPATHETIC NERVOUS SYSTEM PHYSIOLOGY

The aspects of SNS function that are of specific interest in relation to metabolism and obesity concern the regulation of the cardiovascular system, gastrointestinal function, pancreatic hormone secretion, and adipose tissue lipolysis. The single most important role of the SNS is the maintenance of an adequate blood pressure to maintain the functioning of vital organs. This is achieved principally by the sympathetic

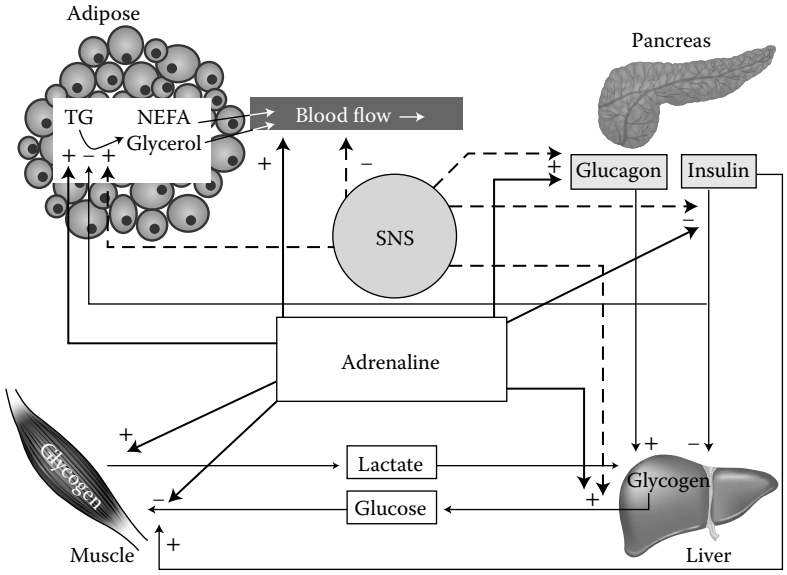

FIGURE 17.1 Summary of the metabolic effect of the sympathetic nervous system (SNS) and plasma adrenaline: shaded boxes represent plasma compartments for hormones or substrates, solid lines represent the effect of adrenaline from the adrenal medulla, and dashed lines represent activities mediated by sympathetic nerves. Other thin lines represent exchanges through the bloodstream. (From Astrup A and IA Macdonald, *Handbook of Obesity*, Marcel Dekker, New York, 1998.)

control of cardiac output and blood vessels, although it should be recognized that the parasympathetic innervation of the heart has a part to play. In most tissues or organs, the stimulation of sympathetic nerves produces vasoconstriction, reducing blood flow and potentially raising blood pressure. However, in some tissues (e.g., adipose tissue, skeletal muscle, and some skin areas) sympathetic activation can produce vasodilatation, increasing the blood flow. Nevertheless, in most cases when tissue blood flow increases it does so either because of the effects of local metabolites or because of a reduction in sympathetic vasoconstriction. The importance of the SNS in the control of the cardiovascular system should not be overlooked, as any nonspecific stimulation or antagonism of the SNS intended to produce metabolic effects will also have significant cardiovascular effects that could be undesirable.

SNS activation has a general inhibitory effect on gastrointestinal function, reducing intestinal motility and gastric emptying. This contrasts with its general stimulatory effect on many other physiological processes. The SNS has a major role in the control of lipolysis in adipose tissue, both directly and due to the effects on pancreatic hormone secretion.[1] The major metabolic effects of the SNS and plasma adrenaline are summarized in Figure 17.1.

In most physiological situations, the SNS is activated in a discrete manner, with the stimulation of some tissues and no effect on others. This was clearly identified by Muntzel et al.,[3] who showed that intracerebroventricular administration of insulin to rats activated sympathetic outflow to the hind limbs (mainly skeletal muscle) but not to other areas. It is only in extreme circumstances, for example, profound hypotension or the "fight or flight" response, that a generalized sympathetic activation may occur. In metabolic situations such as overfeeding, fasting, or hypoglycemia in rats, there is selective activation or inhibition of sympathetic activity in some organs, with no change in others.[4] Thus, any consideration of the role of altered SNS or adrenal medullary activity in relation to obesity must take account of the discrete manner in which these systems are involved in physiological regulation.

17.3 VARIOUS COMPONENTS OF ENERGY EXPENDITURE

The daily EE[5] of an individual can be divided into its components as illustrated in Figure 17.2. The resting metabolic rate (RMR) comprises 50%–80% of the total daily EE and varies greatly among individuals. About 70%–80% of this variance can be accounted for by differences in fat-free mass, fat mass, age, and gender.[6]

The thermic effect of food (TEF) is commonly defined as the increase in EE in response to food intake. Although TEF accounts for only approximately 10% of daily EE, many researchers have argued that a low TEF plays a role in the development of obesity. Some data supporting this view have been presented, but the issue is still debated.[7,8] Importantly, in the only prospective study to date a low TEF was not associated with weight gain.[9]

When confined to a respiratory chamber, individuals differ as to how much they move around spontaneously, change position, and fidget. This "spontaneous physical activity" can be measured,[6] and a low spontaneous physical activity is a risk factor for body weight gain in men.[10] Levine et al.[11] showed that subjects who unconsciously increased their spontaneous physical activity in response to overfeeding were resistant to weight gain compared to those who did not. They coined the term NEAT for this "nonexercise activity thermogenesis" component of EE.

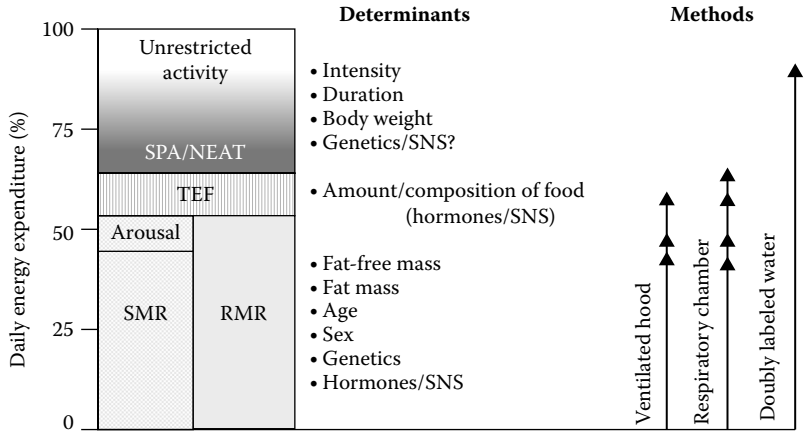

FIGURE 17.2 Components of daily energy expenditure, their major determinants, and the methods by which they can be measured: SPA, spontaneous physical activity; SMR, sleeping metabolic rate. (From Astrup A and IA Macdonald, *Handbook of Obesity*, Marcel Dekker, New York, 1998.)

17.4 CONTRIBUTION OF THE SYMPATHETIC NERVOUS SYSTEM TO ENERGY EXPENDITURE AND ITS COMPONENTS

17.4.1 Energy Expenditure (24-Hour Energy Expenditure and Resting Metabolic Rate)

Observations in rats indicate that the SNS stimulates thermogenesis and that dietary manipulation influences noradrenaline turnover. These findings have promoted interest in the role of the SNS in body weight regulation in humans. During short-term studies, sympathomimetic agents clearly increase EE.[5] In a long-term crossover study in seven white males, 24-hour EE tended to be lower during the administration of the β-antagonist propranolol than placebo or the β_2-adrenergic agonist terbutaline.[12] However, lipid oxidation was increased by terbutaline.[12] In another study,[13] 24-hour EE measured in a respiratory chamber was positively correlated with urinary noradrenaline excretion. Furthermore, administration of the β-antagonist propranolol caused a 4% decrease in RMR in white people but, interestingly, not in Pima Indians,[13] suggesting a dissociation of SNS and RMR in Pima Indians, a population with one of the highest prevalence rates of obesity in the world. In yet another study,[14] adjusted 24-hour EE, sleeping metabolic rate, and RMR were correlated with muscle sympathetic nerve activity (MSNA) in white people, but, again, there was no relationship in Pima Indians. Noradrenaline turnover studies have shown that most of the variability in RMR not explained by body size and composition is related to differences in SNS activity.[15,16] Taken together, the aforementioned studies suggest that SNS activity does modulate RMR, the largest component of daily EE in most people.

17.4.2 Thermic Effect of Food

Studies in which β-blockade is used have demonstrated a facultative, β-adrenergically mediated component of glucose-induced thermogenesis. Furthermore, it has been shown, by measurement of plasma noradrenaline turnover,[17,18] that the increased SNS activity in response to a meal accounts for at least part of the meal-induced TEF. The major drive for the increase in SNS activity in response to a meal seems to be insulin.[19] Despite the clear impact of SNS activity on TEF, the contribution of TEF to total EE may be too small to have an impact on body weight gain, as suggested by prospective data.[9]

17.4.3 Spontaneous Physical Activity

The relationship between spontaneous physical activity and noradrenaline appearance rate[20] is consistent with the idea that SNS activity is a determinant of how much subjects move around, change position, and fidget, all of which contribute to total EE. In other words, "fidgeters" seem to have higher SNS activity. It remains to be determined, however, whether increased SNS activity is a contributing factor to fidgeting, or secondary to the increased activity associated with fidgeting. The mechanisms underlying the variability in the induction of spontaneous activity in response to overfeeding are unknown, and it will be interesting to test the impact of the activity of the autonomic system on this variability. Data from the National Institutes of Health (NIH) group in Phoenix, Arizona, showed that spontaneous physical activity measured in a respiratory chamber is related to the level of physical activity in free-living conditions.[21] Taken together, the results suggest that a higher sympathetic tone may drive an increase in both spontaneous physical activity and habitual physical activity, therefore protecting individuals against body weight gain.

17.4.4 Substrate Oxidation

The effects of the SNS on metabolism appear to influence the relative amounts of substrate oxidized.[12] Accordingly, an inverse relationship was demonstrated in white people between 24-hour respiratory quotient (RQ) (measured in a respiratory chamber) and basal MSNA (measured immediately after the stay in the respiratory chamber).[22] The relationship between RQ and SNS activity was independent of the percentage of body fat and clearly indicates an association

between a low SNS activity and a low lipid oxidation. A possible explanation for this observation is the stimulatory effect of noradrenaline on intracellular lipolysis and on nonesterified fatty acids (NEFAs) uptake in the muscle, which seem impaired in previously obese subjects.[23]

17.4.5 Responsiveness to Sympathetic Stimuli

Decreased responsiveness to sympathetic stimuli may be as equally important as decreased activity of the SNS for the development of obesity. Defects of catecholamine-induced lipolysis have been observed in a number of obese subjects, but polymorphisms of the β_2-[24] and β_3-receptors[25] were proposed as explanations for the impaired lipolysis. Using an in vivo model for studies of neural control of adipose tissue lipolysis (intraneural electrical stimulation of the lateral cutaneous femoral nerve), Dodt et al.[26] showed that human obesity is characterized by a profound unresponsiveness of the subcutaneous adipose tissue to lipolysis. Decreased responsiveness could possibly be caused by polymorphisms in the genes encoding the various types of adrenoceptors, but it may also be due to a reduced number of those receptors in the obese. A variant in the gene encoding for the β_3-adrenoceptor, resulting in the substitution of tryptophan with arginine in position 64 (trp64arg) of the receptor protein, has been associated with obesity and diabetes in some studies[27] and exhibits impaired signaling when expressed in Chinese hamster ovary cells under certain, but not all, experimental conditions.[28] A number of genetic polymorphisms in the β_2-adrenoceptor have also been reported,[24] some of which are associated with functional abnormalities and some with obesity but none of which are associated with both.[24] At the intracellular level, cAMP released owing to SNS stimulation may affect the expression and the thermogenic function of uncoupling proteins (UCPs). Lately, attention has been focused on uncoupling protein 3 (UCP3), which is mostly expressed in muscles. UCP3 mRNA expression increases in response to overfeeding and fasting (probably through the increased availability of NEFAs) and in response to adrenergic stimulation. The UCP3 and uncoupling protein 2 (UCP2) genes are located adjacent to each other in a region implicated in linkage studies as contributing to obesity,[29] and a polymorphism in the gene encoding for UCP3 has been associated with reduced fat oxidation.[30] However, the potential uncoupling activity of UCP2 and UCP3 is still debated[31] despite the fact that massive overexpression of human UCP3 in mice was associated with increased metabolic rates.[32]

17.5 SYMPATHETIC NERVOUS SYSTEM FUNCTION AND BODY WEIGHT

In rodents, administration of the adipocyte hormone leptin promotes negative energy balance, the latter partly mediated by increased SNS outflow to a number of organs including brown adipose tissue (BAT). Accordingly, animals with defective leptin biosynthesis or receptor function (e.g., the *ob/ob* mouse, the *db/db* mouse, or the *fa/fa* rat) have markedly reduced SNS activity and become obese. Rodents made obese by lesions of the ventromedial hypothalamus have a reduced firing rate of sympathetic nerves to BAT in the basal state and in response to dietary and environmental stimuli. This reduced SNS activity is associated with low metabolic rate and hyperphagia.[33] Studies in humans in whom SNS activity or adrenal medullary function is compared between lean and obese subjects have yielded very conflicting results,[34] probably because comparisons of lean and obese subjects provide only very limited information about the role of the SNS in the etiology of obesity as they do not discern between causes and consequences of weight gain. A better approach is to establish the relationship between SNS activity and subsequent weight gain. The only such report we are aware of[35] demonstrates a relationship between low urinary noradrenaline excretion and weight gain and a relationship between low urinary adrenaline excretion and development of central obesity. These results strongly suggest that a low SNS activity is also a risk factor for weight gain in humans. SNS activity increases in response to weight gain, thereby attenuating the original impairment. It is of interest to note that basal MSNA for a given percentage of body fat is lower in Pima Indians compared to white people,[12,14] possibly contributing to the propensity to obesity in Pima Indians.

17.6 THYROID HORMONE PHYSIOLOGY

Thyroid hormones (THs) are crucial determinants of metabolic activity in most, if not all, cells in the body. TH, in the form of triiodothyronine (T_3), acts by modifying gene transcription in almost all tissues to change rates of protein synthesis and substrate turnover.[36] Extranuclear actions of thyroxine (T_4) and T_3 are usually mediated by interactions with membrane receptors, organelles, and components of the signal transduction system.[37]

TH (T_4 and T_3) production and secretion from the thyroid gland is regulated by pituitary thyrotropin (TSH). Circulating T_4 and T_3 enter cells by diffusion and, in some tissues, like the brain, by active transport.[38] T_3 is also produced in some cells from T_4, and the locally produced T_3 provides most of the hormone that is bound to T_3 nuclear receptors in different organs. In general, about 80% of circulating T_3 in humans is derived from the extrathyroidal conversion of T_4 to T_3.[39]

17.6.1 Thyroid Hormone and Energy Balance

THs have been known for decades as hormones with profound effects on EE and the ability to control weight, with the activity of the hypothalamus–pituitary–thyroid axis being a significant influence on energy homeostasis.[40,41] Hyperthyroidism, a clinical disorder involving excess production of THs (T_4 and T_3), produces a hypermetabolic state characterized by raised EE and weight loss, in spite of noticeable hyperphagia.[41,42] However, much of this weight loss is from the loss of body protein, leading to serious consequences as cardiac muscle protein becomes depleted.

TH action is an essential component of obligatory thermogenesis, as a result of the stimulation of numerous metabolic pathways involved in tissue growth, tissue repair, and availability of energy. In addition, TH action is essential for

thermogenic mechanisms critical for survival in homeotherms such as Na/K-ATPase, which maintains membrane potentials and Ca^{2+} cycling in muscle.[40]

THs have been known to stimulate basal metabolic rate for over a century.[43] It is estimated that the actions of THs to increase the utilization of adenosine triphosphate (ATP) are only responsible for approximately 50% of the thermogenic effect of THs.[44] Thus, a large fraction of TH thermogenesis may result from the hormone, decreasing the efficiency of ATP synthesis, that is, increasing the fraction of energy lost as heat in its synthesis.

THs also play an important role in thermogenesis by interacting with the SNS at the level of the adrenoceptor and the adenyl cyclase complex, as well as distally from this point.[45] In addition, in BAT T_4-5′-deiodinase plays a central role in controlling heat production. When this enzyme is stimulated by noradrenaline in the euthyroid and hypothyroid conditions, it provides high concentrations of T_3 to BAT; inhibition by T_4 in hyperthyroidism may limit BAT thermogenic responses. Furthermore, hyperthyroidism uniquely decreases the expression of β_3-adrenoceptors in BAT, thus restricting BAT thermogenesis in hyperthyroidism.[46]

Although most effects of THs on energy homeostasis are exerted peripherally,[40,41,47] further evidence from animal studies indicates that hypothalamic neurons sense nutritional deficit through a mechanism that involves local generation of T_3, leading to the induction of UCP2.[48]

It has long been recognized that T_3 stimulates food intake. In humans, one of the characteristics of hyperthyroidism is hyperphagia,[42] with an increased appetite for carbohydrates possibly because of an increased sympathetic tone and a reduced plasma tryptophan/neutral amino acid ([Trp]/[NAA]) ratio.

The reduction in plasma [Trp]/[NAA] ratio and increased SNS activity in hyperthyroid conditions have the potential to hinder the synthesis of 5-HT and activate adrenoceptors in the brain. As a consequence, energy intake increases considerably in the hyperthyroid state, particularly in relation to carbohydrate consumption, with less effect on protein and fat intakes.[42]

THs have a major effect on lipid metabolism. Hyperthyroidism increases fatty acid synthesis in liver, kidney, heart, BAT, and white adipose tissue[49,50,51] but not in the entire brain.[50] However, T_3 may selectively regulate lipid metabolism in specific areas of the hypothalamus and thus affect energy balance.[52,53] For example, hyperthyroidism induces a marked upregulation of de novo lipogenesis in the hypothalamus and activates BAT via the SNS.[54] If similar effects occur in adult humans, it may explain how the hyperthyroid state leads to weight loss despite increased energy intake.

17.6.2 Thyroid Functions and Body Weight

Since BMR is elevated in patients with hyperthyroidism weight loss is a common consequence, and hyperthyroid patients who are treated successfully gain nearly 4 kg/year.[55] On the other hand, patients with hypothyroidism usually gain weight due to the slowing of metabolic rate (some of this gain is fat). Although the weight gain is usually modest, TH therapy has not shown significant weight loss,[56] raising the question of whether variation in thyroid function within the physiologic range may affect body weight. Even small differences in thyroid function with TSH variation within the normal laboratory range for patients on T_4 substitution therapy are associated with measurable differences in RMR.[57] A prolonged decrease in RMR might well lead to increased body weight in the current environment of food availability and physical inactivity. An acute reduction in T_4 replacement therapy (to 50% of the optimal level) for patients treated for hyperthyroidism by thyroid ablation is associated with a reduction in RMR of approximately 10%.[58] This indicates that physiologically relevant variations in thyroid status are only likely to have modest effects on RMR, but in the long term this could have an appreciable effect on energy balance. Recent evidence indicates that increasing serum TSH concentrations within the normal range is associated with a modest increase in body weight in adults,[59,60] although treatment of subclinical hypothyroidism does not appear to be associated with weight loss.[61,62]

17.7 HYPOTHALAMUS–PITUITARY–ADRENAL AXIS AND ENERGY BALANCE

The hypothalamus–pituitary–adrenal (HPA) axis is a complex system with direct effects and feedback interactions in the hypothalamus, pituitary gland, and adrenal glands. Together, this forms the HPA axis, which regulates reactions to stress and influences many body processes, including EE, food intake, and body fat storage.

17.7.1 Hypothalamus–Pituitary–Adrenal Axis Physiology

The HPA axis is a neuroendocrine system involved in stress response, by regulating the secretion of cortisol.[63] The cascade of the HPA axis activities starts with the hypothalamus producing and releasing corticotropin-releasing hormone (CRH), which then stimulates the synthesis and release of adrenocorticotropin (ACTH) from the anterior pituitary. ACTH subsequently stimulates the synthesis and release of cortisol by the adrenal cortex.[63]

Acute physical or psychological stress may activate the HPA axis, resulting in increased plasma ACTH and cortisol concentrations.[64]

On the other hand, feedback inhibition of ACTH secretion by glucocorticoids occurs at the pituitary and hypothalamus. In the pituitary, glucocorticoids inhibit ACTH secretion rapidly and ACTH synthesis more slowly.[65]

17.7.2 Hypothalamus–Pituitary–Adrenal Axis Activity and Energy Expenditure

Peripheral CRH administration in humans can lead to a 14% increase in RMR.[66] CRH may also activate the SNS, both in the hypothalamus and in the locus coeruleus of the brain stem.[67] However, as the increase in RMR following CRH infusion was not associated with an increment in plasma catecholamines, different mechanisms may also be engaged.

Shorter term infusions of glucocorticoid (cortisone) for 16–60 hours can increase RMR by up to 15%,[49,68] but longer term administration (for 168 hours) had no effect.[69] In addition, chronic dexamethasone treatment in infants did not affect EE.[70] These different influences of glucocorticoids on EE indicate that the acute effects[49,68] may be offset by inhibitory effects over longer term exposure,[40] such as suppression of CRH release, as part of the negative feedback regulation of the HPA axis.[67] In addition, chronic increase in cortisol in Cushing's disease/syndrome causes the breakdown of muscle and may eventually result in lower EE by decreasing muscle mass.[71] Glucocorticoids may also inhibit TH production and the conversion of T_4 to T_3, decreasing plasma T_3 levels[67] and reducing RMR.[40]

17.7.3 Hypothalamus–Pituitary–Adrenal Axis Activity and Energy Intake

There is substantial evidence from animal studies that the HPA axis stimulates food intake,[72,73] with the limited human studies generally supporting these findings.[74,75] Human studies have shown an increased desire for highly saturated fat and sweet foods[76–78] and increased snack consumption during stress,[79] but it is not known whether these effects are due to the glucocorticoids released in response to stress.

17.7.4 Hypothalamus–Pituitary–Adrenal Axis Functions and Body Weight

The HPA axis may be involved in the pathogenesis of human obesity, especially in visceral fat deposition. Glucocorticoids have been proposed to be potentially important in visceral adiposity since they assist the differentiation and proliferation of human adipocytes.[80] It is also mentioned that glucocorticoid receptors are denser in visceral than in subcutaneous adipose tissue,[81] which suggests that abdominal fat distribution and HPA axis activity are linked. However, studies on the relationship between the HPA axis and fat storage and distribution have not resolved this issue.[82]

People with idiopathic obesity have normal circulating cortisol concentrations, which are independent of fat stores but are related to an augmented cortisol turnover rate.[83] On the other hand, differences have been demonstrated not only in basal activity of the HPA axis but also in sensitivity to ACTH and glucocorticoids in obese women with abdominal versus peripheral body fat distribution.[84] Interestingly, further studies indicate that abdominal adipose tissue distribution, which has major effects on human health, in obese patients is related to enhanced HPA axis reactivity.[85] There may also be reduced cortisol levels during the day and increased levels at night with increasing degree of adiposity,[86] but the underlying mechanisms need further investigation.

17.8 INSULIN, LEPTIN, AND ENERGY BALANCE

It is likely that the central nervous system plays the key role in the control of energy homeostasis. However, to balance the energy equation, the brain must receive information about the status of peripheral energy stores in the form of adipose masses. There is now substantial evidence that insulin and leptin are significant regulators of food intake and energy balance.[87,88]

Insulin (released from the pancreatic β cells) is central to regulating carbohydrate and fat metabolism in the body. Insulin causes muscle and fat tissue to take up glucose from the blood and promotes the storage of glycogen in muscle and liver and fat in adipose tissue. Leptin is an adipose tissue–derived hormone that appears to play a key role in regulating energy intake and EE, including appetite and metabolism.[89]

Early studies introduced insulin as an adiposity signal.[90,91] It was shown that plasma insulin levels were directly associated with body weight and particularly with adiposity.[92–94]

Acute changes in energy status may also affect plasma insulin levels, with increases occurring during any condition of positive energy balance, such as during meals, and decreases occurring during negative energy balance (e.g., fasting). The degree of glucose-stimulated insulin secretion is a direct function of body fat content.[92–94] The secretion of insulin in response to a meal is dependent on the rise in blood glucose (although this can be enhanced by gut peptides, amino acids from dietary protein will also stimulate insulin secretion). The plasma half-life of insulin is approximately 6 minutes, and so levels decline quite rapidly when blood glucose levels fall.

In addition to the important peripheral action of insulin on the metabolism of fuels, insulin may also be an adiposity signal, affecting energy intake and expenditure, as administration of insulin in small doses, or as a continuous infusion, elicits decreased food intake and increased EE after several hours and lasts for the duration of the treatment.[91,95]

Administration of insulin into the brain also potentiates the anorexic effects of peripherally administered cholecystokinin,[96,97] suggesting that insulin modulates the body's response to short-term signals that terminate meals. Importantly, administration of insulin peripherally, in amounts that do not cause hypoglycemia, decreases food intake.[98,99]

Leptin was identified in the early 1990s as an adiposity hormone,[89] and plasma leptin levels are directly associated with adiposity. Leptin acts in the brain to reduce food intake and increase EE, and prolonged administration of leptin causes loss of body fat and body weight. The release of leptin from adipose tissue is mainly proportional to the fat mass and also modulated by the ongoing state of energy balance to provide a signal to the brain related to overall nutritional status.[100] Animal studies show that exogenous leptin administration into the brain reduces food intake and body weight.[101,102] During weight loss, plasma leptin decreases.[103–105] On the other hand, weight gain is associated with an increase in leptin secretion.[103,104,106]

Interestingly, when insulin and leptin are administered into the brain in combination they initially interfere with each other's action such that the net catabolic effect is less than the sum of the individual effects. However, the effects of the two hormones are additive after 4 hours.[106] It should be mentioned that further research is needed to explore the details of effects of insulin and leptin on energy balance.

17.9 CONCLUSION

Obesity is a disorder of energy balance in which energy stores, especially in the adipose tissue, are increased because of increased energy intake and/or reduced EE. Our understanding of the endocrine mechanisms involved in the determination of energy balance has increased substantially during the past decade, with a number of SNS and endocrine factors affecting energy balance through effects on energy intake and/or EE. Some hormones may also have effects on fat distribution.

There is evidence that SNS activity regulates RMR in most people and that the increased SNS activity in response to a meal accounts for at least part of the TEF. It is also known that low SNS activity is a risk factor for weight gain in humans.

THs have profound effects on EE, in particular RMR, and thus body weight. It has also been recognized that T_3 stimulates food intake, whereas patients with hypothyroidism usually gain weight because of a slowing of metabolic rate.

The HPA axis is a neuroendocrine system involved in energy balance and the pathogenesis of human obesity, especially in visceral fat deposition. Short-term infusions of glucocorticoid can increase RMR, but longer term administration appears to have no effect. In addition, chronic increase of cortisol in Cushing's disease/syndrome may eventually result in reduced EE by decreasing muscle mass.

There is now substantial evidence that insulin and leptin are significant regulators of food intake and energy balance. Plasma insulin levels are directly associated with body weight and particularly with adiposity. In addition to the important action on the metabolism of fuels, insulin may also be an adiposity signal, affecting energy intake and expenditure. Leptin also acts in the brain to reduce food intake and increase EE, and prolonged administration of leptin causes loss of body fat and body weight in some circumstances.

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18 Insulin Resistance and Obesity

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CONTENTS

18.1 INTRODUCTION

The discourse about whether "insulin resistance leads to obesity" or "obesity leads to insulin resistance" has been a long-lasting debate. There is now convincing evidence that in most cases, obesity itself deteriorates insulin sensitivity in proportion to the degree and the duration of the obesity. The location of the excess fat in obese individuals is an important determinant of the magnitude of insulin resistance. In this chapter, we review (1) the evidence that lead researchers to conclude that obesity is a condition leading to insulin resistance and eventually to type 2 diabetes mellitus (T2DM); (2) the methods used to measure insulin sensitivity in the clinic; (3) the physiological mechanisms by which an expanded fat mass leads to insulin resistance; and (4) the molecular mechanisms underlying impaired insulin signaling.

18.2 OBESITY LEADS TO INSULIN RESISTANCE

As early as the 1930s, Sir Harold Percival Himsworth and colleagues described the existence of a type of diabetes caused not by a lack of insulin but rather insensitivity to insulin. By performing two oral glucose tolerance tests (OGTTs) in the same individuals, one with, and one without a concomitant injection of insulin, Himsworth observed that subjects with insulin insensitivity were unable to lower their glucose levels after insulin injection, compared to insulin-sensitive subjects. He noted that this type of diabetes was more common, but not confined to elderly subjects and may be preceded by obesity.[1] Himsworth also found that weight loss not only removed the symptoms of diabetes but also restored the glucose-tolerance response to almost normal.[2] The condition Himsworth described is now known as insulin resistance, defined as an impaired ability of insulin to suppress hepatic glucose output and to promote peripheral glucose disposal into tissues.

Insulin resistance is tightly associated with obesity and is a pivotal factor in the pathogenesis of type 2 diabetes mellitus (T2DM). Cross-sectional studies consistently show the presence of insulin resistance in patients with T2DM and prospective studies have shown that insulin resistance is an important risk factor for whether or not an individual will become diabetic later in life. However, it is clear that insulin

resistance per se is not the only factor that predicts diabetes. Insulin resistance is generally compensated by hyperinsulinemia, which is due to a combination of increased insulin secretion and reduced insulin clearance. The degree of compensation is assessed by the "disposition index," the product of insulin sensitivity, and insulin secretion from beta cells, a measure of the ability of beta cells to compensate for insulin resistance with hyperinsulinemia.[3] The disposition index is the strongest predictor of T2DM, implicating the beta cells as well as insulin resistance per se in the pathogenesis of T2DM.[4,5]

One of the earliest longitudinal diabetes surveys was the Oxford Epidemiologic Study, which commenced in 1946.[6] At follow-up 17 years later, diabetes was 5 times more prevalent in subjects with initial postprandial blood glucose between 140 and 169 mg/dL, but 15 times more prevalent in those with initial blood glucose >170 mg/dL. Interestingly, the risk of diabetes in overweight subjects was only significant when blood glucose was above 140 mg/dL, suggesting that obesity is unlikely to be causally related to T2DM.[6] Today, researchers are still trying to unravel the complex etiology linking obesity, insulin resistance, and T2DM. Here, we summarize the major milestones in the field of insulin resistance including Randle's glucose–fatty acid cycle, lipotoxicity, and inflammation. First, we describe the methods for measuring insulin resistance in the clinic.

18.3 METHODS TO MEASURE INSULIN RESISTANCE

There are a plethora of options for how to assess insulin resistance in human beings, ranging from direct methods and indirect methods to surrogate indexes.[7] Decisions on the best technique to use depend on the research question, sample size, budget, and the types of infrastructure and personnel available to perform the testing. An overview of these various methods and their associated advantages and disadvantages is presented in Table 18.1.

18.3.1 Direct Measures of Insulin Sensitivity

18.3.1.1 Hyperinsulinemic-Euglycemic Clamps

Developed by Dr. Ruben Andres and colleagues in 1979,[8] the hyperinsulinemic-euglycemic clamp is the gold standard for assessing insulin resistance in humans. After an overnight fast, insulin (5–120 mU/m^2 × min) is infused at a constant rate, resulting in a new steady-state plasma insulin level that is above the fasting insulin level (hyperinsulinemic). As such, this procedure assumes that at high doses of insulin infusion (>80 mU/m^2 × min), the hyperinsulinemic state is sufficient to completely suppress hepatic glucose production and the infused glucose is disposed into the different organs and tissue with the majority being taken up by skeletal muscle. At the same time as insulin is infused, plasma glucose is analyzed to monitor glucose concentrations every 5 minutes while 20% dextrose is given intravenously at a variable rate to "clamp" blood glucose concentrations. Depending on the insulin dose infused, after several hours, steady-state conditions can be achieved for plasma insulin and glucose concentrations. Under these conditions, the rate of glucose infused is equal to the rate of whole-body glucose disposal (glucose disposal rate [GDR]) or M (metabolizable glucose) and reflects the amount of exogenous glucose necessary to fully compensate for the hyperinsulinemia. GDR is expressed as a function of metabolic body size such as body weight (kg), body surface area (m^2), fat-free mass (FFM, in kg), or, perhaps even better, "metabolic body mass" calculated as (kg FFM + 17.7).[9]

18.3.1.2 Insulin Suppression Test

Introduced by Dr. Gerald Reaven's group in 1970,[10] the insulin suppression test (IST) is another method that directly measures insulin resistance. After an overnight fast, somatostatin (250 μg/h) is intravenously infused to suppress endogenous secretion of insulin and glucagon. Concomitantly, insulin (25 mU/m^2 × min) and glucose (240 mg/m^2 × min) are intravenously infused for 3 hours. Blood samples for glucose and insulin are drawn every 30 minutes for 2.5 hours and then at 10-minute intervals from 150 to 180 minutes ("steady state"). It is assumed that the plasma insulin concentration achieved is similar between subjects. Therefore, the IST provides a direct measure of the ability of exogenous insulin to mediate disposal of an intravenous glucose load under steady-state conditions when endogenous insulin secretion is suppressed. The main outcome measure from the IST is the steady-state plasma glucose concentration.

18.3.2 Indirect Measures of Insulin Resistance

18.3.2.1 Minimal Model Analysis of Frequently Sampled Intravenous Glucose Tolerance Test

Developed by Dr. Richard Bergman in 1979, the minimal model provides an indirect measurement of insulin resistance based on glucose and insulin concentrations collected during a frequently sampled intravenous glucose tolerance test. After an overnight fast, an intravenous bolus of glucose is infused over 2 minutes. Twenty minutes after the start of glucose infusion, a 5-minute insulin infusion is commenced. Blood samples for measuring glucose and insulin concentrations are taken every 1–2 minutes until 30 minutes, followed by every 10 minutes until 180 minutes although the sampling frequency can vary. These data are then entered into the computer program MINMOD to generate an index of insulin sensitivity (Si). The two main equations used for calculating Si describes glucose dynamics, which occurs in a "single compartment," and insulin dynamics, which occurs in a "remote compartment." It is assumed that glucose enters and leaves its space at a rate proportional to the difference between plasma glucose levels and basal fasting levels.

18.3.2.2 Oral Glucose Tolerance Test/Meal Tolerance Test

The OGTT is easy to perform and widely used in clinical practice to diagnose glucose intolerance, prediabetes, and type 2 diabetes (T2DM). After an overnight fast, blood

TABLE 18.1
Direct and Indirect Approaches for Measuring Insulin Sensitivity in the Clinic

Method for Measuring Insulin Sensitivity	Outcome Measure	Advantages	Limitations
		Direct Assessment	
Hyperinsulinemic-euglycemic clamp	Glucose disposal rate (GDR) expressed as a function of metabolic body size (body weight, body surface area [BSA], or fat-free mass), i.e., GDR/weight, GDR/BSA, GDR/fat-free mass	• Gold standard technique for assessing insulin sensitivity in humans; directly measures whole-body glucose disposal at a given level of insulinemia under steady-state conditions • Coupled with the use of radiolabelled glucose tracers, it is possible to quantify hepatic glucose production and therefore hepatic as well as peripheral insulin sensitivity	• The clamp technique is time-consuming, labor-intensive, expensive, and requires an experienced research team to perform • The clamp uses insulin concentrations that are supraphysiological and thus may not accurately reflect physiological insulin action and glucose dynamics
Insulin suppression test (IST)	Steady-state plasma glucose concentration	• Direct measure of the ability of exogenous insulin to mediate disposal of an intravenous glucose load under conditions where endogenous insulin secretion is suppressed	• Unlike the clamp, the IST always uses the same infusion rate and therefore may not be appropriate for all populations • It is almost as labor-intensive and expensive to perform as the clamp
		Indirect Assessment	
Minimal model (FSIVGTT)	• Si (insulin sensitivity index) calculates the glucose disappearance rate per unit of insulin • Other parameters include Sg (ability of glucose to promote its own disposal and inhibit hepatic glucose production in the absence of an incremental insulin effect), ki (fractional metabolic clearance of insulin), and DI (disposition index, reflecting insulin sensitivity normalized to the degree of insulin resistance)	• Less labor-intensive than the clamp and therefore can be more easily applied in large-scale population studies • Information on insulin sensitivity, glucose effectiveness, and β-cell function can be determined from a single dynamic test	• The FSIVGTT is still time-consuming as it requires 3 hours of intravenous infusion and blood sampling • The minimal model is based on the assumption that glucose dynamics occurs in a single compartment and may overestimate Sg and consequently underestimate Si
Oral glucose tolerance test (OGTT)	Blood glucose and insulin levels 2 hours after a standardized glucose load/meal	• Easy to perform • Widely used in clinical practice to diagnose glucose intolerance and type 2 diabetes	• The OGTT measures how efficiently the body disposes of a glucose load and does not provide a measure of insulin sensitivity per se

samples for measuring glucose and insulin are drawn at 0, 30, 60, and 120 minutes after an oral glucose load (usually 75 g) or a standardized meal. Thus, an OGTT/meal tolerance test measures how efficiently the body disposes of a glucose load or "glucose tolerance" and does not provide a measure of insulin sensitivity per se.

18.3.3 Surrogate Indices for Insulin Resistance

There are a variety of simple surrogate indexes for determining insulin resistance, which can be divided into indices derived from fasting measures (fasting insulin, homeostatic model assessment, and quantitative insulin sensitivity check index) and those derived from dynamic tests (Matsuda index, Stumvoll index, Gutt index, etc.). The advantages and disadvantages of these indices have been previously reviewed.[11]

18.4 PHYSIOLOGICAL MECHANISMS OF INSULIN RESISTANCE

18.4.1 Glucose-Fatty Acid Cycle (Randle's Cycle)

In 1963, Sir Philip Randle and colleagues proposed a glucose-fatty acid cycle whereby the relationship between glucose and fatty acid metabolism was reciprocal and independent of hormonal regulation.[12] In isolated rat heart and hemidiaphragm preparations, they demonstrated that under conditions of insulin stimulation, addition of fatty acids to

the perfusion medium led to inhibition of several glycolytic steps, namely, glucose transport and phosphorylation as well as inhibition of 6 phosphofructo-1 kinase (PFK1) and 6-phosphoglucose dehydrogenase. The resulting accumulation of intracellular citrate in turn inhibits PFK1. Inhibition of PFK leads to the accumulation of glucose-6 phosphate, which in turn inhibits hexokinase (Figure 18.1). The reciprocal aspect, whereby high glucose and insulin concentrations can suppress fatty acid oxidation, was later reported by McGarry and Foster in 1977.[13] Thus, the discovery of the "Randle cycle" established the biochemical basis of glucose-free fatty acid (FFA) competition and postulated that enhanced oxidation of fatty acid substrates may be the origin of insulin insensitivity syndromes such as diabetes and obesity.[12] In vivo studies in healthy humans confirmed that experimentally raising plasma FFA concentration by either lipid infusion[14,15] or administration of norepinephrine[16] or heparin plus a high-fat meal[17] reduced glucose tolerance and leads to insulin resistance resembling that found in many obese individuals. Furthermore, glucose tolerance was improved when the rise in plasma FFAs was prevented[16] lending support to Randle's hypothesis. However, not all studies in humans have supported Randle's theory.[18–20]

In the 1990s, a series of papers were published suggesting the inverse of the so-called glucose-fatty acid cycle,[18] that is, that accelerated carbohydrate oxidation directly inhibited fatty acid oxidation. Wolfe proposed that glucose metabolism is regulated primarily by changes in glucose concentration, whereas fat metabolism is regulated primarily by changes in the rate of glucose oxidation.[21] To examine this, the hyperinsulinemic-euglycemic clamp combined with indirect calorimetry and stable isotopes (1-^{13}C-fatty acid) was coupled with lipid and heparin infusion (to keep FFA levels constant) in healthy subjects. Under these conditions, glucose oxidation increased during the clamp and plasma fatty acid oxidation decreased suggesting that contrary to the prediction of the glucose-fatty acid cycle, the intracellular availability of glucose, specifically glucose-6-phosphate, determines the nature of substrate oxidation.[18]

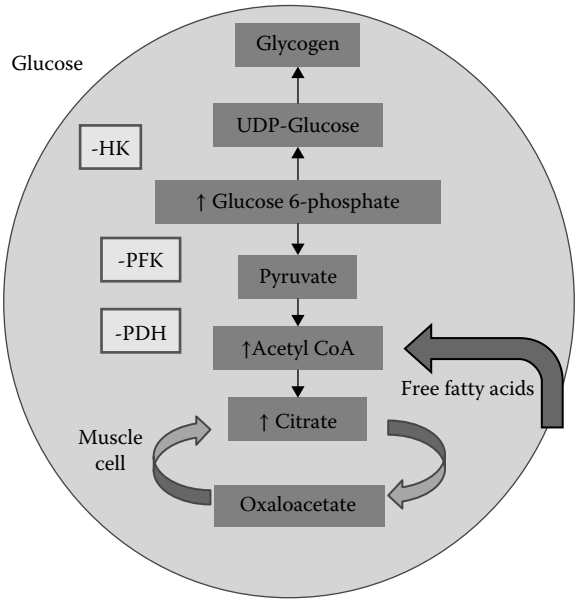

FIGURE 18.1 The Randle cycle. Free fatty acid (FFA) oxidation results in an inhibition of pyruvate dehydrogenase. Citrate inhibits phosphofructokinase and a rise in glucose 6-phosphate inhibits hexokinase. Collectively, these processes reduce glucose uptake and utilization. -HK, hexokinase; -PDH, 6-phosphoglucose dehydrogenase; -PFK, phosphofructo-1 kinase; UDP, uridine diphosphate. (Adapted from Randle PJ et al., *Lancet*, 1, 785–9, 1963.)

18.4.2 Lipotoxicity

In the mid-1990s, there was a shift in the understanding of insulin resistance from a glucocentric to a more lipocentric view. As a result, the concept of lipotoxicity, that is, the accumulation of fat (fatty acids, triacylglycerol, diacylglycerol [DAG], and ceramides) in nonadipose tissue depots (heart, liver, skeletal muscle, and pancreas), emerged as a potential "explanation" for insulin resistance.[22–24] It had been well described that subjects with T2DM have chronically elevated FFA levels, particularly at night.[25] The effects of elevated FFA on insulin secretion was examined in hyperinsulinemic-euglycemic clamp studies in healthy normal glucose-tolerant subjects with and without a family history of T2DM before and after 4 days of continuous lipid infusion. FFA levels were elevated to levels comparable to patients with T2DM, resulting in enhanced insulin secretion rates in subjects with no family history of diabetes. In contrast, subjects with a positive family history of T2DM had 25% and 42% lower (compared to control subjects) first- and second-phase insulin secretion.[26] These results suggest that in subjects with high risk for T2DM, pancreatic beta-cell lipotoxicity may play a role in the transition from normal glucose tolerance to overt hyperglycemia. Indeed, in vitro studies also demonstrate that chronic FFA exposure of pancreatic beta cells causes toxicity by several mechanisms including accumulation of malonyl-coenzyme A (CoA) and long-chain fatty acyl-CoA, increased fatty acid oxidation and esterification, accelerated ceramide synthesis, fatty acid–induced apoptosis, and activation of endoplasmic reticulum (ER) stress.[27] Recent imaging studies have confirmed increased lipid in insulin-resistant individuals, supporting the hypothesis that lipotoxicity impairs the beta cells.

Elevated FFA production also contributes to insulin resistance in peripheral tissues including the skeletal muscle and liver with parallel accumulations of intramyocellular lipid (IMCL) and intrahepatic lipid. Using noninvasive ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) to detect differences between extracellular lipid and IMCL, studies have shown that IMCL is more tightly correlated to insulin resistance than any of the other commonly measured indexes of obesity including BMI, waist-to-hip ratio, or total body fat.[23,28,29] Similar findings have been reported for skeletal muscle triglyceride content.[30] Moreover, these increases in

IMCL content can be induced by experimentally increasing FFA levels. Five-hour hyperinsulinemic-euglycemic clamps were performed in healthy male subjects with and without concomitant intralipid and heparin infusion with IMCL measured using ^{1}H-MRS at baseline and every hour. A rapid elevation of the IMCL pool was seen in both the tibialis anterior (61%) and soleus muscle (22%) only with lipid infusion.[31] Using the same experimental approach albeit with a 3.5-h clamp, Roden et al. reported decreased GDR after 3.5 hours of lipid infusion; oxidative glucose disposal and muscle glycogen synthesis (measured using ^{13}C-MRS) were reduced by 40%–50%.[32] Importantly, these changes were associated with a decrease rather than an increase in the muscle glucose-6-phosphate concentration suggesting that FFA may inhibit glucose transport and/or phosphorylation rather than go through Randle's cycle of excessive fat oxidation. It is likely that the accumulation of FFAs results more from a defect in FFA oxidation rather than an increased accumulation. This impairment in fatty acid oxidation might result from a decrease in mitochondrial oxidative capacity resulting in the accumulation of metabolites such as acyl-CoA, which alters the insulin-signaling pathway.[23] This accumulation in intramuscular long chain fatty acyl-CoAs (palmitoyl CoA, stearate CoA, and linoleate CoA) is markedly decreased following gastric bypass surgery.[33] Another hypothesis that has been proposed is incomplete β-oxidation leading to an accumulation in acylcarnitines.[34]

Collectively, these findings of lipotoxicity in nonadipose tissues are attributed to an impairment in the storage function of adipose tissue characterizing subjects with obesity and T2DM.[35,36] Adipose tissue plays a crucial role in buffering the flux of FFA in the postprandial period by insulin-stimulated suppression of lipolysis, upregulation of lipoprotein lipase, and clearance of circulating triacylglycerol and suppression of endogenous triacylglycerol; these mechanisms are impaired in obesity and insulin resistance. For instance, lipoprotein lipase activity measured in adipose tissue biopsies is increased 124% in lean subjects after a meal, but only 27% in obese subjects.[37] In addition, higher FFA plasma levels coupled with larger adipocyte size, a measure of adipocyte storage capacity, predict the development of T2DM 4 years later, independent of sex, percentage body fat, waist-to-thigh ratio, insulin-mediated glucose uptake, and fasting triglyceride levels.[38]

Perhaps, the most compelling evidence for the importance of adipose tissue in the etiology of insulin resistance is seen in patients with lipodystrophy, a family of rare disorders characterized by total or partial absence of subcutaneous and visceral fat.[39] Patients with lipodystrophy are characterized by hypertriglyceridemia, hepatosteatosis, and severe insulin resistance often accompanied by diabetes, which are reversed following chronic leptin treatment. Leptin treatment in both human and mouse lipodystrophy dramatically decreases the amount of ectopic fat deposition and improves insulin sensitivity.[39–41] In addition, thiazolidiones, drugs that act as insulin sensitizers by stimulating peroxisome proliferator–activated receptor gamma in pre-adipocytes and adipocytes, result in increased adipocyte size and adipocyte differentiation to make new small fat cells for lipid storage. In parallel to its effect on fat mass, thiazolidiones result in improved insulin sensitivity with reduction in both fasting and postprandial glucose and insulin levels.[42]

18.4.3 Inflammation

In the late 1970s, it was observed that infectious states, such as sepsis, were characterized by insulin resistance.[43,44] It is now recognized that many diseases in which chronic inflammation occurs, such as hepatitis C, HIV, rheumatoid arthritis, and psoriasis, are also associated with insulin resistance. In 1993, Hotamisligil and colleagues were the first to demonstrate that adipose tissue from rodent models of obesity expressed high concentrations of tumor necrosis factor-α (TNF-α), a classical proinflammatory cytokine. TNF-α levels were also activated locally in the adipose tissue depots and systemically.[45] Furthermore, neutralization of TNF in obese *fa/fa* rats caused a significant increase in the peripheral uptake of glucose in response to insulin.[45] Since then, over 100 factors have been identified to be produced and released by adipose tissue into the circulation. These include classical cytokines (TNF-α, interleukin [IL]-6, and IL-8), chemokines (macrophage chemoattractant protein 1), growth factors (transforming growth factor β), and proteins involved in vascular homeostasis, lipid metabolism, and glucose homeostasis. There are now several lines of evidence supporting the view that obesity is a state of chronic low-grade inflammation: (1) moderate increases in inflammatory biomarkers in the circulation of obese adults,[46,47] (2) increased inflammation gene expression in adipose tissue of obese individuals,[48] and (3) accumulation and infiltration of immune cells such as macrophages and T cells, infiltrating adipose tissue, particularly visceral adipose tissue, in obese individuals[48–50] (Figure 18.2). Moreover, weight loss reverses these changes in inflammation.[48]

Studies designed to investigate molecular factors upstream of inflammatory cytokines identified the kinases c-jun N-terminal kinase (JNK), inhibitor of kappa B kinase (IKK), and protein kinase R as major intracellular contributors to the induction of inflammation in metabolic tissues.[51] These kinases, as well other kinases such as S6 kinase, protein kinase Cθ, extracellular signal-regulated protein kinase, and mammalian target of rapamycin, are increased in adipose tissue from obese subjects compared to lean subjects and can all target insulin receptor substrate 1 (IRS1) and therefore inhibit insulin signaling.[51] In addition, the immune sensor, the inflammasome,[52] and Toll-like receptors of the innate immune system are also elevated in adipose tissue in obese subjects compared to controls.[53] In summary, there are multiple pathways activated in the cell upon nutrient excess, which lead to inflammation and impaired signaling, and these pathways are currently areas of intense investigation.

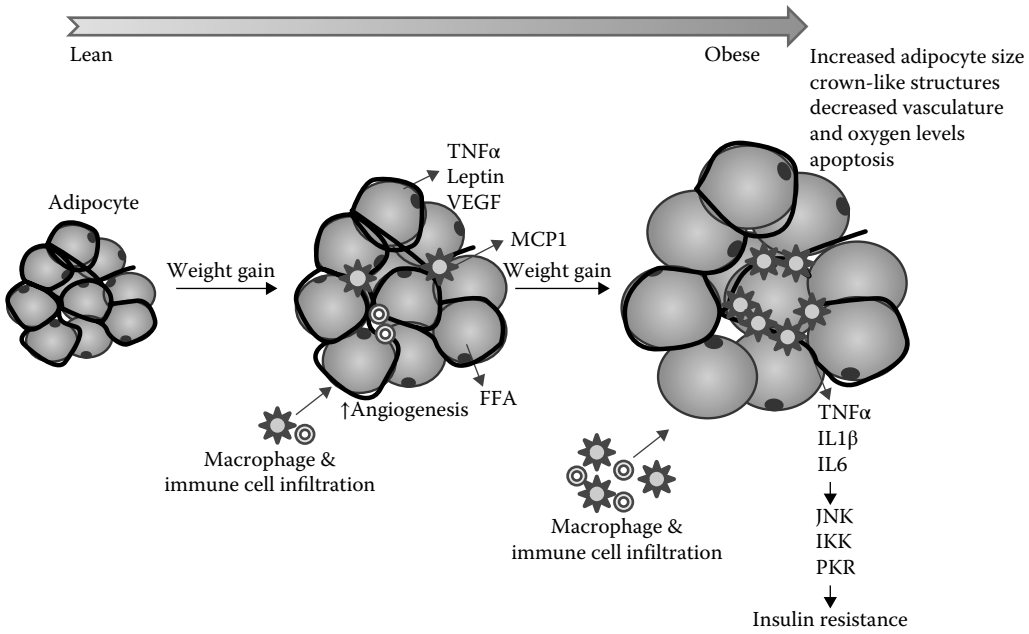

FIGURE 18.2 (**See color insert.**) Inflammatory mechanisms of obesity and insulin resistance. In the lean state, adipose tissue is characterized by relatively small fat cells and a healthy vasculature and extracellular matrix. As weight gain develops, adipocytes expand, secreting leptin and low levels of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). This promotes macrophages and other immune cells (neutrophils, T cells, and mast cells) to infiltrate the adipose tissue, which also secretes proinflammatory cytokines. With obesity, there is a chronic, low-grade state of systemic inflammation and immune cell accumulation. Macrophages surround adipocytes, forming crown-like structures, in an attempt to scavenge the lipid from the dying adipocytes. At the same time, there may be a disconnect between expansion of the fat cell and vasculature, leading to decreased oxygen levels in adipose tissue, which can further promote proinflammatory cytokine secretion. Molecular factors upstream of inflammatory cytokines, including c-jun N-terminal kinase (JNK), inhibitor of kappa B kinase (IKK), and protein kinase R (PKR), are major intracellular contributors to the induction of inflammation in metabolic diseases. MCP1, monocyte chemoattractant protein 1. (Adapted from Wellen KE et al., *J Clin Invest*, 115, 1111–9, 2005.)

18.5 MOLECULAR MECHANISMS OF INSULIN RESISTANCE DUE TO DEFECTS IN INSULIN SIGNALING

It was originally believed that reduced insulin sensitivity was due to diminished insulin receptor number or low affinity for its agonist.[54] However, it is now accepted that insulin resistance is caused by defects at one or several levels of the insulin-signaling cascade in insulin responsive tissues including liver, skeletal muscle, and/or adipose tissue.[55] Insulin signaling is complex, involving multiple levels including insulin receptor expression, binding, phosphorylation state, and kinase activity.[56]

Insulin exerts diverse biological effects by binding to its specific receptor.[57,58] The insulin receptor is a heterotetrameric protein, with two extracellular α subunits and two transmembrane β subunits connected by disulfide bridges.[59,60] Insulin binding to the extracellular α subunit activates the tyrosine kinase domain by autophosphorylation of the intracellular portion of the β subunit,[61,62] where phosphorylation of several tyrosine residues is required for kinase activity.[63] Insulin receptor tyrosine kinase activity then catalyzes phosphorylation of several proteins: IRSs, and several Src-homology/collagen proteins[64,65] which then sequentially activate several signaling intermediates. The clarification of the intracellular steps of insulin signaling has led to intensive investigation to understand the molecular mechanisms of insulin resistance through animal and clinical studies.

18.5.1 Reduced Insulin-Stimulated Tyrosine Kinase Activity

The intrinsic tyrosine kinase activity of the insulin receptor is indispensable for insulin action. Insulin action is initiated by binding to its receptor and phosphorylation of tyrosine residues located in the cytoplasm, which activates the receptor's intrinsic protein tyrosine kinase activity.[66] Mutations in human beings causing partial kinase inhibition are associated with severe insulin resistance.[67]

The insulin receptor is a tetrameric protein with two extracellular α subunits and two transmembrane β subunits.[58] The binding of insulin to the α subunit of the insulin receptor causes conformational changes in the receptor leading to the activation of the tyrosine kinase β subunit. The activated insulin receptors have the ability to autophosphorylate as well as phosphorylate intracellular substrates that are essential for initiating other cellular responses of insulin[64,68,69] through the activation of downstream signaling molecules that participate in the insulin-signaling pathway. Insulin signaling, including activation of insulin receptor tyrosine kinase activity, is impaired in most patients with diabetes mellitus. Thus, resistance to insulin contributes to hyperglycemia and other metabolic impairments.[70] Mutagenesis studies demonstrated that the insulin receptor tyrosine kinase activity is absolutely required for

the biological effects of insulin.[68] One study in 1987 demonstrated that the ^{125}I-insulin binding to the receptor was impaired in both obese and obese T2DM patients; this was associated with decreased insulin receptor tyrosine kinase activity; however, insulin-stimulated autophosphorylation remained the same between control subjects and obese patients with and without T2DM.[71] Similarly, a reduction in ^{125}I-insulin binding was observed in adipose tissue from subjects with T2DM and insulin resistance as well as a decrease of insulin-stimulated insulin receptor kinase activity in patients with T2DM.[72]

18.5.2 Reduced Activation of Tyrosine Phosphorylation of the Insulin Receptor

The tyrosine kinase domain of the human insulin receptor has provided unique understanding of the regulation of the insulin receptor enzyme activity and mechanism of autophosphorylation.[73] The β chain (306 amino acids), which contains the three tyrosine sites for autophosphorylation and activation, is essential for receptor kinase activity toward exogenous substrates.[74] In the 1980s, a study in rat models of insulin resistance and streptozotocin-induced diabetes demonstrated that diminished autophosphorylation of the insulin receptor and kinase activity in the muscle can explain "post-binding insulin resistance" in diabetic rats.[75] In addition, it has been demonstrated in rats that impairments in insulin receptor tyrosine phosphorylation capacity are an early response to a diet high in fat and refined sugar, appearing before other abnormalities of the insulin-signaling pathway and before any measurable increase in adiposity.[76]

With euglycemic clamps, Nolan et al.[77] demonstrated that obese patients with and without T2DM had a modest impairment of autophosphorylation of the insulin receptor when compared to lean control subjects. In several studies, tyrosine phosphorylation has been studied and the majority of cases demonstrated slight or no change in activation of the insulin receptor.[78,79]

18.5.3 Reduced Postreceptor Phosphorylation (IRS, PI3-Kinase, Akt, PKC)

18.5.3.1 IRS

The insulin receptor tyrosine kinase phosphorylates the IRS proteins. It has been demonstrated that the IRS family contains several tyrosine phosphorylation sites and about 50 serine/threonine phosphorylation sites.[80] The tyrosine phosphorylation sites Tyr^{608} and Tyr^{628} have been shown to positively regulate IRS function, whereas Ser/Thr phosphorylation sites Ser^{307}, Ser^{612}, and Ser^{632} have been shown to negatively regulate IRS function by increasing release of IRS from its internal membrane pools and promoting proteosomal degradation. Therefore, generally, tyrosine phosphorylation activates IRS, and serine phosphorylation deactivates IRS. But it is also possible that Ser/Thr phosphorylation of IRS Ser^{789} positively regulates IRS function.[81] Metabolic actions of insulin in liver, adipose tissue, and skeletal muscle depend on tyrosine phosphorylation of the IRS family. In skeletal muscle and adipose tissue, IRS1 proteins are associated with glucose uptake and increased IRS1 degradation in adipocytes, with subsequent impairment of insulin-dependent glucose transporter (GLUT4) mobilization playing a role in reduced glucose uptake in insulin-resistant rats.[82] In contrast, stimulated IRS1 by regular exercise in humans enhances insulin-mediated glucose uptake.[83] On the contrary, in the liver, IRS2 is indispensable for suppression of endogenous glucose production, and in the pancreas, it is essential for beta-cell proliferation.[84,85] In addition, it has been reported that IRS3 plays a role in adipose tissue.[84] Reduction of tyrosine phosphorylation of IRS1 and phosphatidylinositol 3 kinase (PI3-kinase) activation is related to a decrease in muscle glucose uptake in insulin-resistant animals as well as in T2DM patients.[86] Additionally, low levels of IRS1 protein and IRS1 tyrosine phosphorylation have been shown in 30% of first-degree relatives of T2DM and obese patients[86,87] who are at greater risk of T2DM. Knockout mice lacking a single allele of the *IRS1* gene did not show any significant phenotype, while homozygous disruption of the *IRS1* gene showed mild insulin resistance.[88] In addition, *IRS1* homozygous null mice (*IRS1*$^{-/-}$) do not demonstrate a diabetic phenotype, because of pancreatic beta-cell compensation. However, *IRS2*$^{-/-}$ mice developed severe insulin resistance with beta-cell failure.[84,89]

18.5.3.2 PI3-Kinase

Tyrosine-phosphorylated and activated IRS binds to the Src homology 2 domain–containing adaptor protein p85, a regulatory subunit of PI3-kinase, resulting in activation of the catalytic p110 subunit of PI3-kinase. The activation of PI3-kinase generates 3′-phosphoinositides (phosphatidyl-inositol-3,4-bisphosphate and phosphatidyl-inositol-3,4,5-trisphosphate), which bind to the phosphoinositide-dependent kinase 1 (PDK1).[90] PDK1 is phosphorylated and activated by serine kinases to phosphorylate v-akt murine thymoma viral oncogene (Akt), also known as protein kinase B. Akt activation phosphorylates and activates additional downstream substrates,[91] a cascade that finally ends in the metabolic action of insulin. PI3-kinase is a heterodimer, containing a regulatory subunit p85 associated with a catalytic subunit p110. There is a balance between the free p85 monomer and the p85-p110 heterodimer, which regulates PI3-kinase activity. These subunits compete for the same binding sites on the tyrosine-phosphorylated IRS proteins; an imbalance could induce either increased or decreased PI3-kinase activity.[92–94] IRS1-associated PI3-kinase activity is decreased in the muscle after lipid infusion, indicating that lipid-induced decreased insulin-stimulated glucose transport is due to impaired signal transduction.[95] An additional mechanism of insulin resistance involves endothelial insulin signaling, which mediates insulin-stimulated capillary recruitment and increase of interstitial insulin concentrations and consequently facilitates glucose uptake by the skeletal muscle.[96] The latter mechanism is likewise inhibited in obesity and T2DM.

18.5.3.3 Akt

Akt plays an important role in the relationship between the insulin-signaling pathway and GLUT4 (Figure 18.3). In skeletal muscle and adipose tissue, Akt activates GLUT4, which migrates to the cell surface to allow transport of glucose into the cell.[97–99] Mice lacking Akt2 have insulin resistance, progressing to a phenotype reminiscent of T2DM in humans.[100] In addition, a mutation in the kinase domain of Akt2 was detected in a family of severely insulin-resistant patients[101] further supporting a central role of Akt2 in insulin resistance.

18.5.3.4 PKC

FFA increase results in insulin resistance. The mechanism by which FFA alters insulin signaling remains unclear. It is likely that accumulation of intracellular fatty acids or their metabolites results in an impairment of signaling through the IRS/PI3-kinase and a decrease in the recruitment of GLUT4 transporters to the cell membrane.[102]

In muscle, increases in lipid metabolites, such as fatty acyl-CoAs and/or DAG, can activate a serine/threonine kinase cascade and lead to defects in insulin signaling by altering Ser/Thr phosphorylation of IRS1. DAG has been shown to increase in muscle during both lipid infusions and fat feeding and is a known activator of phosphokinase C (PKC) isoforms.[103] PKC isoforms are categorized as classical (cPKCα, βI, βII, γ), novel (nPKC δ, ε, θ, η), or atypical (aPKC ζ, λ). There is a link between nPKCs and FFA-induced insulin resistance: lipid infusion in rats and humans activated PKCθ and PKCδ[104,105] and concomitantly impaired insulin-stimulated glucose disposal in the muscle. Infusion of lipid for 5 hours caused insulin resistance in muscle that was associated with accumulation of intracellular DAG and activation of PKCθ.[106] The reduction in tyrosine phosphorylation of IRS1 was associated with insulin resistance and lipid-induced insulin signaling.[107] However, phosphorylation of IRS1 at the serine-307 residue was increased, inhibiting IRS1 from interacting with the insulin receptor. In addition, other PKCs are involved in insulin resistance, as seen by the activation of both muscle PKCβ2 and PKCδ after lipid infusions[108] and of PKCθ in patients with T2DM.[108] PDK1 can directly phosphorylate all PKCs including nPKCs.[109] There is constitutive phosphorylation of PKCε by FFA in a PDK1-independent manner and that is related to insulin resistance.[110] Thus, FFA could cause PDK1-independent phosphorylation of PKCε, which translocates to the nucleus, causing inhibition of insulin receptor gene transcription.

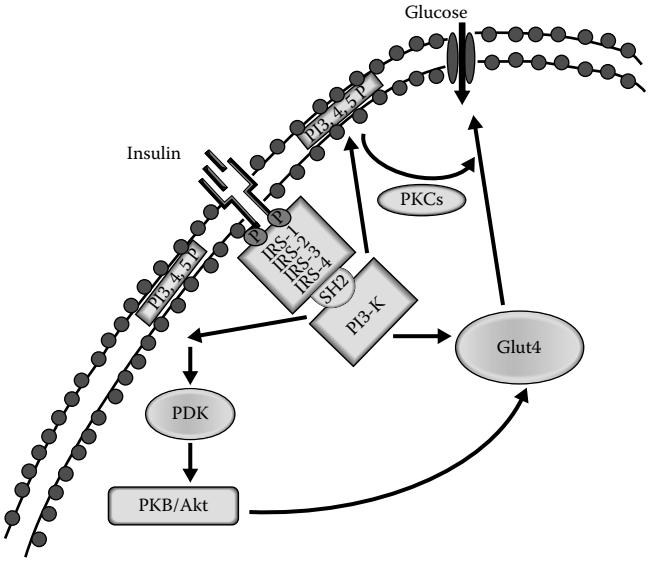

FIGURE 18.3 (**See color insert.**) Molecular mechanism of insulin-mediated glucose transport. The insulin-dependent glucose transporter (GLUT4) is translocated by a phosphatidylinositol 3 kinase (PI3-K)–dependent pathway including protein kinase B (PKB)/v-akt murine thymoma viral oncogene (Akt) and protein kinase C (PKC) stimulation downstream of PI3-K. IRS, insulin receptor substrate; PDK, phosphoinositide-dependent kinase; SH2, Src homology 2. (Adapted from Matthaei S et al., *Endocr. Rev.*, 21, 585–618, 2000.)

18.5.3.5 Insulin Receptor Inactivation

Inactivation of the insulin receptor is complex; this molecular pathway functions in hepatocytes, adipocytes, and myocytes. Phosphorylated PKC starts a downstream activation of two serine kinases, the JNK and IKK. JNK and IKK associate with IRS1, promoting its serine-phosphorylation on Ser^{312} in humans[111] and Ser^{307} in rodent models of insulin resistance (Wistar rats fed Western diets or low-salt diets).[80,112,113] The serine phosphorylation is responsible for blocking IRS1 and induction of insulin resistance by interrupting the insulin receptor/IRS interaction and increasing of IRS1 protein degradation.[111] The inactivated insulin receptor is then internalized into the cell and catabolized by lysosomes.

18.6 CONCLUSIONS

Insulin resistance plays a major role in the pathogenesis of type 2 diabetes mellitus (T2DM) and the metabolic syndrome. In this chapter, we summarized milestones in the field of insulin resistance, methods for assessing insulin resistance in the clinic, and our latest understanding of the insulin-signaling pathway. Cellular and molecular techniques that generate knockout or transgenic mice have attracted major interest in components of the insulin signaling pathway including insulin receptor tyrosine phosphorylation, IRS1, PI3-kinase, Akt, and PKCs. It is clear that our understanding of the etiology of insulin resistance is far from complete. Future studies are needed to further examine impaired insulin signaling in different tissues leading to novel therapeutic strategies for insulin resistance and T2DM. However, it is important to recognize that insulin resistance per se cannot cause T2DM; the disease is due to insulin resistance *uncompensated* by appropriate beta-cell insulin secretion. Only when beta-cell function degrades to the point at which the islets cannot compensate for insulin resistance does T2DM ensue.[114]

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19 White and Brown Adipose Tissue Development

Meghan E. McDonald and Stephen R. Farmer

CONTENTS

19.1 INTRODUCTION

The connection between obesity and the risk of developing type 2 diabetes is now well established and supports a role for adipose tissue dysfunction in obese individuals. Investigation into the development and biology of adipose tissue is a very active area of biological research and will continue to provide new insights and lead to novel strategies to combat obesity, type 2 diabetes, and other associated metabolic disorders therapeutically. Topics including white, brown, and beige/brite adipose tissue; adipogenesis and important transcriptional regulators of this process; and the developmental origins of adipocytes are reviewed in this chapter.

19.2 WHITE ADIPOSE TISSUE

White adipose tissue (WAT) is specialized for the storage of energy in the form of triglycerides, which are metabolized in times of fasting to supply fuel for other tissues. WAT is mainly composed of unilocular, lipid-laden adipocytes with their committed precursors (preadipocytes) and, to a lesser extent, mesenchymal stem cells (MSCs), endothelial cells, fibroblasts, macrophages, and T cells. In obese individuals, WAT undergoes expansion to accommodate triglyceride overload, characterized by enlarged existing adipocytes (hypertrophy) and/or an increase in the number of adipocytes (hyperplasia)[1].

Not only a site of energy storage, WAT is a major endocrine organ that secretes steroid hormones and adipose-specific proteins, termed "adipokines." Examples of adipokines include leptin, adiponectin, and resistin, which can act at paracrine, autocrine, and endocrine levels. Adipose tissue deficiency (lipodystrophy) and excess (obesity) result in adverse metabolic consequences, highlighting this tissue's important endocrine role. Obesity is associated with insulin resistance, hyperglycemia, dyslipidemia, hypertension, and proinflammatory states; mounting evidence suggests that these are likely a result of adipokine secretion dysregulation.[2]

WAT exists in several regions of the human body and can be divided into two general categories: the subcutaneous depot, located in the hypodermal region of the abdomen and buttocks and thighs; and the visceral depot, which is found in the intra-abdominal region surrounding vital organs. WAT is also observed in many other regions, including the retro-orbital space and cranial and facial regions, as well as extremities. Each depot is characterized by distinct patterns of gene expression and, consequently, distinct functions that implicate them to varying degrees in obesity.[3] The distribution of fat between these depots is associated with varying degrees of risk for poor metabolic health. In particular, enlarged visceral adipose storage, as observed in "apple-shaped" obesity, is associated with an increased risk of development of metabolic disorders and type 2 diabetes,

whereas increased subcutaneous fat storage ("pear-shaped" obesity) is not generally associated with such a risk.[4]

19.3 BROWN ADIPOSE TISSUE

Brown adipose tissue (BAT) is functionally and morphologically distinct from WAT, being composed mainly of smaller adipocytes with multilocular lipid droplets and abundant mitochondria, which contribute to the red–brown color of the tissue. Whereas the principal function of WAT is the storage of excess energy, BAT functions as a thermogenic tissue, catabolizing lipid by mitochondrial β-oxidation and dissipating energy as heat in response to cold and sympathetic innervation. These functions are possible because of the expression of uncoupling protein 1 (UCP1), a protein that is specific to BAT. UCP1 is activated by free fatty acids, and its principal function is to dissipate the proton electrochemical gradient that is generated across the mitochondrial membrane during respiration; this process effectively uncouples substrate oxidation from adenosine triphosphate production and releases energy as heat.[5]

Until recently, BAT was believed to exist only in newborn humans as an adaptation to combat cold exposure after birth, with this tissue gradually diminishing by adulthood. However, more recent analysis of existing positron emission tomography (PET)–computed tomography scans in cancer patients has identified metabolically active BAT in adult humans in the neck, cervical, supraclavicular, and paravertebral regions.[6–9] These studies have concluded that BAT levels and/or activity were higher in women than men and correlated with young age, cold environment, and positive metabolic resting rate; BAT was negatively correlated with smoking, use of β-blockers, and percentage of body fat. The discovery that BAT persists into adulthood suggests that this depot may have a significant role in energy balance, and this has spurred a renewed interest in understanding BAT's development and overall physiological importance. Because of BAT's unique function in the balance of energy, enhancing BAT mass and/or activity is an attractive therapeutic approach for individuals suffering from obesity and type 2 diabetes.

19.4 BRITE/BEIGE ADIPOCYTES AND THE BROWNING OF WHITE ADIPOSE TISSUE

An additional population of brown-like *Ucp1*$^+$ adipocytes develops within the WAT of mice in response to stimuli such as cold exposure,[10,11] with β3-adrenergic receptor agonist treatment[12] or with peroxisome proliferator-activated receptor γ (PPARγ) agonist administration.[13,14] These brown-like adipocytes have been designated "brite" (brown in white) or "beige" adipocytes. Recent studies have also described the development of brown adipocytes within WAT in response to the release of secreted molecules from distant sites: exogenous delivery of the fibroblast growth factor (FGF) 21 acts on both white subcutaneous adipose tissue and BAT to increase UCP1 expression and the abundance of multilocular adipocytes[15]; the recently identified hormone irisin is secreted from muscle in response to exercise and stimulates the thermogenic program in white adipocytes, resulting in increased energy expenditure.[16] Additionally, cardiac natriuretic peptides induce a thermogenic program in both mouse and human white adipocytes.[17]

19.5 ADIPOGENESIS

Investigations into the mechanisms regulating adipose tissue formation have elucidated several key processes and components of the adipogenic program. The process of adipogenesis has largely been revealed using 3T3-L1 preadipocytes, whereby growth-arrested, postconfluent cells are induced to differentiate using a differentiation cocktail composed of fetal bovine serum, dexamethasone, isobutylmethylxanthine, and insulin. Preadipocytes then undergo one of two well-defined phases: clonal expansion, in which the cells reenter the cell cycle and undergo at least two cell-cycle divisions, and terminal differentiation, which commences as the dividing cells enter quiescence.

Studies over the past two decades have identified a cascade of nuclear transcription factors that regulate adipogenesis in both white and brown adipocytes.[18] Among the most prominent factors regulating adipogenesis are PPARγ and CCAAT/enhancer-binding protein α (C/EBPα). PPARγ is the crucial "master regulator" of adipogenesis, essential for both white and brown adipocyte formation. Identified PPARγ target genes number in the hundreds and include genes that are important for lipid and glucose metabolism, mitochondrial biogenesis, and adipokine secretion, processes that are common to white and brown adipocytes. Among the earliest factors induced are two members of the C/EBP family of transcription factors, C/EBPβ and C/EBPδ, which are expressed prior to C/EBPα induction and are responsible for regulating its expression.[19] C/EBPδ expression is elevated by glucocorticoids and by the activity of C/EBPβ. Evidence suggests that C/EBPβ expression is initiated by the cAMP-responsive element–binding protein[20]; this also explains the necessary inclusion of cAMP-inducing phosphodiesterase inhibitors, such as isobutylmethylxanthine, in adipogenic cocktails. Ectopic expression of C/EBPβ in non-adipogenic NIH 3T3 fibroblasts, alone or in combination with C/EBPδ, activates the expression of PPARγ2 and facilitates robust adipocyte differentiation.[21,22]

C/EBPα acts to potentiate the activity of PPARγ by maintaining PPARγ expression in the mature adipocyte.[23] C/EBPα, although not needed for the initiation of adipogenesis, appears to have a critical role in terminal differentiation of adipocytes, as C/EBPα-deficient cell culture models are insulin resistant, and *Cebpa* knockout mice are unable to develop WAT.[23–25] Although essential for the formation of white adipocytes, C/EBPα is not required for the development of BAT, indicating that other factors in the brown adipocyte maintain PPARγ activity.

19.6 PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR γ

PPARγ belongs to the PPAR family of ligand-activated nuclear hormone receptors, which also includes PPARα and PPARδ. Common to the PPAR transcription factor family is a highly

conserved DNA-binding domain; however, the C-terminal ligand-binding domain is divergent among members of the group. PPARs also exhibit distinct tissue distributions—PPARα and PPARγ are predominantly expressed in liver and adipose tissue, whereas PPARδ expression is detected ubiquitously, with low levels in liver.[26] Ligand binding to the C-terminal ligand-binding domain results in the heterodimerization of PPARs with the retinoid X receptor and binding to specific DNA sequences, PPAR responsive elements, within target gene promoters. Members of the PPAR family vary in their affinity for PPAR responsive elements as well as their individual ligands, coactivators, and corepressors.[27,28] Consistent with this variability, PPARs have distinct biological functions.

PPARγ is a unique member of this family in that it has been established as the master regulator of adipogenesis. PPARγ exists as two different isoforms: PPARγ1 and the nearly identical PPARγ2, which has an additional 30 amino acids at its N terminus.[29] Expression of PPARγ1 is observed in several tissues; however, PPARγ2 is exclusive to adipose tissues.[30] Gain-of-function studies, in which the PPARγ2 isoform was ectopically expressed in mouse fibroblasts with little adipogenic potential, have demonstrated that PPARγ alone is sufficient to initiate a full differentiation program.[31] Consistent with these observations, *Pparg*-deficient precursor cells are unable to undergo adipogenesis.[32] PPARγ is therefore both necessary and sufficient to direct a full adipogenic program.

Pparg-null mice are nonviable because of placental defects; however, heterozygous mice are protected from insulin resistance and high fat diet–induced obesity.[33] Mice with adipose tissue–selective knockout of *Pparg2* demonstrate impaired adipose tissue development and insulin sensitivity, but they are protected from insulin resistance and high fat diet–induced obesity.[34] These observations strongly imply that PPARγ2 is the key regulator of adipose tissue development and adipocyte differentiation and that PPARγ1 can compensate for some, but not all, of the functions of PPARγ2.[35]

In the adipocyte, the principal role of PPARγ is to direct multiple gene expression programs to facilitate adipogenesis. This process requires the interaction of PPARγ with transcriptional cofactors, which include both coactivators and corepressors.[18] Activation of PPARγ target genes requires its interaction with an endogenous ligand or agonist, leading to the disassociation of promoter-resident corepressors, a group that includes the nuclear receptor corepressor, silencing mediator for retinoid and thyroid hormone receptors (also known as nuclear receptor corepressor 2), and histone deacetylase 3. This process facilitates the recruitment of transcriptional coactivators and chromatin-remodeling histone acetyltransferases and leads to the initiation of transcription at target gene promoters. Examples of the former are PPARγ coactivators (PGC-1α and PGC-1β), which positively regulate many transcription factors and have demonstrated roles in regulating energy balance in cooperation with PPARγ.[36]

PPARγ belongs to the nuclear hormone family of receptors and, by definition, requires endogenous ligand binding to be fully activated and initiate adipocyte differentiation. The few natural ligands that have been identified include the polyunsaturated fatty acids oleate and linoleate and a rare prostanoid, 15-deoxy-$\Delta^{12,14}$ prostaglandin J_2, which can bind and activate PPARγ in the micromolar range.[37] Several PPARγ synthetic ligands have been produced, with the best described being the thiazolidinedione (TZD) class of insulin sensitizers, used in the treatment of diabetes. These drugs, which include pioglitazone, troglitazone, and rosiglitazone, are potent PPARγ agonists, acting in the nanomolar range. Although TZDs are recognized as effective insulin sensitizers, in recent years TZD treatment has been associated with several adverse effects, including weight gain, edema, and heart failure.[38]

TZD treatment in cultured cells or in mice results in a selective induction of BAT-selective genes, including *Ucp1*, and the simultaneous repression of white adipokine production.[13,14,39,40] This "browning" of WAT depots is likely indicative of either induction of these BAT-selective genes within white adipocytes or recruitment of brown adipocytes to WAT depots. Activation of PPARγ by TZDs, then, specifically enhances some unknown BAT-specific functions of PPARγ in WAT, possibly via mechanisms regulating PR domain zinc finger protein 16 (PRDM16) activity.[41,42]

Growing evidence documenting the adverse effects associated with TZD treatment has prompted the search for novel insulin-sensitizing drugs. Most recently, PPARγ non-agonists have received some attention for their antidiabetic properties. Interestingly, despite displaying poor PPARγ agonist activity, some PPARγ ligands, such as the benzyl indole MRL24, retain excellent antidiabetic effects.[43] This selective effect is proposed to occur via the non-agonist's ability to inhibit cyclin-dependent kinase 5-mediated phosphorylation of PPARγ at Ser273.[44] Inhibition of phosphorylation at this site leads to changes in the expression of a subset of metabolic genes, including adipsin (also known as complement factor D) and adiponectin, a phenomenon that is independent of the genes' general receptor transcriptional activity. Compounds with similar non-agonist profiles may prove to have therapeutic potential in diabetic patients and fewer adverse side effects than observed with TZD treatment.

19.7 BROWN ADIPOGENESIS

Among the earliest nuclear factors identified to be associated with the development of brown adipocytes was PGC-1α.[45] Expression of PGC-1α, now considered a global regulator of energy balance, is detected at high levels in brain, liver, skeletal muscle, and heart, as well as in BAT. Importantly, PGC-1α is more abundant in BAT relative to WAT, regulating mitochondrial biogenesis and thermogenesis by acting as a transcriptional coactivator for numerous transcription factors.[36] Although PGC-1 coactivators appear to be central to thermogenesis, they are not essential for brown adipogenesis. Knockdown of *Ppargc1a* (which encodes PGC-1α) in cultured brown adipocytes results in thermogenic deficiency,

without affecting brown adipogenesis; brown preadipocytes deficient in both PGC-1α and PGC-1β demonstrate deficits in mitochondrial biogenesis with no observable effect on adipogenesis.[46]

19.8 PRDM16: THE MASTER REGULATOR OF BROWN ADIPOCYTE DIFFERENTIATION

By definition, the master regulator of brown adipogenesis must be a nuclear factor necessary for the induction of genes associated with BAT functions: mitochondrial biogenesis, oxidative phosphorylation, and lipid oxidation. A novel zinc finger transcription factor, PRDM16, was recently proposed by Seale et al. [47] as the master regulator of brown adipocyte formation. Identified in a screen of murine transcriptional components, PRDM16 (PRD1-BF-1-RIZ1 homologous) was identified as a factor that is abundant in BAT relative to WAT, along with two additional transcription factors, LIM/homeobox protein LHX8 and zinc finger protein ZIC1. In this initial study, Seale et al. showed that PRDM16 is able to induce a program of brown gene expression and mitochondrial biogenesis in white preadipocytes; knockdown of *Prdm16* in brown preadipocytes abolishes the BAT-selective phenotype. PRDM16 appears to modulate the activity of transcription factors by recruiting coregulators to the promoters of target genes.[48] PRDM16 is able to control a WAT/BAT switch, as it interacts with PGC-1α/β to activate the expression of BAT-selective genes, including *Ucp1*; simultaneously, PRDM16 can recruit corepressors such as C-terminal-binding proteins 1 and 2 to mediate the repression of WAT-selective genes, including resistin. The mechanisms responsible for recruiting PRDM16 to respective target genes are currently not known. Additional PRMD16-interacting proteins have been discovered, and this group includes liver-enriched transcriptional activator protein, the active form of C/EBPβ. Kajimura and colleagues[49] demonstrated that PRDM16 forms a transcriptional complex with C/EBPβ that is both necessary and sufficient to induce a functional brown fat program in naive fibroblastic cells.

Most recently, transcriptome analyses have identified the novel gene placenta-specific 8 (*Plac8*), which functions as an upstream regulator of C/EBPβ and PRDM16 expression.[50] In this study, the authors demonstrated that PLAC8 is required for a transient interaction with C/EBPβ that initiates brown adipogenesis; PLAC8 subsequently interacts with the C/EBPβ promoter to promote both C/EBPβ and PRDM16 expression. In support of these findings, PLAC8 is required for the differentiation of BAT in vivo, and it promotes resistance to cold and obesity.

19.9 ADIPOSE TISSUE PLASTICITY

Several recent studies have suggested that distinct WAT depots (visceral, abdominal, and gonadal) have varying effects in regulating energy metabolism; it is conceivable that separate BAT depots, derived from distinct precursors, may also have unique functions in regulating the balance of energy. One provocative hypothesis suggests that adipose tissues are representative of a multidepot organ, the "adipose organ."[51] This theory proposes that the adipose organ exists as a "spectrum" of adipose tissues, plastic in nature, characteristically highly vascularized and innervated, with adipocytes that are able to "transdifferentiate" from white to brown adipocytes. Considering the highly variable nature of adipose tissue within the adipose organ, identification of the origins of specific adipose depots and the extracellular and intracellular factors that regulate the commitment of progenitors to various adipose depots is of great interest.

19.10 ADIPOSE TISSUE DEVELOPMENT

Notwithstanding the growing clinical significance of obesity, the development of adipose tissue in vivo is not well understood. Increased adipose tissue mass occurs as the result of an increase in adipose tissue size (hypertrophy) and an increase in adipocyte quantity (hyperplasia).[1] Mature adipocytes are postmitotic; therefore, this observed hyperplasia requires that newly formed adipocytes develop from undifferentiated precursor cells.

Several studies have demonstrated the adipogenic potential of precursor cells derived from the stromal vascular fraction of WAT, although these adipocyte-derived stem cells undergo limited differentiation in vivo.[52] Adipocyte-derived stem cells are not limited to adipocyte differentiation; observations from many groups have demonstrated that these progenitors are able to differentiate into a variety of cell types, including osteoblasts, chondrocytes, skeletal myoblasts, cardiac myoblasts, smooth muscle cells, hematopoietic and endothelial cells, neurons, epithelial cells, hepatocytes, and pancreatic islets (reviewed by Cawthorn et al.[52]). Using fluorescence-activated cell sorting analysis, Rodeheffer et al.[53] were the first group to identify a population of white adipocyte progenitor cells that have proven adipogenic potential in vivo. These precursors are also resident in adult WAT stroma and are characterized by the expression of particular cell surface markers, including Lin^{-}:$CD29^{+}$:$CD34^{+}$:$Sca1^{+}$:$CD24^{+}$ (lineage-negative:integrin β-1+:hematopoietic progenitor cell antigen $CD34^{+}$:lymphocyte antigen 6A-2/6E-1:signal transducer $CD24^{+}$). Importantly, this population of precursors is able to functionally reconstitute a normal WAT depot and reverse the diabetic phenotype in lipodystrophic mice.

Observations from several groups have suggested a close association between adipose progenitors and the adipose tissue vasculature. As previously described, adipose progenitors can be isolated from the stromal vascular fraction of adipose tissue. Growing evidence asserts that these progenitors are actually pericytes; these elongated, undifferentiated contractile cells are found wrapped around precapillary arterioles outside the basement membrane in various tissues.[54–56] Decades of microscopic studies support this hypothesis, establishing that developing adipocytes reside in a pericyte position along capillary endothelial cells (reviewed by Gupta et al.[57]).

Localization of white adipose progenitors to the mural cell (pericyte) compartment of the tissue vasculature has also arisen from lineage tracing studies using *Pparg* regulatory

elements to drive expression of the tracer.[58] Tang et al. demonstrated that PPARγ-expressing progenitors also express the pericyte markers, aortic smooth muscle actin; platelet-derived growth factor receptor β (PDGFRβ); and chondroitin sulfate proteoglycan NG2. Similarly, Cinti and collaborators have suggested a perivascular origin for brown adipose cell progenitors.[59] Thus, it seems likely that adipose tissue vasculature is the location of a progenitor niche that may contribute to growing adipocyte numbers during obesity (Figure 19.1).

Support for the vascular endothelial origin of adipocytes has recently emerged based on intriguing genetic and morphological data. The studies have independently demonstrated that adipose-derived perivascular cells have the potential to undergo adipogenesis.[54,60] Lineage tracing studies using the vascular endothelial–cadherin promoter revealed that both brown and white adipocytes originate from cells that display endothelial characteristics, which are lost in response to PPARγ activation and the initiation of adipogenesis.[59] Furthermore, pericytes and a subset of endothelial cells in adipose tissue express green fluorescent protein driven by the zinc finger protein 423 (*Zfp423*) promoter, a newly identified transcription factor that marks committed preadipocytes.[57] If vascular endothelial cells prove to be a progenitor niche capable of producing adipocytes for a growing adipose tissue mass, many more questions will need to be addressed. In particular, the processes required to allow a vascular endothelial cell to develop into a mature adipocyte are not evident. One attractive hypothesis suggests that endothelial cells, like epithelial cells, may be able to undergo a mesenchymal transition, developing into a multipotent stem-like cell with the potential to submit to a variety of cell fates. Whether adipocyte precursors represent a population of endothelial cells that have undergone an endothelial-to-mesenchymal transition to a multipotent MSC intermediate has not yet been demonstrated.

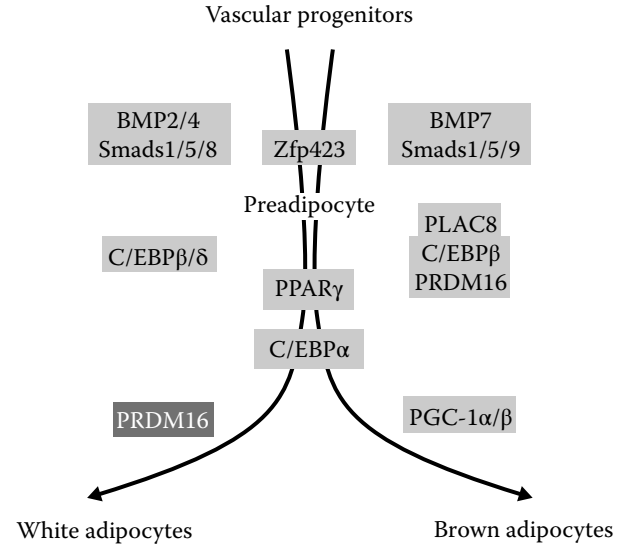

FIGURE 19.1 Transcription factors and nuclear regulators controlling the development of white versus brown adipocytes: the factors regulating commitment of progenitors to the adipogenic lineage (preadipocytes) are essentially unknown. Very recent studies, however, have started to identify potential regulators of preadipocyte formation, including the transcription factor Zfp423 and components of bone morphogenetic protein signaling pathways including Smads (mothers against decapentaplegic homologs). The differentiation of committed white and brown preadipocytes shares a common transcription cascade comprising several nuclear factors, with the most notable being CCAAT/enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ). Formation of brown adipocytes requires additional factors, most notably placenta-specific gene 8 protein, PR domain zinc finger protein 16 (PRDM16), C/EBPβ, and the PPARγ coactivators PGC1α and PGC1β, which induce the brown phenotype (mitochondria biogenesis and thermogenic function). Activation of PRDM16 in white adipocytes suppresses the expression of select white genes while stimulating brown adipogenesis.

19.11 BROWN ADIPOSE TISSUE DEVELOPMENT

Until very recently, the accepted view was that white and brown adipocytes likely derive from a common precursor cell in the process of mammalian development. Shared characteristics of cell morphology, lipid metabolism, and gene expression patterns between white and brown adipocytes provided convincing evidence to many investigators that they shared developmental origins. A 2007 study[61] was the first to establish that white and brown adipocytes actually originate from distinct cell lineages; this conclusion was based on microarray analysis, which demonstrated that brown preadipocytes, but not white preadipocytes, possessed a myogenic gene signature. This finding was the first to provide a probable explanation as to why brown adipocytes are specialized for lipid catabolism rather than lipid storage, a function that is most closely associated with skeletal muscle.

Skeletal muscle progenitors develop into mature myocytes via the orchestrated transcriptional activity of multiple transcription factors, including paired box proteins Pax-3 and Pax-7 and myogenic factor 5 (Myf5).[62] These muscle precursors are resident in the dorsal epithelium of somites, or the dermomyotome, during embryonic development. A seminal study by Seale et al.[63] provided convincing evidence that BAT and skeletal muscle are more closely related than BAT and WAT. Using in vivo fate mapping, the authors elegantly demonstrated that Myf5$^+$ progenitors give rise to both classical, interscapular BAT and skeletal muscle, but not WAT. This finding is supported by previous data suggesting that some BAT depots derive from homeobox protein engrailed-1 (En1$^+$) progenitors, resident in the central dermomyotome.[64] Additionally, the study linking Myf5 to BAT also established that PRDM16 controls a bidirectional fate switch that promotes the development of brown adipocytes as opposed to skeletal myoblasts. Loss of *Prdm16* from precursors results in a loss of BAT characteristics and expression of skeletal muscle genes; strikingly, ectopic expression of *Prdm16* in myoblasts induces their differentiation into brown adipocytes. These findings do not rule out the possibility that BAT and WAT share a common progenitor; it is possible that the Myf5$^+$ progenitors represent one lineage that has, at some earlier stage of development, diverged from the WAT lineage.

Present data suggest that there are distinct developmental processes that regulate prenatal development of classical BAT and postnatal formation of brown adipocytes in WAT. Intriguingly, Seale et al.[63] showed that the brown adipocytes that develop within WAT after β3-adrenergic stimulation are not derived from *Myf5*$^+$ precursors. Consistent with these results, previous studies have shown that genetic variability due to mouse strain affects the formation of these WAT brown-like cells, but not interscapular BAT.[65] The anatomical or developmental origins of these brown-like adipocytes, designated the brite (brown in white) or beige adipocytes, are poorly defined.[40,66] Current hypotheses propose that brite adipocytes may derive from the transdifferentiation of existing white adipocytes and beige cells might arise from the differentiation of precursor cells resident in the WAT depot.[66,67] Use of fluorescence-activated cell sorting has identified stem cells in WAT and skeletal muscle of mice and humans that give rise to either white or UCP1$^+$ adipocytes. Notably, human skeletal muscle CD34$^+$/CD146$^-$/CD45$^-$/CD56$^-$ cells (CD34$^+$/cell surface glycoprotein MUC18$^-$/receptor-type tyrosine-protein phosphatase C$^-$/neural cell adhesion molecule),[60] mouse WAT Sca1$^+$/CD45$^-$/Mac1(integrin α-M$^-$),[68] and mouse PDGFRα$^+$/CD34$^+$/Sca1$^+$[69] cells have each been shown to have brown adipogenic potential. With the goal of determining the molecular and phenotypic identity of WAT-UCP1$^+$ adipocytes, Wu et al.[66] isolated CD137$^+$/TMEM26$^+$ (tumor necrosis factor receptor superfamily member 9$^+$/transmembrane protein 26$^+$) subcutaneous WAT stromal vascular cells that differentiate into beige adipocytes. These cells express a broad gene program that is distinct from white and classical interscapular BAT. Importantly, human brown adipose tissue obtained through biopsies of PET-positive supraclavicular regions has a signature of gene expression resembling beige adipocytes.[66]

19.12 STEM CELL COMMITMENT TO THE ADIPOCYTE LINEAGE

Development of mature adipocytes occurs in two stages: (1) the commitment of multipotent progenitors such as MSCs to the adipocyte lineage, and (2) the terminal differentiation of committed preadipocytes into mature adipocytes. The sequential steps of terminal differentiation have been carefully elucidated, as discussed in Section 19.8 and elsewhere in the literature.[18] The molecular events required for the commitment of multipotent MSCs to the adipocyte lineage, in contrast, are not well understood. Existing studies of the commitment processes have largely made use of the C3H10T1/2 cell culture system, which faithfully models the multipotent MSCs at an earlier developmental stage than preadipocytes. C3H10T1/2 MSCs are multipotent—these cells have the capacity to undergo differentiation to various cell types, including osteoblasts, chondrocytes, myocytes, and adipocytes, making them an ideal model for elucidating the molecular mechanisms controlling their fate.[70] Primary cultures of MSCs derived from the bone marrow and adipose tissue stroma also have proven potential to differentiate into adipocytes and are thus valuable in the verification of findings obtained from the immortalized 10T1/2 cells.

Cell fate determination is initiated by external developmental cues originating from the proximate microenvironment, or "stem cell niche," a specialized compartment that functions to control proliferation and determine the fate of stem cells.[71] The identification of stem cell niches has proved to be difficult because of the low abundance of stem cells and the lack of specific stem cell markers. Current evidence indicates that the stem cell niche likely includes the stem cells themselves, soluble factors, stromal support cells, the extracellular matrix, neural input, and the tissue vasculature.[72] External cues driving the commitment process are integrated with the activity of intrinsic cell factors and are mediated by intracellular signaling molecules and nuclear transcription factors. Numerous embryonic morphogens are known to influence the commitment of mesodermal precursor cells to the adipocyte lineage; these morphogens include members of the transforming growth factor-β (TGFβ) superfamily, most notably TGFβ itself and bone morphogenetic proteins (BMPs). Additional regulators include FGFs, proto-oncogene wingless (Wnt), the hedgehog protein family members, and others. These developmental proteins activate signaling pathways that converge on the promoters of lineage-specific transcription factors, often promoting one lineage pathway while simultaneously inhibiting another.[73] Consequently, the balance of these proteins in the extracellular milieu determines the specified developmental pathway of pluripotent stem cells (Figure 19.2).

Members of the Wnt and hedgehog families have well-established anti-adipogenic effects on MSCs. Evidence suggests that hedgehog signaling inhibits adipogenesis and promotes osteoblast differentiation in stromal progenitors.[74] Interestingly, a 2010 study of mice with adipose-specific hedgehog activation confirmed its role as a negative regulator of white, but not brown, adipose tissue formation, suggesting that hedgehog may not have an inhibitory role in BAT formation.[75] The Wnt family of secreted glycoproteins has relatively more complex effects on adipogenesis. Some evidence suggests that activation of the Wnt pathway is coincident with MSCs that have undergone commitment to the adipocyte lineage.[76] Wnt proteins, however, inhibit the differentiation of bone marrow progenitors to adipocytes while promoting their development into osteoblasts.[77] This apparently paradoxical effect is likely controlled by the activity of distinct Wnt family members and/or by the transient activation of Wnt signaling during commitment and differentiation.

FGF family members have also been linked to the process of adipose development. In particular, FGF1 and FGF10 have demonstrated roles in the development of WAT by facilitating the differentiation of human white preadipocytes.[78,79] FGFs 16, 19, and 21 are involved in the development of BAT by promoting the proliferation of BAT precursors, increased BAT mass, and the browning of WAT.[80–82]

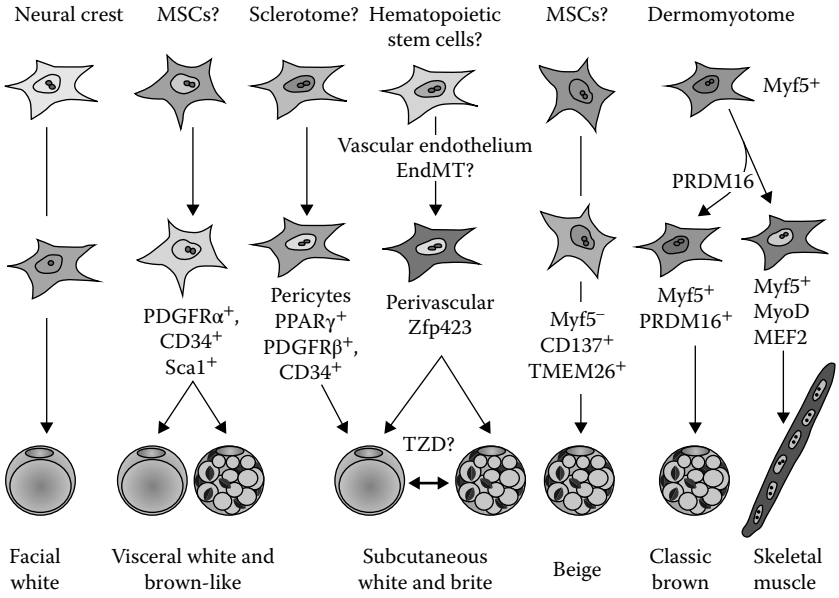

FIGURE 19.2 **(See color insert.)** Putative stem cell lineages that give rise to white and brown adipose depots: CD34, hematopoietic progenitor cell antigen CD34; CD137, tumor necrosis factor receptor superfamily member 9; EndMT, endothelial-to-mesenchymal transition; MEF2, myocyte enhancing factor 2; MyoD, myogenic differentiation 1; Sca1, lymphocyte antigen 6A-2/6E-1.

19.13 TRANSFORMING GROWTH FACTOR-β

Members of the TGFβ family are recognized for their roles in the development of various tissues. TGFβ potently inhibits adipocyte differentiation in vitro; this occurs via a mechanism involving the downstream TGFβ effector Smad3 (mothers against decapentaplegic homolog 3) interacting with C/EBP and repressing the activation of its target genes.[83] Despite this inhibitory effect of TGFβ on adipogenesis, levels of TGFβ are elevated in the adipose tissue of obese mice.[84] The mechanisms responsible for this higher level of TGFβ expression are not clear. However, excess TGFβ likely contributes to the overall fibrotic nature of obese adipose tissue. Recent work by Yadav et al.[85] illustrates an important role of the TGFβ/Smad3 pathway in the browning of WAT. In this study, mice deficient in *Smad3*, and hence exhibiting a blockade of TGFβ signaling, revealed a strong recruitment of brown adipocytes to WAT, with an enhanced bioenergetic profile and brown-myogenic gene expression profile within WAT. Importantly, these mice are protected from obesity, diabetes, and hepatic steatosis.

19.14 BONE MORPHOGENETIC PROTEINS

BMPs belong to a large group of growth factors within the TGFβ superfamily that are recognized for orchestrating tissue architecture during embryonic development.[86] In contrast to TGFβ, BMPs are considered to promote adipogenesis in vivo as well as in vitro. Several studies have demonstrated that exposing multipotent MSCs to BMP2 or BMP4 gives rise to a population of preadipocyte-like cells that have the capacity to fully differentiate to mature adipocytes.[87,88] Proliferating C3H10T1/2 MSCs express the BMP receptors BMPr1 and BMPr2, which when bound to ligand phosphorylate and activate Smads 1, 5, and 9, leading to their heterodimerization with co-Smad4 and nuclear translocation.[89] Overexpression of a constitutively active BMPr1 induces adipocyte lineage commitment in C3H10T1/2 MSCs, even in the absence of BMP2/4; conversely, expression of a dominant negative BMP receptor or knockdown of co-Smad4 completely disrupts this commitment process.[90] Interestingly, Medici et al.[91] demonstrated that BMP induces endothelial-to-mesenchymal transition in vascular endothelial cells, resulting in a population of stem-like cells that have the potential to differentiate into osteoblasts, chondrocytes, or adipocytes.

Researchers have elucidated a role for BMPs in the determination and commitment of precursors to the BAT lineage. BMP7, in particular, has emerged as an initiating factor in the commitment of MSCs to the BAT lineage.[92] Tseng et al. demonstrated that UCP1 expression and total BAT mass are significantly reduced in *Bmp7* knockout mice. C3H10T1/2 MSC exposure to BMP7 activates the expression of key factors of brown adipogenesis, including transcription factors specifying early brown fat fate (PRDM16 and PGC-1α) and brown fat-selective UCP1. Concomitantly, mitochondrial biogenesis is initiated and is regulated by p38 MAP kinase– and PGC-1-dependent pathways. Reports have also indicated that BMP7 is able to suppress the expression of factors that are enriched in preadipocytes, including protein δ homolog 1 and necdin, which prevent the progression of preadipocyte development into mature adipocytes.[92,93]

Since BMP7 is able to promote the commitment of MSCs to brown preadipocytes, using BMP7 as a tool to delineate the key early events in the development of BAT is an attractive scientific approach. As a natural product, BMP7 has significant therapeutic potential; although extensive studies must

first be performed in animals, it is possible that BMP7 could be used to promote the commitment and differentiation of precursors to the BAT lineage in vitro for reimplantation into human adipose depots, or it could be directly administered into adipose depots to direct browning of the adipose tissue.

19.15 MECHANISMS OF COMMITMENT TO THE ADIPOCYTE LINEAGE

Although there is ample research on the developmental signals initiating adipose development and the processes regulating differentiation of preadipocytes to mature adipocytes, surprisingly very little is known about the molecular mechanisms regulating stem cell commitment to adipose lineages. In addition to the various extracellular factors discussed in Section 19.12, investigators have also uncovered roles for cell shape, cytoskeletal tension, and transforming protein RhoA (ras homolog family member A) activity in regulating the fate of MSCs.[94] Results from the studies demonstrated that cell morphology is a determinant of cell fate; human MSCs that adhere to a surface and flatten undergo osteogenesis, whereas MSCs that are not permitted to spread adopt a round shape and commit to the adipocyte lineage. The authors went on to show that cell shape regulates cell fate by modulating RhoA activity, an important pathway that regulates the formation of actin microfilaments from monomeric globular actin. Most recently, the same group reported that cell adhesion to the extracellular matrix and its effects on cell shape and cytoskeletal mechanics regulate BMP-induced signaling and osteogenic differentiation of human MSCs. In support of these findings, Huang et al.[95] reported that BMP2/4 selectively upregulates the expression of cytoskeleton-associated proteins, coincident with a dramatic change in cell shape during the commitment process.

Identifying nuclear factors (transcription factors and their coregulators) responsible for directing the commitment program is currently a subject of intense investigation. In a comparative study of clonal populations of adipogenic and non-adipogenic fibroblasts, Gupta et al.[96] identified PPARγ2 and Zfp423 as factors enriched in adipogenic cell lines. Although Zfp423 expression is not induced during adipocyte differentiation, ectopic expression of Zfp423 in non-adipogenic cell lines is sufficient to enhance PPARγ2 expression and direct full differentiation. Interestingly, the *Zfp423* gene contains a Smad-binding domain and has been characterized as a BMP-dependent transcriptional coactivator of Smad protein, indicating that Zfp423 sensitizes fibroblasts to the effects of BMPs.[96,97]

19.16 SUMMARY

The early 1990s to the present witnessed an explosion of knowledge identifying the mechanisms controlling the formation and function of adipocytes. This knowledge has provided explanations for some of the malfunctions resulting from the deposition of excess fat in various adipose depots. For instance, the attenuation of PPARγ activity by inflammatory cytokines in the adipose tissue of obese individuals leads to a decrease in adiponectin production, which results in systemic insulin resistance. The next challenge for obesity researchers is to gain a better understanding of the function of individual adipose depots since it has become increasingly clear that each depot contributes differently to obesity-associated comorbidities. Recent expression data suggest that the depots are likely composed of a heterogeneous population of adipocytes that arise from several different developmental progenitors. The dramatic differences in the response of individual depots to obesity, therefore, can be explained if each depot comprises a unique set of developmentally derived fat cells that express a corresponding unique signature of proteins participating in different functions. We can look forward to a continuing accumulation of important discoveries, some of which will explain the origins of adipose depots and their unique functions as outlined in Section 19.12. The knowledge obtained will lead to the development of more selective anti-obesity therapeutics.

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20 Adipose Tissue Metabolism, Adipokines, and Obesity

Dominique Langin and Max Lafontan

CONTENTS

20.1 INTRODUCTION

A major physiological role of white adipose tissue (WAT) is to store energy in the form of triacylglycerol (TAG) and to supply energy in the form of free fatty acids (FFAs) as needed by other tissues. Many other tissues contain reserves of glycogen, lipid, or protein, but these are only limited energy stores. Total glycogen stores (about 500 g, in liver and skeletal muscle) equate to about 1 day's worth of normal energy expenditure, and liver glycogen is completely depleted after fasting for 24 hours. Proteins tend to be conserved and are catabolized in large amounts only during prolonged starvation.

The TAG stored in WAT is therefore the body's main long-term repository for storing energy that is in excess of requirements and the most important fuel store for survival during starvation. Because of the high energy content of TAG (9 kcal/g) and its hydrophobicity, the storage of energy as TAG is highly efficient: 1 kg of WAT contains only 100 g of water but 800 g of TAG and, thus, about 7000 kcal of energy. In theory, a typical body fat mass of 15 kg would provide enough energy for 50–60 days of total starvation, and this is in agreement with the survival limit of initially normal-weight adults under famine conditions. Obese subjects, by virtue of their increased fat mass, can survive starvation for much longer, over 120 days in some cases. This highlights the crucial importance of fat storage as a survival advantage during most of human evolution, during which famine has been a powerful selection force. Until relatively recently, the ability to store excess energy safely as TAG in adipocytes must have conferred enormous survival benefits; however, in an energy-replete environment the ability to promote TAG storage encourages the spread of obesity. The processes of fat deposition and mobilization are regulated by integrated endocrine and neural mechanisms, which cooperate to keep fat mass relatively constant under habitual conditions. This is achieved in part by the adipocyte's ability to signal the size of the body's TAG stores to the brain, through leptin and other mechanisms (see Section 20.3).

20.2 ADIPOSE TISSUE METABOLISM

20.2.1 Fat Storage

In humans, a large fraction of the TAG stored in adipocytes is derived from the uptake of FFAs from the bloodstream, either FFAs bound to albumin or those released by the hydrolysis of circulating TAG through the action of lipoprotein lipase (LPL).[1] In turn, circulating TAG comes either from very-low-density lipoproteins secreted by the liver or, after eating, from chylomicrons that transport TAG reconstituted from the digestion products of dietary fat (Figure 20.1). LPL-catalyzed reaction products, fatty acids (FAs), and monoacylglycerol (MAG) are in part taken up to be stored as TAG in WAT.[2] In WAT, LPL is powerfully upregulated by insulin, and this gives WAT a special role in clearing circulating TAG after eating and in reconstituting it for storage in adipocytes. LPL is synthesized in adipocytes and then exported to the capillaries, where it binds to the luminal surface of endothelial cells by interacting with cell-surface glycosaminoglycans and several interacting factors. Glycosylphosphatidylinositol (GPI)-anchored high-density lipoprotein–binding protein 1 (GPIHBP1) of capillary endothelial cells shuttles LPL from subendothelial spaces to the capillary lumen.[3]

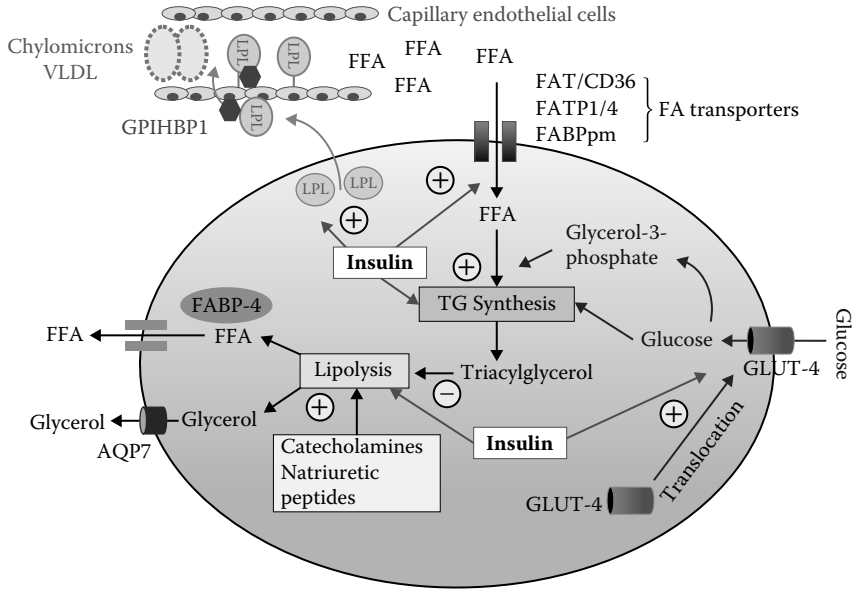

FIGURE 20.1 **(See color insert.)** Overview of fat storage and fat mobilization in the white adipocyte: lipoprotein lipase (LPL) synthesized in the adipocyte is transferred to the capillary lumen. Glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 (GPIHBP1) of capillary endothelial cells shuttles LPL from subendothelial spaces to the capillary lumen. The endothelium-bound LPL acts on chylomicron particles in the vascular space to liberate free fatty acids (FFAs), which then cross the endothelium to be taken up by adipocytes via several fatty acid (FA) transporters. Glucose uptake is under the control of glucose transporter (GLUT-4) translocation. Insulin has major positive impacts on LPL synthesis and activation, FA and glucose uptake, and FA esterification while exerting potent antilipolytic effects. AQP7, aquaporin-7; FABP-4, FA-binding protein 4; FAT/CD36, FA translocase/CD36; FATP1/4, FA transport protein 1/4; FABPpm, plasma membrane FA-binding protein (identical to mitochondrial aspartate aminotransferase); GLUT-4, insulin-responsive glucose transporter type 4; TG, triacylglycerol; VLDL, very-low-density lipoprotein; (+), stimulation; (–), inhibition.

Lipoproteins are too large to penetrate the endothelium; the endothelium-bound LPL acts on these particles in the vascular space to liberate FFAs, which then cross the endothelium to be taken up by adipocytes.

Long-chain FAs can diffuse rapidly across phospholipid bilayers, but there is now overwhelming evidence that their uptake is facilitated by integral or membrane-associated proteins. In adipocytes, the FA translocase (also known as the scavenger receptor CD36) and FA-binding proteins (especially FATP1) play an important role in FA uptake.[4,5] The transport of FFAs across the adipocyte membrane is intimately associated with their "activation," that is, esterification with coenzyme A (CoA) to form fatty acyl-CoA, a necessary step for TAG synthesis.

An alternative pathway for generating FAs is their synthesis from glucose, that is, de novo lipogenesis. Under normal dietary conditions, this pathway is not thought to play a major role, as the activity of the rate-limiting enzyme, ATP citrate lyase (ATP refers to adenosine triphosphate), is very low.[6] However, this pathway could theoretically become significant in subjects eating a high-carbohydrate, high-energy diet.[7] Besides the quantitative contribution, it is also plausible that de novo lipogenesis exerts a regulatory role in WAT.[8]

The process for esterifying FAs to form TAG in adipocytes involves the sequential addition of fatty acyl-CoA residues to a glycerol "backbone," mainly via the glycerol-3-phosphate pathway. This starts with glycerol-3-phosphate, produced in the fed state from glucose by glycolysis in the adipocyte. Indeed, the glycerol formed during lipolysis is not reutilized to a major extent by white fat cells because they contain minimal amounts of the enzyme glycerol kinase necessary for glycerol metabolism. However, expression of glycerol kinase can be induced in human white fat cells, thereby allowing a futile cycle of lipolysis and reesterification.[9,10] Importantly, the esterification pathway is also stimulated by insulin. Considerable knowledge has been gained on the cascade of enzymatic reactions leading to TAG synthesis (Figure 20.2).[11]

During fasting, a significant proportion of FFAs is reesterified into TAG. The amount of released FFAs is therefore a balance between TAG breakdown and resynthesis. Reesterification requires glyceroneogenesis, which is defined as the de novo synthesis of glycerol-3-phosphate from pyruvate, lactate, or certain amino acids.[12] The key enzyme in this process is the cytosolic isoform of phosphoenolpyruvate carboxykinase.

20.2.2 Fat Mobilization

Catecholamines (the neurotransmitter noradrenaline and the hormone adrenaline), natriuretic peptides, and insulin are considered to represent the major regulators of lipolysis in humans (Figure 20.3). Adrenaline, but not noradrenaline, has been shown to be a major determinant of exercise-induced lipid mobilization in human subcutaneous WAT.[13]

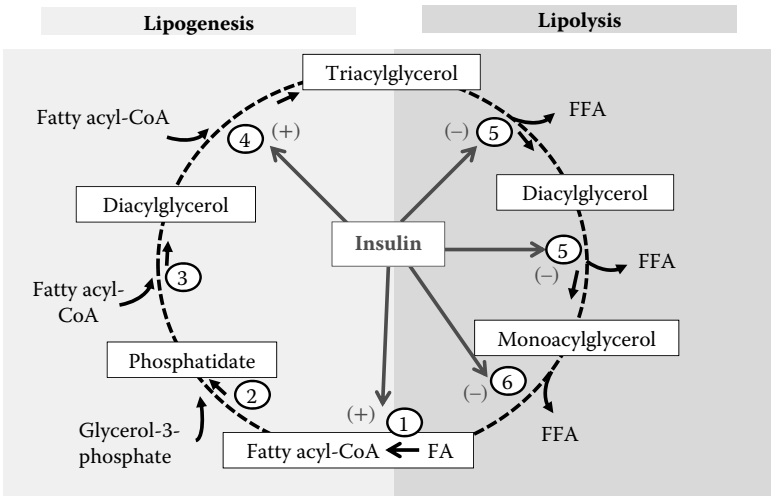

FIGURE 20.2 Fatty acid synthesis and esterification and lipolysis in white adipocytes: major steps of fatty acid esterification, triglyceride synthesis, and free fatty acid (FFA) and glycerol release. Lipogenic and lipolytic enzymes are indicated in the diagram (numbers): (1) fatty acyl-CoA synthase, (2) glycerol-3-phosphate acyltransferase, (3) phosphatidate phosphohydrolase, (4) diacylglycerol acyltransferase, (5) adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), and (6) monoglyceride lipase. Insulin action is indicated by (+) for stimulation of enzyme activity or (–) for inhibition of lipolytic processes.

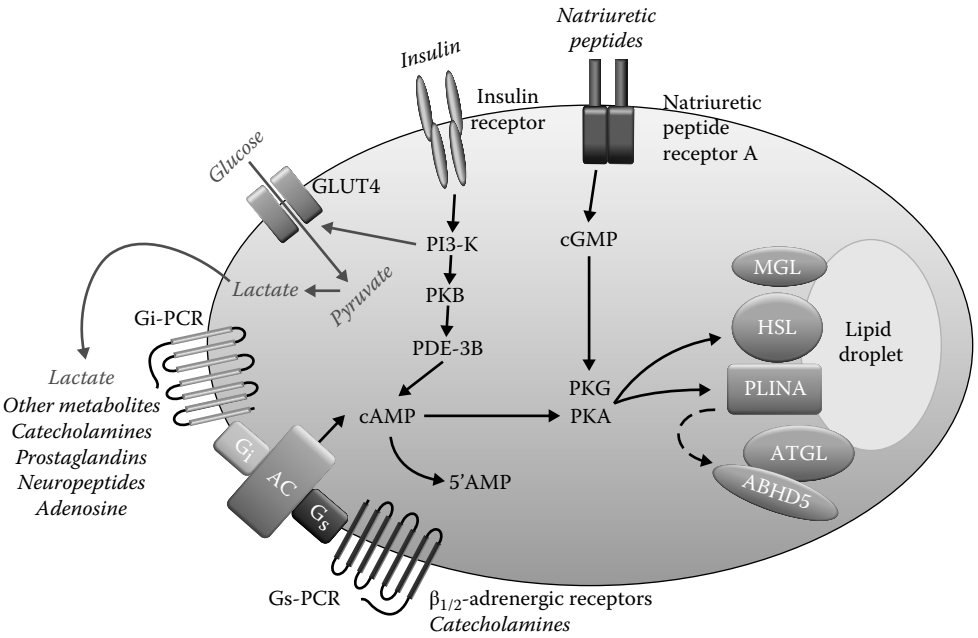

FIGURE 20.3 **(See color insert.)** Regulation of lipolysis in human adipocytes: binding of catecholamines to Gs-protein-coupled $\beta_{1/2}$-adrenergic receptors stimulates cyclic adenosine monophosphate (cAMP) production by adenylyl cyclase and activates protein kinase A (PKA). Conversely, the stimulation of Gi-protein-coupled receptors reduces cAMP and PKA activation. Insulin favors cAMP degradation through the activation of phosphatidylinositol-3 phosphate kinase (PI3-K) and protein kinase B (PKB) and the stimulation of phosphodiesterase 3B (PDE3B) activity. Natriuretic peptides promote cyclic guanosine monophosphate (cGMP) accumulation and protein kinase G (PKG) activation. PKA and PKG phosphorylate hormone-sensitive lipase (HSL) and perilipin A (PLINA). Adipose triglyceride lipase (ATGL) and its cofactor ABHD5 and monoacylglycerol lipase (MGL) also participate in the hydrolysis of triglycerides. A new pathway (shown by blue arrows) involving the glucose transporter GLUT-4, glycolysis-mediated lactate production, and the Gi-protein-coupled lactate receptor GPR81 has been proposed to be involved in the insulin-induced antilipolytic effect. It is unknown whether this pathway participates in the control of human fat cell lipolysis. Gs-PCR and Gi-PCR refer to Gs- and Gi-protein-coupled receptors, respectively.

However, the physiological significance of a number of other lipolytic and antilipolytic agents, especially paracrine and autocrine factors, remains to be elucidated. Lipolytic and antilipolytic molecules activate receptors present at the surface of fat cells. However, their action can be indirect. Notably, it has recently been shown in rodents that insulin, which is known to directly activate fat cell insulin receptors, exerts part of its antilipolytic action through hypothalamic control of the sympathetic nervous system. Indeed, insulin infusion into the mediobasal hypothalamus of rats suppresses lipolysis.[14] It is unknown whether the hypothalamic insulin action also plays an important physiological role in human WAT lipolysis. It is well recognized that sympathetic nervous system oscillations and pulsatile hormone secretion occur. Intrinsic lipolytic oscillations that are glucose dependent and modulated by FAs have been described in perifused rat fat cells.[15] Rapid oscillations of lipolysis reflected in oscillatory patterns of plasma FFAs and glycerol have been described in dogs and humans.[16] The oscillatory component of lipolysis involves the sympathetic nervous system.[17] The release of the products of lipolysis from human WAT is pulsatile.[16]

The activation or inhibition of plasma membrane adenylyl cyclase activity via receptors from the seven-transmembrane-domain G-protein-coupled receptor family controls the formation of cyclic adenosine monophosphate (cAMP) from ATP. An increase in intracellular cAMP enhances protein kinase A (PKA) activity and stimulates lipolysis, whereas the inhibition of lipolysis is associated with the lowering of cAMP levels. Catecholamines stimulate lipolysis through the activation of β-adrenergic receptors (β-ARs). Their stimulation increases intracellular cAMP levels in fat cells of various species, although considerable species-specific differences exist.[18] In human white fat cells, both β_1-AR and β_2-AR stimulate lipolysis in vitro and in vivo.[19] Although its role in rodent white and brown fat cells is established, β_3-AR does not contribute to catecholamine-induced lipolysis in human subcutaneous adipocytes. The recent rediscovery of brown adipose tissue (BAT) in human adults will undoubtedly stimulate new investigation on β_3-AR.

Surprisingly, the number of molecules and receptors involved in the inhibition of lipolysis through Gi-protein-coupled receptors is very large. Ligands include neuropeptides, paracrine factors, and autacoid agents (adenosine; prostaglandins and their metabolites; and other small molecules such as short-chain FAs, β-hydroxybutyrate, and lactate) originating from not only adipocytes themselves but also preadipocytes, endothelial cells, macrophages, and sympathetic nerve terminals. Catecholamines have a special status since they are able to stimulate both β-ARs and a major antilipolytic pathway involving α_2-ARs. Through the activation of GPR81, a Gi-protein-coupled receptor, lactate may be involved in the inhibitory effect of insulin on lipolysis.[20] Insulin stimulates glucose uptake by fat cells. Glucose is metabolized by the glycolytic pathway into lactate, which is released in significant amounts by adipocytes and activates GPR81. For a long time, it was considered that cAMP constituted the only second messenger involved in the control of adipose tissue (AT) lipolysis. However, the discovery of a new hormonal lipolytic pathway in human fat cells challenged this view.[21] Atrial natriuretic peptides and brain natriuretic peptides, released by cardiomyocytes, stimulate human fat cell lipolysis through type A natriuretic peptide receptors. The stimulation of these receptors, which possess guanylyl cyclase activity controlling cyclic guanosine monophosphate production, leads to the activation of protein kinase G (PKG) and lipolysis, as does the activation of PKA.

Insulin exerts a potent antilipolytic effect of major physiological relevance. Failure to suppress FFAs in response to the ingestion of a meal and the subsequent rise in insulinemia leads to abnormal elevations of plasma FFAs. Insulin controls cAMP levels and lipolysis through the activation of cyclic nucleotide phosphodiesterase 3B (PDE3B). The importance of PDE3B in the regulation of lipolysis and insulin-induced antilipolysis was confirmed in PDE3B-null mice.[22] Insulin activates PDE3B and initiates PDE3B-dependent degradation of cAMP to 5′-AMP, a decrease in cAMP, and the inactivation of PKA, thus inhibiting lipolysis. Insulin could also control WAT lipolysis through lactate production and indirectly through central activation of the sympathetic nervous system.[14,20]

During lipolysis, intracellular TAG is sequentially hydrolyzed into diacylglycerol (DAG), MAG, and glycerol, releasing one molecule of FA at each step. Three major lipases are involved: adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and MAG lipase (MGL). Other lipases may play a minor role. FFA and glycerol efflux from fat cells is followed by transport of these metabolites in the bloodstream to other tissues (mainly liver for glycerol; and skeletal muscle, liver, and heart for FFAs). The mature white adipocyte comprises a large lipid droplet occupying the major part of the cell. Lipid droplets are considered dynamic organelles that are critical for the management of cellular lipid stores and lipolytic processes.[23]

Lipolysis requires that soluble cytosol lipases (i.e., ATGL and HSL) can access the highly hydrophobic TAG substrates coated by proteins surrounding the lipid droplet. During lipolysis, adipocyte lipid droplets undergo an important structural reorganization involving lipid droplet–associated proteins (e.g., perilipin), lipases (e.g., ATGL and HSL), and cofactors (e.g., lipase cofactor CGI-58/1-acylglycerol-3-phosphate *O*-acyltransferase ABHD5, a coactivator of ATGL) (Figure 20.3). PKA and PKG activation leads to perilipin phosphorylation and release of CGI-58.

ATGL enzymology, gene, and protein structure have recently been reviewed.[24] ATGL exhibits a 10-fold-higher substrate specificity for TAG than DAG. Extensive studies of ATGL- and HSL-deficient mice have provided strong support for designating ATGL as the major TAG lipase in WAT and for designating HSL as the primary DAG lipase in vivo.[25] The pivotal role of ATGL in both basal lipolysis and stimulated lipolysis has also been demonstrated in human fat cells.[26] Adipose-specific ablation of ATGL in mice converted BAT to a WAT-like tissue.[27] The mice exhibited severely impaired thermogenesis, revealing the requirement of ATGL-catalyzed lipolysis for maintaining a BAT phenotype.

In vitro, HSL catalyzes the hydrolysis of TAG into DAG and DAG into MAG. The relative acylglycerol hydrolase activity of HSL in vitro is 10-fold greater against DAG than TAG and MAG. Unlike other known mammalian TAG lipases, HSL is activated by PKA- and PKG-mediated phosphorylation and inhibited by AMP-activated protein kinase–mediated phosphorylation.[28] Conversely, the phosphorylation of ATGL by AMP-activated protein kinase may increase its TAG hydrolase activity.[27] An important step in lipolysis activation is the translocation of HSL from a cytosolic compartment to the surface of the lipid droplet. HSL-null mice eating high-fat diets unexpectedly failed to become obese.[25] Reduced fat deposition could result from impaired adipogenesis and/or adipocyte maturation due to a defect in the production of peroxisome proliferator-activated receptor γ (PPARγ) ligands. DAG accumulation, retinoic acid metabolites, and local inflammation may also interfere with adipocyte differentiation in this model. Moreover, WAT shows metabolic BAT-like features.

MGL is required in the final hydrolysis of the two MAGs produced by HSL. It hydrolyses the 1(3) and 2-esters bonds of MAG at equal rates and is without in vitro catalytic activity against DAG and TAG. Because of its abundance in WAT, MGL was thought not to be limiting. However, ex vivo stimulated lipolysis has been shown to be decreased in MGL-null mice.[29] In this mouse model, MAG hydrolase activity was not abolished because of partial compensation by HSL.

20.2.3 Dysregulation in Obesity

Lipid turnover is an essential process determining the development of obesity and its complications. Recently, the dynamics of lipid turnover were determined in human subcutaneous WAT.[30] During the life span of an adipocyte (i.e., about 9.5 years in subcutaneous WAT),[31] TAG is replaced six times on average. Obesity is characterized by both increased lipid storage and decreased lipid removal. An increased capacity to store fat with low net mobilization leads to an expansion of fat mass; this may also be viewed as a way to safely deposit lipids into a harmless compartment. Indeed, according to the WAT expandability hypothesis, as long as an individual has the capacity to store fat in WAT there is no ectopic deposition of lipids and are no resulting metabolic complications. However, when the storage capacity is exceeded[32] ectopic deposition of lipids in liver and skeletal muscle may favor the development of insulin resistance through lipotoxic mechanisms. This is exemplified in familial combined hyperlipidemia, a hereditary lipid disorder predisposing to premature coronary heart disease. In this condition, both TAG storage and lipid removal rates were shown to be low.[30] This defect induces a routing of FAs to the liver where FA overflow contributes to the mixed dyslipidemia characteristic of the condition. Similarly, lipodystrophic patients who have a defect of TAG storage in WAT, resulting in lipid accumulation elsewhere in the body, develop severe insulin resistance.

Against conventional wisdom, fasting plasma FFA concentration is largely unrelated to body fat mass.[33] In the fasting state, plasma FFAs arise almost entirely from the hydrolysis of TAG within adipocytes. In the obese state, the lack of increase in plasma FFAs is partly explained by a decrease in subcutaneous WAT FFA production; the majority of FFAs originate from this depot. Impairment in the catecholamine-induced lipolysis in subcutaneous WAT is a common feature of obese subjects.[28] This lipolytic resistance has been related to alterations in the lipolytic cascade at multiple levels. Defects in the expression of HSL, ATGL, β-ARs, perilipin, or the regulatory subunit of PKA have been described in obese subjects. In addition to changes in the stimulatory system, lipolytic resistance to catecholamines may involve increased antilipolytic responsiveness of α_2-ARs. WAT is highly vascularized, and the release of FFAs from WAT is determined by lipolysis and also by WAT blood flow, which increases in response to nutritional stimuli (e.g., glucose uptake) and facilitates the removal of FFAs and glycerol. Decreased WAT blood flow in obesity is one of the components contributing to decreased FFA delivery in obese individuals. Impaired regulation of AT blood flow may be an important facet of the insulin resistance syndrome.[34] Insulin does not have a direct effect on WAT blood flow but probably operates via sympathetic nervous system activation.[35] The dynamics of the microcirculation in subcutaneous WAT are impaired in the postprandial state in type 2 diabetes.[36]

20.3 ADIPOKINES

WAT is now recognized as an endocrine organ, as it has been shown to secrete molecules with hormonelike activities. It also produces a flurry of protein and lipid species with paracrine and autocrine activities. WAT is made up of, in addition to lipid-laden adipocytes, several cell types constituting the stromal-vascular fraction, that is, microvascular endothelial cells, pericytes, immune cells including macrophages and lymphocytes, and fibroblast preadipocytes or stromal/stem cells. Subpopulations of precursor cells have been characterized in the stromal-vascular fraction of rodent and human WAT.[37–39] These cells are assumed to self-renew and be responsible for the maintenance of WAT and its potential to expand in response to chronic energy overload.[31] WAT-secreted factors can therefore be divided into adipocyte-secreted and stromal-vascular fraction–secreted factors.

20.3.1 Adipocyte-Secreted and Stromal-Vascular Fraction–Secreted Factors

It became evident in the early 1990s that WAT is a secretory organ. Adipocytes secrete not only LPL but also other proteins such as the serine protease adipsin (also known as complement factor D), later implicated in acylation-stimulating protein (ASP or C3ades-Arg) synthesis,[40,41] a mitogen factor,[42] tumor necrosis factor-α (TNF-α) (a proinflammatory peptide).[43] The seminal discovery of leptin, a cytokine-like hormone, in 1994[44] was followed by a wide interest on this hormone with pleiotropic actions.[45] Rapidly, it was confirmed that WAT has important and highly diversified endocrine functions. The discovery of adiponectin, an abundant plasma protein secreted by human and rodent adipocytes, initiated extensive

investigations. Adiponectin exerts multiple actions on skeletal muscle, liver, and vessels via adiponectin receptors (AdipoR1 and AdipoR2). In addition to its insulin-sensitizing effects, adiponectin also exerts anti-inflammatory and antiatherogenic effects. The roles of adiponectin and adiponectin receptors in the peripheral tissues and sympathetic nervous system have been extensively reviewed and are not detailed here.[46]

Other secreted factors originating from adipocytes and/or various cells of the stroma vascular fraction are considered briefly as follows:

- Several WAT-secreted factors including the peptides resistin, vaspin (also known as serpin A12), omentin (also known as intelectin-1), and hepcidin have been described. Plasminogen activator inhibitor 1, angiotensin II (secreted by the renin–angiotensin system of the adipocyte), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), and metallothioneins also join the long list.
- In addition to TNF-α, the inflammatory cytokines interleukin (IL)-1β, IL-6, and IL-8 and monocyte chemoattractant protein-1 (MCP-1) (also known as chemokine [C-C motif] ligand 2, CCL2), as well as anti-inflammatory agents such as the IL-1 receptor antagonist (IL-1RA) and IL-10, were identified in WAT. Several chemokines such as C-C motif ligands 3 (MIP-1α), 4 (MIP-1β), 5 (RANTES), and 20 (MIP-3α) and CXC ligands 5 and 14 (MIP-2γ) are also produced in WAT. ILs, cytokines, and chemokines are primarily secreted by stromal-vascular fraction cells, notably macrophages and T lymphocytes.[47]
- Pigment epithelium-derived factor (PEDF), a multifunctional protein with neurotrophic and antiangiogenic properties, was found to be one of the most abundant adipokines in human WAT. Its secretion is inversely regulated by insulin and hypoxia and could be important in obesity-related disorders.[48]
- The secreted fasting-induced adipose factor (FIAF), also known as PGAR (for PPARγ angiopoietin-related protein) or ANGPTL4 (for angiopoietin-like protein 4), is a powerful regulator of lipid metabolism and adiposity. Apelin, a small peptide, is produced and secreted by adipocytes and has emerged as a new factor with potent functions in energy metabolism. Apelin treatment has been shown to improve insulin sensitivity and increase FA oxidation, mitochondrial oxidative capacity, and biogenesis in the muscle of insulin-resistant rodents.[49,50]
- Osteocalcin, a marker of bone formation and a circulating hormone, was identified in subcutaneous and omental differentiated adipocytes.
- Autotaxin, an enzyme released by adipocytes that possesses lysophospholipase D activity, is upregulated during adipocyte differentiation and obesity. It is involved in the local production of lysophosphatidic acid (1- or 2-acyl-*sn*-glycerol 3-phosphate), a phospholipid that, via its interactions with G-protein-coupled receptors, controls both the proliferation and the differentiation of preadipocytes.[51]
- An important extracellular matrix (ECM) remodeling occurs during WAT development and obesity.[52] The composition and stiffness of the ECM plays an important role in adipogenesis. The enzyme system that contributes to ECM remodeling and adipogenesis involves several WAT-secreted matrix metalloproteinases (i.e., MMP-2 and MMP-9), tissue inhibitors of metalloproteinases, and cysteine proteases (e.g., cathepsins), which are secreted in the extracellular milieu and modulate the degradation of matrix proteins. Moreover, the production of various types of collagens contribute to the development of WAT fibrosis, which has been suggested to limit adipocyte hypertrophy and thereby favor the development of metabolic disorders associated with obesity.
- The proteomic profiling of the human adipocyte secretome identified dipeptidyl peptidase 4 (DPP4), which is known for its degradation of incretins (i.e., glucagon-like peptide 1 and gastric inhibitory polypeptide), as a novel adipokine. Its involvement in insulin sensitivity impairment in autocrine and paracrine fashions is suspected.[53]

Fat cell secretions have been considered in several comprehensive reviews.[54–57] WAT secretory products have been implicated in a variety of processes, ranging from food intake and blood pressure regulation to the control of lipid metabolism, initiation of insulin-sensitizing effects, inflammatory processes, and immune responses. Adipokines and their major roles are summarized in Table 20.1. Some WAT-borne factors are known to act as hormones, whereas many others are limited to an autocrine or a paracrine action within the cells of the stromal-vascular fraction.

20.3.2 Mechanisms of Secretion and Methods of Investigation

The mechanisms controlling the production and secretion of adipokines remain poorly known and require further investigation using appropriate cellular models. One of the most abundant adipokine, adiponectin, is composed of three different oligomeric forms and is assembled in the endoplasmic reticulum prior to its secretion. This process has been investigated more deeply, and various intracellular partners have been identified. The endoplasmic reticulum oxidoreductase ERO1-L-α and the effectors modulating PPARγ and nicotinamide adenine dinucleotide–dependent deacetylase sirtuin-1 activities have been shown to regulate the secretion of adiponectin from 3T3-L1 adipocytes.[58] In addition, cytoplasmic nuclear factor RIP140, which is highly expressed in mature adipocytes and functions as a corepressor for gene expression involved in lipid and glucose metabolism, has been shown to regulate adiponectin secretion via a RIP140-interacting protein.[59]

TABLE 20.1
Adipose Tissue–Secreted Molecules

Adipokines	Lipid Metabolism, Energy Homeostasis, and Insulin Sensitivity	Immune System, Acute-Phase Reactants	Promitogenic and Proangiogenic Agents	ECM Components
LPL	X			
CETP	X			
ASP	X			
Autotaxin	X			
RBP4	X			
Adipsin (factor D)	X	X		
Adiponectin	X		X	X
Apelin	X	X		
Resistin	X	X		
Omentin	X			
Visfatin	X		X	
Leptin	X	X	X	
Vaspin	X			
Osteocalcin	X			
IGF-1	X		X	
ANGPTL4-FIAF	X			
TNF-α	X	X		
IL-1β, IL-4, IL-6, IL-8, IL-10, and IL-18		X		
IL-1RA		X		
MIP-1β (CCL4)		X		
Factors C3, B, and D		X		
MIF		X		
MCP-1 (CCL2)		X		
SAA-3		X		
α1-Acid GP		X		
RANTES (CCL5)		X		
Haptoglobin		X		
Cathepsin S and L		X		
Pentraxin-3		X		
FGF			X	
HGF			X	
SDF-1			X	
VEGF			X	
NGF			X	
Tissue factor			X	
TGF-β			X	
Angiopoietin-1/2			X	
PEDF			X	
Collagens I, III, and IV				X
Collagen VI				X
MMP-1, -2, -7, -9, -10, -11, -14, and -15				X
α1-Macroglobulin				X
Gelsolin				X
Lysyl oxidase				X
Fibronectin				X
DPP4	X			

Note: This list of secreted products originating from adipocytes and/or various cells of the stromal-vascular fraction is nonexhaustive. The factors are grouped according to their contribution to the control of major functions. Some adipokines possess pleiotropic actions and are found in multiple groups. The list of adipokines increases regularly. Original references for each factor and detailed biological effects are available in the literature.[54–57,80] α1-Acid GP, α1-acid glycoprotein; CETP, cholesterol ester transfer protein; factors C3, B, and D, factors C3, B, and D of alternate complement system; FGF, fibroblast growth factor; HGF, hepatic growth factor; IGF-1, insulin-like growth factor 1; IL-1β, IL-4, IL-6, IL-8, IL-10, and IL-18, interleukins; MIF, macrophage migration inhibitory factor; MIP-1β, macrophage inflammatory protein 1β; MMP-1, MMP-2, MMP-7, MMP-9, MMP-10, MMP-11, MMP-14, and MMP-15, matrix metalloproteinases; RANTES, regulated on activation normal T cell expressed and secreted; RBP4, retinol-binding protein 4; SAA-3, serum amyloid A3; SDF-1, stromal cell–derived factor 1; TGF-β, transforming growth factor-β.

Membrane vesicles originating from the plasma membrane have been shown in various living cells. Morphological studies have reported the existence of cytoplasmic projections and cytoplasmic invaginations showing numerous pinocytic vesicles from adipocytes oriented toward the capillary wall in adipocytes of fasting rats during lipid loss.[60] Recently, 3T3-L1 and rat primary adipocytes were shown to secrete adipocyte-derived microvesicles that are composed of milk fat globule–epidermal growth factor 8. These microvesicles secreted by 3T3-L1 adipocytes showed heterogeneity in size and comprised both smaller exosome-like and larger membrane vesicles. Several integral, cytosolic, and nuclear proteins such as caveolin-1, c-Src kinase, and heat shock protein 70 were also microvesicle components. Other studies have revealed that plasma membrane vesicles, called adiposomes, which harbor the GPI protein cAMP-binding ectoprotein (Gce1) and CD73, are released by rat adipocytes when exposed to palmitate or H_2O_2. GPI proteins are transferred from plasma membrane microdomains to adipocyte lipid droplets prior to their release into adiposomes.[61] Proteomic analysis of the microvesicles revealed that many other proteins such as ECM-related proteins[62] and multiple angiogenic factors were also present.[63] Specific transcripts and microRNAs may be secreted into the plasma from adipocyte Gce1-/CD73-harboring microvesicles.[64] The discovery of adipocyte-derived microvesicles might represent a novel component of fat cell biology. The transfer of information molecules, packaged into microvesicles, enriches the possibilities of signaling processes since various messengers, including proteins, microRNAs, and specific subsets of transcripts, could be delivered at once.

Secretion of many WAT factors has been identified in vitro using murine preadipose cell lines, human and rodent isolated adipocytes, and stromal-vascular fraction cells. Proteomic approaches have revealed novel secreted factors with functions that have been partially characterized over the past few years. The proteomes of mature adipocytes and stromal-vascular fraction cells have also been investigated in human WAT.[65–67] When transferred into the interstitial fluid of a given tissue, secreted molecules, according to their molecular radii, can leave by the lymphatic and/or capillary routes. The secretion of hormones and small-molecular-size molecules from endocrine glands is facilitated by the presence of fenestrated capillaries, which have not been clearly identified in WAT. Most adipokines are relatively large molecules, which are supposed to exit WAT by lymphatic and capillary routes. In vivo explorations of the exit of adipokines from WAT were initially based on measurements of arteriovenous differences and microdialysis. The evaluation of secretion rates from subcutaneous WAT by arteriovenous sampling techniques was used for leptin, IL-6, and TNF-α.[68–70] Detection of adipokines in WAT interstitial fluid using large-pore microdialysis probes or the open-flow microperfusion technique[71] allowed the identification of several proinflammatory cytokines in the interstitial fluid.[72] However, it has been shown that tissue trauma caused by insertion of microdialysis probes leads to changes in the interstitial concentrations of IL-1β, IL-6, IL-8, MCP-1, TNF-α, and adiponectin.[73] A study of differences in adipokine concentrations between subcutaneous and femoral WAT revealed that leptin was 2.5-fold higher in femoral WAT than in the former.[74]

An innovative method was recently designed to reassess the secretion of adipokines by human WAT in vivo.[75] An estimation of the total secretion rates of several adipokines and their partitioning between the capillary and lymph routes was performed. Leptin, MCP-1, and IL-6 were secreted at the highest rate; the capillary and lymphatic routes were equally important for leptin and MCP-1. IL-6 was mostly transported by lymph and IL-8 mostly by capillaries. The transport of IL-1β was predominant in the lymph. TNF-α was transported entirely using the lymphatic route. This study revealed that the lymphatic/capillary partitioning of adipokines is a function of their molecular size and may affect both their regional and systemic effects in vivo.[75]

20.3.3 Dysregulation in Obesity

Expansion of WAT in obesity alters adipokine secretion, which may contribute to the development of metabolic diseases. There is emerging evidence that adipocyte size is an important determinant of adipokine secretion, and there is a differential expression of pro- and anti-inflammatory factors with increasing adipocyte size. For instance, there is a strong correlation between adipose tissue–derived TNF-α activity and cell size; large fat cells secrete more TNF-α in rodents.[76] Moreover, expression and secretion of proinflammatory adipokines (i.e., leptin, IL-6, IL-8, TNF-α, and MCP-1) seem to be related to human fat cell hypertrophy.[77,78] Although inflammation and endoplasmic reticulum stress could cause adipocyte dysfunction, the exact etiology of many of these pathophysiological processes remains under debate.[79] The links between adipocyte hypertrophy and differential secretion of adipokines will certainly merit deeper attention in the future. Paracrine factors other than those cited here could be proliferative triggers, secreted by the enlarged fat cells, and could act on preadipocytes and other cell types of the stromal-vascular fraction. Detailed studies of the cross talk between adipocytes and other WAT cells are expanding rapidly. In the obese state, an enhanced release of ILs and other cytokines has been observed in human WAT. This increased release was primarily due to nonfat cells.[47] It was rapidly established that the production of adipokines by WAT is strongly influenced by the presence of infiltrating macrophages.

The immune system has come at the forefront of WAT research.[80,81] Seminal observations of three separate groups have demonstrated that macrophages, now called AT macrophages (ATMs), and also T lymphocytes[82] are recruited in the WAT of obese rodents[83] and humans.[84,85] In humans, the expression of ATM-specific genes has been shown to increase with the degree of adiposity and to correlate with markers of insulin resistance and the metabolic syndrome to a similar degree in subcutaneous and visceral WAT.[86] The increase in adiposity and the worsening of metabolic status have been associated with a coordinated downregulation of

metabolism-related gene expression and an upregulation of immune response–related gene expression.[87] ATMs have been shown to promote inflammation in rodents.[88] Human ATMs are composed of distinct macrophage subsets, and fat mass enlargement is associated with ATMs that exhibit a particular remodeling phenotype.[89,90] The recruitment and polarization of macrophages is a highly complex process that is still imperfectly understood in WAT.[81] Of note, important differences have been described between murine and human macrophages.[91,92]

20.4 SUMMARY AND CONCLUSIONS

To conclude, the past decade has been marked by the discovery of several mechanisms related to the control of fat storage and mobilization and the partitioning of lipids in various depots. Several new enzymes and proteins acting either as cofactors or as components controlling the dynamics of lipid droplets have been identified. Alterations of these pathways in obesity and insulin resistance are still imperfectly understood despite major effort from in vivo approaches using stable isotopes in humans to molecular dissections in animal and cellular models. Recent human data on fat cell turnover and turnover of lipids within fat cells pave the way for future studies on fat metabolism. In addition to its role as the main storage depot for triglycerides, adipose tissue has been recognized as an active endocrine organ. WAT possesses important and highly diversified endocrine functions. A host of adipose tissue–derived factors (adipokines) have been identified. The majority of adipokines characterized to date originate from adipocytes, adipose tissue macrophages, and other immune cells. Variations in adipokine production according to the anatomic location of fat have been reported. Peptides and proteins influence organs involved in energy homeostasis and modulate signaling pathways in target tissues. Adipokines influence organs critical for energy homeostasis through their endocrine, autocrine, and paracrine functions. Adipokine levels are positively correlated with fat mass, with very few exceptions such as adiponectin and adipsin. Dysregulation of the secretion of adipokines is seen in obese individuals, resulting in modifications to insulin sensitivity and metabolism targeting liver and skeletal muscle. Among adipokines, adiponectin and apelin are the most potent molecules with respect to insulin-sensitizing activity. Despite the potent physiological effects reported for adipokines, the number of therapeutic applications to date is limited. Understanding the importance of and interplay between adipokines in complications of human obesity remains a daunting challenge.

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21 Visceral Adipose Tissue and Ectopic Fat Deposition

Amalia Gastaldelli

CONTENTS

21.1 INTRODUCTION

The major site of fat accumulation is subcutaneous adipose tissue (SAT), which is considered the "good" fat. However, significant adipose tissue accumulation has been found intra-abdominally (i.e., visceral), as well as in the intrathoracic area (Figure 21.1).[1] Visceral adipose tissue (VAT) could be up to 38% of total fat,[2,3] whereas fat in the thorax is limited by the lack of space and is usually not more than 1%–2% of total fat (Table 21.1). Both VAT and intrathoracic adipose tissue are recognized as risk factors for cardiovascular and coronary artery disease stronger than obesity per se.[4–6]

It is now recognized that the adipose tissue is not only an energy storage tissue but also a metabolically active organ secreting a variety of biologically active mediators collectively called adipokines.[7] VAT is associated with increased insulin resistance, dyslipidemia, glucose intolerance, and several pathologies such as diabetes and hypertension.[8,9] Visceral adipocytes, when compared in vitro to subcutaneous adipocytes, have been shown to be more proinflammatory and lipolytic[10] and more resistant to insulin suppression of lipolysis.[11] However, triglyceride deposition has been found as ectopic fat within cells of nonadipose tissue that normally contain only small amounts of fat. Magnetic resonance spectroscopy has highlighted the fact that ectopic fat accumulates mainly in liver, heart, and muscle and also in pancreas. This leads to the so-called cell lipotoxicity that is associated with hepatic and peripheral insulin resistance, β cell and cardiac dysfunction, explaining in part why ectopic fat accumulation increases cardiometabolic risk.

This chapter reviews the relationship between visceral and ectopic fat accumulations, as well as their metabolic and cardiovascular implications.

21.2 VISCERAL AND ECTOPIC FAT

21.2.1 Fat Distribution: Impact of Obesity and Gender Differences

As subjects become obese, fat mass increases not only as subcutaneous but also as intra-abdominal (visceral and intrathoracic) fat (Figure 21.1). Both abdominal[12] fat and intrathoracic[9] fat increase linearly with body mass index (BMI) (Figure 21.2). This is accompanied by an increase in fatty acid turnover, and because of increased fatty acid release in the systemic circulation triglycerides accumulate in lipid droplets as ectopic fat in nonadipose tissues, for example, liver, muscle, pancreas, and heart. Ectopic fat increases with BMI and is usually not limited to one organ, and strong associations have been observed between visceral and hepatic,[13,14], cardiac,[9,15] and muscle[2] fat accumulation.

In the abdominal area VAT tends to accumulate more in men than women (Table 21.1), and for the same BMI the slope of the relationship between VAT and BMI is steeper in men[12] (Figure 21.2). From studies employing magnetic resonance imaging (MRI), it can be estimated that for an average BMI of 27 kg/m^2 women have approximately 2.7 kg of VAT versus approximately 5.0 kg in men[3] (Table 21.1). Ectopic fat is also increased with an increase in BMI.[2,3,13,16,17] In obese

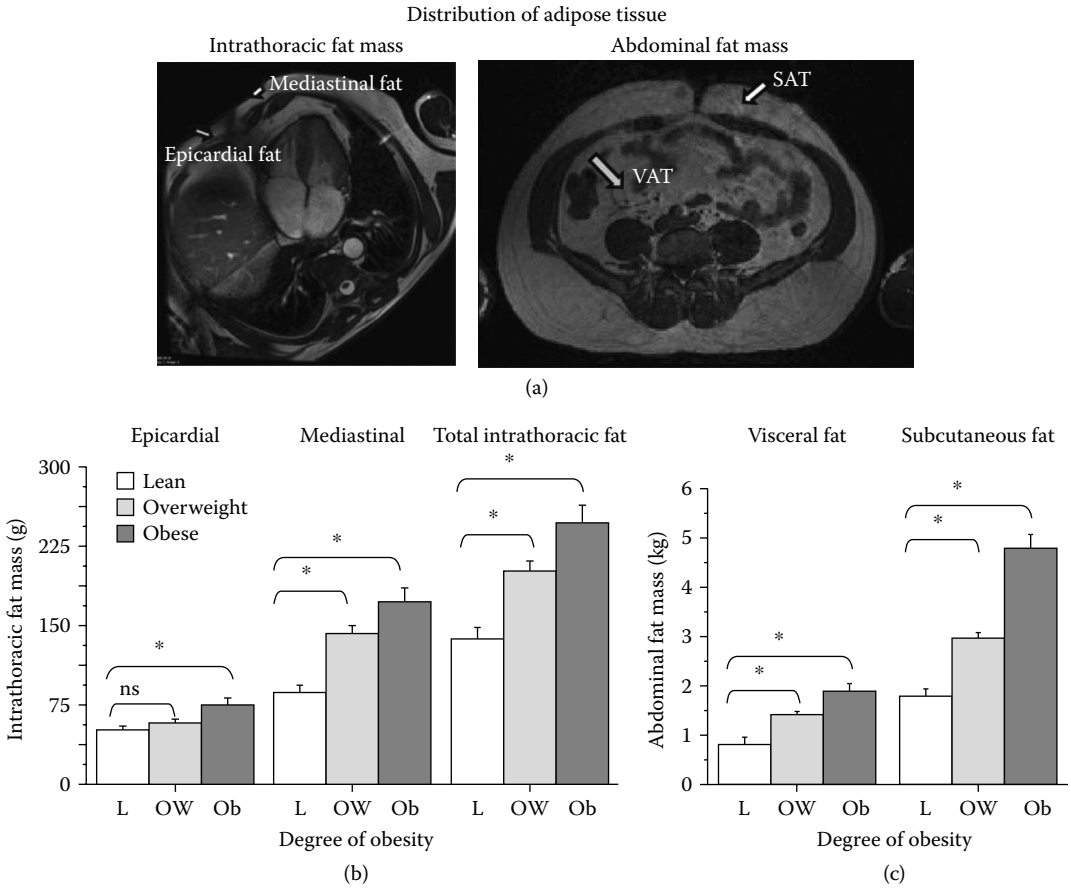

FIGURE 21.1 **(See color insert.)** (a) Intrathoracic and abdominal images obtained using magnetic resonance spectroscopy. (b) Intrathoracic adipose tissue accumulation (epicardial, mediastinal, and total cardiac fat). (c) Abdominal adipose tissue accumulation (visceral and subcutaneous). Data shown for lean (body mass index [BMI] < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obese (BMI > 30 kg/m^2) subjects. * $p < .05$ versus lean in each group. NS = not significant. (Reproduced from Sironi AM et al., *Diabet. Med.*, 29, 622–7, 2012.)

subjects with similar BMI values, women tend to accumulate less hepatic,[18,19] visceral, and pancreatic fat,[17] with a slight increase in SAT[17] (Table 21.1). Hepatic fat is strongly associated with cardiac,[20] muscle,[21] and pancreatic fat.[22]

In the thoracic area, fat can significantly accumulate around the heart, that is, within the pericardial sac (named epicardial adipose tissue), outside the pericardium (named mediastinal or extra-pericardial adipose tissue)[6,23] (Figure 21.1), or as ectopic fat in cardiomyocites.[24,25] Intrathoracic fat increases proportionally with BMI (Figure 21.1), and as for VAT, for the same BMI, women tend to have less fat accumulated around the heart than men (Figure 21.2).[6] After weight gain cardiac fat increases,[26] and it decreases, along with other fat depots, after weight loss[27–29] and/or regular exercise.[30] However, fat accumulation inside the epicardial sac is limited,[31] and thus as subjects become more obese the major increase is shown in the extra-pericardial site; it constitutes the majority of fat around the heart[6] (Figure 21.1). Although intrathoracic adipose tissue is higher in men, the proportion of epicardial/intrathoracic adipose tissue and extra-pericardial/intrathoracic adipose tissue is similar in the two genders (Table 21.1). Both epicardial and extra-pericardial adipose tissue correlate with increased VAT.[9,32,33] As subjects become more obese, fat accumulates not only around the heart but also as intramyocardial triglycerides, although not extensively.[24,25] Increased intramyocardial triglyceride accumulation was found to be associated with increased intrathoracic and visceral fat.[34] In healthy subjects intramyocardial triglyceride content is not fixed but varies depending on nutritional conditions, whereas in patients with type 2 diabetes (T2DM) and heart failure intramyocardial triglycerides are often increased.[24,35]

21.2.2 Adipose Tissue Accumulation, Lipolysis, and Lipotoxicity

Fat is stored as triglycerides within discrete lipid droplets in subcutaneous and visceral adipocytes. The overall triglyceride content within these droplets is ultimately dependent on the balance between the rates of triglyceride hydrolysis and fatty acid uptake, oxidation, and storage. Fat is mobilized by the activation of lipolytic enzymes, which degrade triglycerides and release free fatty acids (FFAs) into the circulation for use as an energy substrate. From a systemic viewpoint, fatty acids can be derived from both intracellular and extracellular sources and, with the exception of adipose tissue, the latter are most prevalent because of limited intracellular stores. Several isoforms of lipases have been discovered, from circulating lipases such as lipoprotein lipase (LPL) and hormone-sensitive lipase to

TABLE 21.1
Different Fat Distribution and Ectopic Fat Accumulation in Men and Women

Reference		Number of Cases (Men/Women)	Men Mean (Range)	Women Mean (Range)	*p* Value Men vs. Women
3	Body weight (kg)	139/155	78 (56–117)	66 (44–117)	N/A
	BMI (kg/m^2)	139/155	27.5 ± 3.5	26.0 ± 4.5	N/A
	TAT (kg) % Body weight	139/155	20 (8.4–39.5) 15%–41%	22 (7.6–53.4) 18%–53%	N/A
	Total SAT (kg) % TAT	139/155	15 (6.8–30.3) 62%–91%	20 (6.8–46.4) 77%–95%	N/A
	VAT (kg) % TAT	139/155	5.0 (1.3–9.7) 9%–38%	2.7 (0.7–7.0) 5%–23%	N/A
2	BMI (kg/m^2)	243/234	27.3 (18.6–44.5)	26.2 (15.5–57.3)	<.05
	Total SAT (kg)	243/234	19 (4.2–58.8)	27 (7.3–90.5)	<.001
	Abdominal SAT (kg)	243/234	5.3 (0.7–20.2)	7.6 (1.5–29.7)	<.001
	VAT (kg)	243/234	3.5 (0.2–9.4)	2.3 (0.4–9.6)	<.001
	Liver (%)	243/234	6.8% (0%–89%)	2.9% (0%–65%)	<.0001
	S-IMCL	243/234	15.5 (2.9–100)	11.5 (2.3–51)	<.0001
	T-IMCL	243/234	6.3 (0.2–30)	6.7 (1.0–35)	NS
6	BMI	94/19	27.3 (18.4–38)	27.2 (19.5–40.4)	NS
	Abdominal SAT (kg)	94/19	2.9 (0.9–6.7)	4.2 (0.6–8.3)	<.002
	VAT (kg)	94/19	1.5 (0.1–4.5)	1.1 (0.0–2.6)	<.05
	IT-AT (g) % Body fat	94/19	205 (32–471) 0.01%–0.19%	143 (35–297) 0.02%–0.09%	<.003
	EPI (g) (% IT-AT)	94/19	62 (10%–83%)	55 (17%–59%)	NS
	PAT (g) (% IT-AT)	94/19	143 (17%–90%)	88 (41%–83%)	<.002
4	BMI	522/633	28.8 ± 4.3	27.5 ± 5.5	NS
	VAT (kg)	522/633	2.3 ± 1.0	1.5 ± 0.8	<.0001
	IT-AT (g)	522/633	388	280	<.0001
	EPI (g) (% IT-AT)	522/633	126 (38%)	101 (32%)	<.0001
	PAT (g) (% IT-AT)	522/633	262 (70%)	179 (68%)	<.0001
17	BMI	40/98	35.1 (≥30)	35.0 (≥30)	NS
	Pancreatic fat (%)	40/98	8.3% ± 3.8%	6.4% ± 3.2%	<.006
	Abdominal SAT (kg)	40/98	13.3	14.9	NS
	VAT (kg)	40/98	2.5 (0.1–6.5)	1.6 (0.1–6.5)	<.0001
	Liver fat (%)	40/98	7.5% (1%–28%)	5.4% (1%–28%)	.0001

Note: EPI = epicardial adipose tissue; IT-AT = intrathoracic adipose tissue; N/A = not applicable; NS = not significant; PAT = extra-pericardial adipose tissue; S-IMCL = soleus intramyocellular lipid content; T-IMCL = tibialis intramyocellular lipid content; TAT = total adipose tissue.

intracellular forms such adipose tissue triglyceride lipase (ATGL), hepatic lipase, and endothelial lipase.[36] In particular, ATGL is responsible for the first step in the hydrolysis of triglyceride to diglyceride and circulating LPL for the hydrolysis of circulating triglyceride. Variations in the expression of LPL, hormone-sensitive lipase, and ATGL in SAT and VAT have been reported.[37] In both subcutaneous and visceral fat ATGL mRNA expression levels tended to be higher in adipose tissue of obese than lean subjects, but this increase was not related to BMI.[37] ATGL is essential for efficient triglyceride lipase activity, but ATGL protein expression is not related to triglyceride lipase activity in SAT or VAT from lean or obese subjects.

In obese subjects with increased VAT and SAT, whole-body lipolysis is increased compared to lean subjects.[38,39] In comparison with subcutaneous fat, VAT is more sensitive to catecholamine-induced lipolysis and less sensitive to insulin.[39] Visceral fat releases FFAs directly into the portal vein,[12,39] therefore explaining the close relationship between visceral, liver, and pancreatic fat.[13,40] The fatty acids released after lipolysis participate in a variety of cellular processes, including membrane biosynthesis, signal transduction, and adenosine triphosphate (ATP) production after β-oxidation. Under postprandial conditions approximately 30% of total energy expenditure is reliant on fatty acids derived from adipose triglyceride hydrolysis, and this becomes quantitatively more important with extended fasting or exercise.[41] In cases of caloric surplus leading to obesity, elevated circulating fatty acids may contribute to the accumulation of ectopic fat,

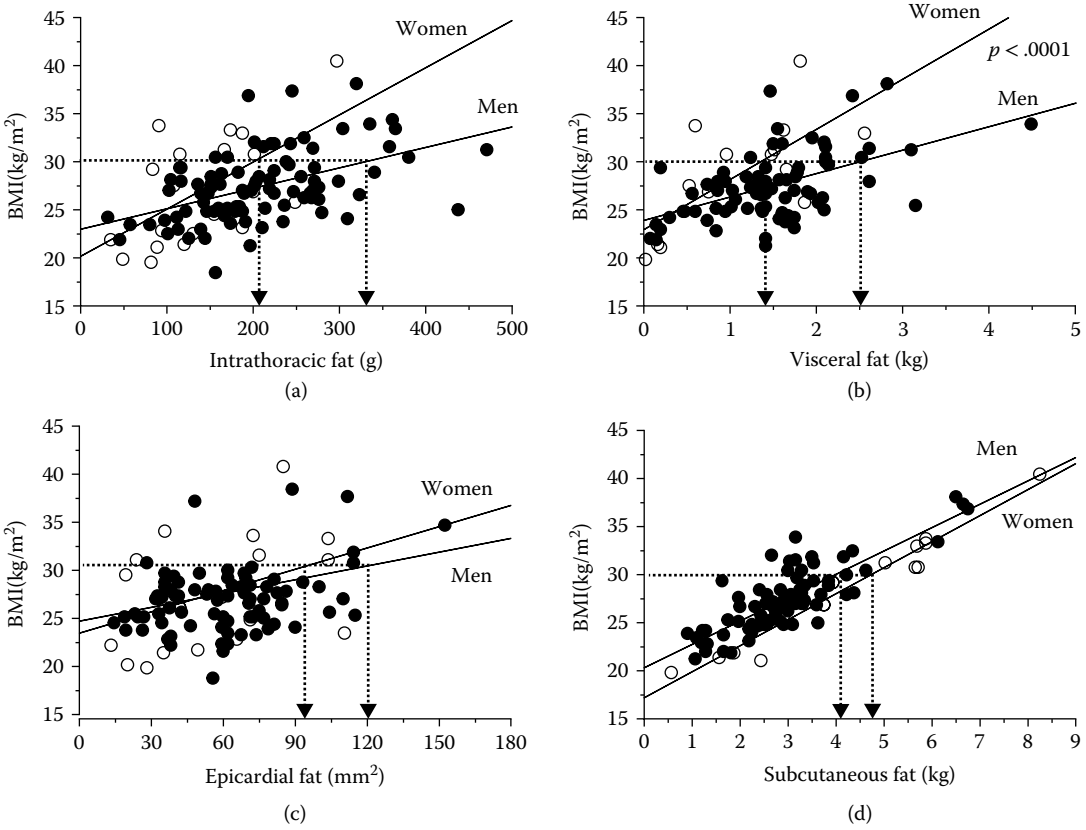

FIGURE 21.2 (a) Relationship between body mass index (BMI) and intrathoracic fat in men ($r = 0.49$, $p < .0001$) and women ($r = 0.58$, $p < .0009$). (b) Relationship between BMI and visceral fat in men ($r = 0.53$, $p < .0001$) and women ($r = 0.71$, $p < .003$). (c) Relationship between BMI and epicardial fat in men ($r = 0.39$, $p < .001$) and women ($r = 0.34$, $p = .09$). (d) Relationship between BMI and subcutaneous fat in men ($r = 0.98$, $p < .0001$) and women ($r = 0.83$, $p < .0001$). The differences between slopes are significant only for visceral fat versus BMI, $p < .0001$. (Redrawn from Sironi AM et al., *Diabet. Med*., 29, 622–7, 2012.)

mainly intramyocellular and hepatic lipids, but also cardiac and pancreatic fat, which are associated with secondary metabolic complications such as insulin resistance.[41] Therefore, liberation of fatty acids from adipocyte triglyceride and their release into the systemic circulation are under most conditions the first points of control in the regulation of fatty acid metabolism and, accordingly, tight control of adipocyte lipolysis is a critical mediator of whole-body metabolic homeostasis.

In insulin-resistant conditions, the adipose tissue becomes resistant to the antilipolytic effect of insulin and the release of fatty acids is increased.[42] This results in fatty acid overloads towards other organs saturating their oxidative capacity and thus accumulating as ectopic fat. An emerging body of evidence indicates that triglyceride accumulation within ectopic tissues, such as liver, pancreas, heart, and skeletal muscle, leads to cell lipotoxicity[42,43] with the alteration of organ metabolism.[13,22,40,44]

Lipotoxicity triggers multiple cellular processes, including impaired insulin signaling,[45,46] oxidative stress,[47,48] alterations in the local renin–angiotensin system,[49] enhanced adrenergic sensitivity of vascular smooth muscle cells,[50] and mitochondrial dysfunction.[43] The first alteration caused by lipotoxicity is the impairment of insulin signaling because FFAs reduce basal and insulin-stimulated glucose uptake,[51] muscle ATP synthesis,[52] and nitric oxide production[46] and impair insulin-stimulated activation of phosphoinositol-3 kinase, pyruvate dehydrogenase kinase, isozyme 1, RAC-α serine/threonine-protein kinase (also known as proto-oncogene c-Akt), and endothelial nitric oxide synthase.[46] Moreover, FFA exposure increases cellular levels of diacylglycerols, ceramide, and long-chain fatty acyl-coenzyme A (CoA); and lipid metabolites that activate transcription factors such as nuclear factor-κB, which is involved in the inflammation processes.[53] Long-chain acyl-CoA esters directly stimulate the opening of ATP-sensitive potassium channels, leading to K^+ efflux, shortened action potentials, reduced Ca^{++} influx, and decreased contractile force.[54] Mitochondrial dysfunction increases oxidative stress and uncouples oxidative phosphorylation.

21.3 VISCERAL FAT AND ABDOMINAL ECTOPIC FAT

21.3.1 Liver Fat, Visceral Fat, and Hepatic Insulin Resistance

The liver is an important site of ectopic fat accumulation since intrahepatic triglyceride (steatosis) leads to nonalcoholic fatty liver disease (NAFLD), which can progress to nonalcoholic steatohepatitis, cirrhosis, and/or hepatocellular carcinoma.[18]

VAT accumulation is strongly related to intrahepatic triglyceride and NAFLD.[13] Subjects with NAFLD, even when not obese and without the metabolic syndrome, tend to have a preferential accumulation of visceral fat.[13] This phenomenon is more prevalent in male subjects (Table 21.1) and is increased with obesity and with diabetes.[13,55,56] VAT can have a direct effect on the development of hepatic insulin resistance observed in subjects with NAFLD. Studies in humans have shown that upper body obesity is associated with increased FFA release and impaired suppression of lipolysis during insulin infusion.[41] Visceral fat is highly lipolytic and releases FFAs directly into the portal vein and thus into the liver.[12,39] Thus, in upper body obesity portal FFA concentrations, resulting from both systemic and VAT lipolysis, may be significantly greater than arterial FFA concentrations, exposing the liver to even greater amounts of FFAs. Thus, VAT could be one of the causes of liver steatosis through portal overload of FFAs.[13,39,41]

Fatty acid overload is also related to hepatic insulin resistance, and subjects with increased VAT[13,57] and with NAFLD[58] both have increased rates of gluconeogenesis (GNG) (Figure 21.3). Physiological elevation of plasma FFA levels stimulated GNG during an extended overnight fast, whereas decreasing FFA levels inhibited GNG in both diabetic and control subjects.[59] However, an increase in GNG does not always translate into an increase in endogenous glucose production because of "hepatic autoregulation,"60 which, by decreasing glycogenolysis, maintains endogenous glucose production within normal ranges. While hepatic autoregulation is maintained, glucose concentrations remain within normal levels. When fasting hyperglycemia starts to develop, endogenous glucose production increases and is proportional to GNG.[61]

Intrahepatic triglyceride and VAT appear to contribute differently to metabolic function.[56] Subjects with similar VAT show altered hepatic, adipose tissue, and muscle insulin sensitivity only when they also have increased intrahepatic triglyceride (Figure 21.3).[56] Moreover, VAT reduction by omentectomy does not further improve peripheral and hepatic insulin sensitivity (Figure 21.3).[62] Although a correlation is found between intrahepatic triglyceride and VAT and peripheral glucose clearance,[13,16,63] it is unlikely that intrahepatic triglyceride and VAT could contribute directly to muscle insulin resistance, except through cytokines released by the dysfunctional tissues. On the other hand, subjects with NAFLD have an increased very-low-density lipoprotein (VLDL) triglyceride secretion rate, but elevated FFAs also stimulate VLDL triglyceride production in the face of hyperinsulinemia.[41] No difference in VLDL triglyceride secretion was observed between subjects with different VAT volumes, matched on intrahepatic triglyceride content.[56]

Subjects with NAFLD are also at high risk of developing T2DM and cardiovascular diseases, possibly because of the associated risk factors, in particular obesity and insulin resistance. Moreover, they also accumulate cardiac,[20] pancreatic,[17,40] and muscle fat.[21] NAFLD is associated with increased insulin resistance at the level of muscle and adipose tissue,[13,64] decreased insulin clearance,[13,16] and impaired cardiac metabolism[20] and is now considered the hepatic manifestation of metabolic syndrome (Figure 21.3). Recently, it has been reported that subjects with increased intrahepatic triglyceride levels have elevated levels of plasma biomarkers of inflammation, endothelial dysfunction,[65] and early carotid changes[66] even when they do not have diabetes and hypertension.[67] Carotid intima-media thickness was found to be different according to liver disease: the lowest values were observed in controls, the intermediate values in patients with hepatitis B virus or hepatitis C virus, and the highest values in those with NAFLD.[66] The associations between liver disease and carotid atherosclerosis are independent of classical risk factors, metabolic syndrome components, and insulin resistance,[66,68–71] indicating that other factors might be involved. Moreover, NAFLD is associated with greater overall mortality and independently predicts the risk of future cardiovascular disease events.[72] Overall, the current body of evidence strongly suggests that NAFLD is associated with increased cardiometabolic risk and raises the possibility that NAFLD may be not only a marker but also an early mediator of atherosclerosis.[66]

21.3.2 Pancreatic Fat, Visceral Fat, and Impaired β-Cell Function

Ectopic triglyceride accumulation in the pancreas has been recently shown in humans using imaging techniques and has been related to alterations in glucose metabolism and insulin secretion.[17,22,40,73] As for other ectopic fat depots, pancreatic fat is increased with BMI, is found more frequently (25%) in men than in women (Table 21.1), and is associated with the presence of ectopic fat in other depots.[17,40]

Intrapancreatic triglyceride accumulation could be related to impaired insulin secretion and β-cell dysfunction. In vitro studies have shown increased pancreatic triglyceride deposition after incubation of human pancreatic islets with FFAs.[74] This also resulted in a defect in insulin secretion and decreased insulin content and glucose-stimulated insulin release.[74] In subjects with a family history of T2DM, a sustained physiological increase in plasma FFAs impaired insulin secretion in response to mixed meals and to intravenous glucose; this suggests that β-cell lipotoxicity may play an important role in the progression from normal glucose tolerance to overt hyperglycemia in subjects at high risk of developing T2DM.[75] Imaging studies have proved that pancreatic fat is increased in subjects with impaired fasting glucose and/or impaired glucose tolerance independently of BMI,[73] and intrapancreatic triglyceride is inversely related to β-cell function measured by the disposition index (i.e., the insulin product of insulin secretion and insulin sensitivity).[73] These results were confirmed by another study that showed an association between pancreatic fat and impaired insulin secretion in response to an oral glucose tolerance test (measured as incremental area under the curve of insulin to glucose), but this was true only in impaired fasting glucose/impaired glucose tolerance subjects.[40] In a 2010 study in Zucker diabetic fatty rodents, fat accumulation in the exocrine and endocrine pancreas preceded the onset of T2DM, peaking at 10 weeks of age when hyperglycemia

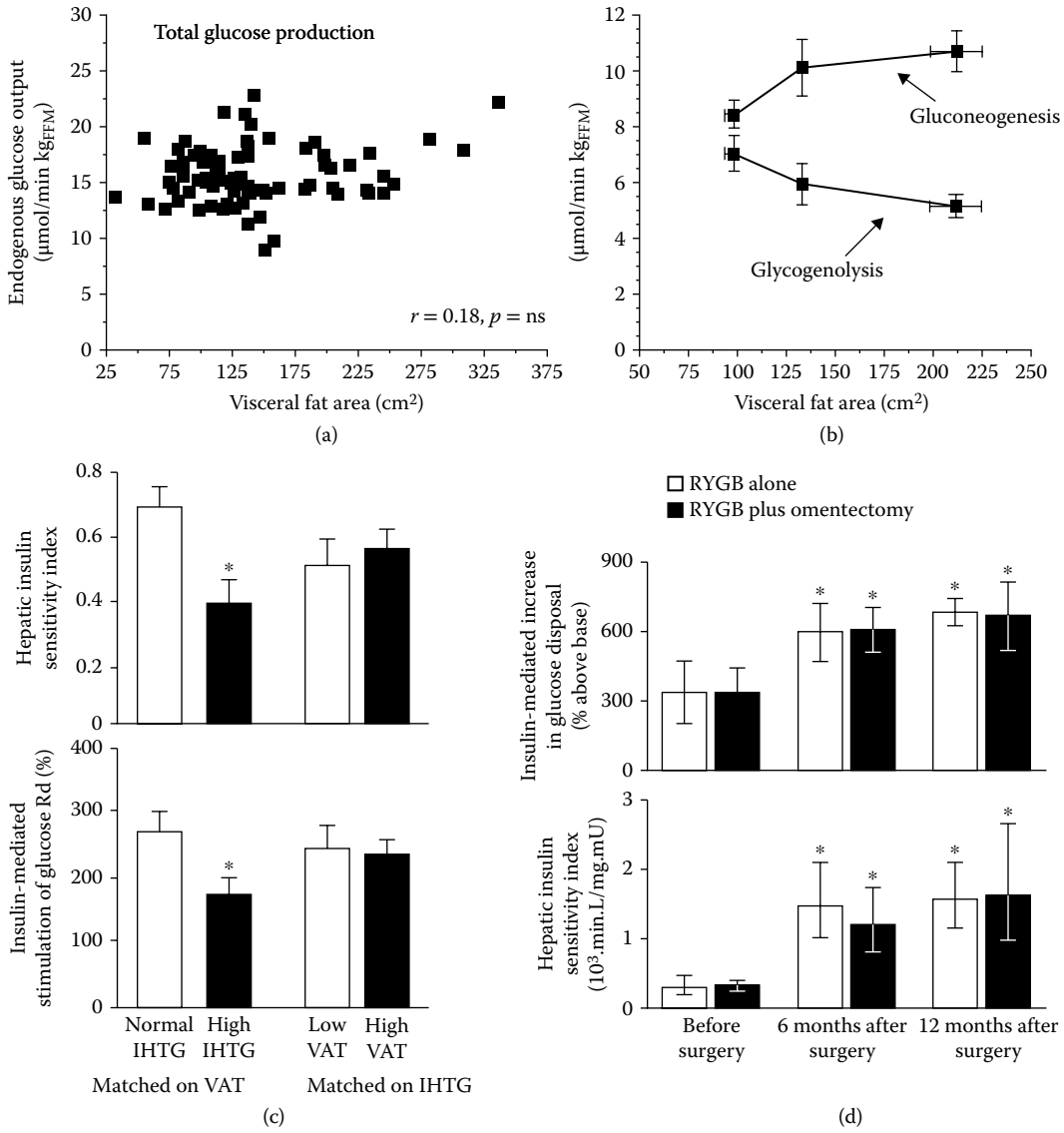

FIGURE 21.3 Relationship between visceral and hepatic fat and insulin resistance. (a) Total endogenous glucose production (EGP) is given by the sum of gluconeogenesis and glycogenolysis. (b) shows that subjects with increased visceral fat have a proportional increase in gluconeogenic rate. However, hepatic autoregulation maintained total EGP within normal ranges (a) by decreasing glycogenolysis (b). (Reproduced from Gastaldelli A et al., *J Clin Endocrinol Metab*, 87, 5098–103, 2002. With permission.) (c) Hepatic and skeletal muscle insulin sensitivity in subjects matched on visceral adipose tissue (VAT) volume with either normal or high intrahepatic triglyceride (IHTG) content and subjects matched on IHTG content who had either low or high VAT volume. Rd = rate of disappearance. (Reproduced from Fabbrini E et al., *Proc Natl Acad Sci*, 106, 15430–5, 2009. With permission.) (d) Hepatic and skeletal muscle insulin sensitivity at baseline, 6 months, and 12 months after Roux-en-Y gastric bypass (RYGB) surgery, alone or in combination with omentectomy. (Reproduced from Fabbrini E et al., *Gastroenterology*, 139, 448–55, 2010. With permission.)

first appeared.[76] Although no epidemiological data in humans have shown a direct link with diabetes, it is clear that intrapancreatic triglyceride could modify insulin response and be implicated in the pathophysiology of β-cell dysfunction.

A direct role of visceral fat in β-cell function is still a topic of debate. Portal FFAs could be implicated in intrapancreatic triglyceride accumulation, and intrapancreatic triglyceride has been found to be positively associated with VAT, SAT, intrahepatic triglyceride, and waist circumference after adjustment for age and gender.[17,40] Although insulin secretory response to a glucose load is increased in nondiabetic subjects with VAT accumulation, this is a response to fully compensate for the insulin resistance, but the dynamics of β-cell function (glucose sensitivity, rate sensitivity, and potentiation) in these subjects are largely preserved.[8]

21.4 VISCERAL AND ECTOPIC MUSCLE FAT: INTRAMYOCELLULAR FAT, VISCERAL FAT, AND PERIPHERAL INSULIN RESISTANCE

There is substantial evidence supporting the notion that excessive VAT is predictive of peripheral insulin resistance and the presence of related metabolic abnormalities commonly referred to as the metabolic syndrome (Figure 21.4).[12,13]

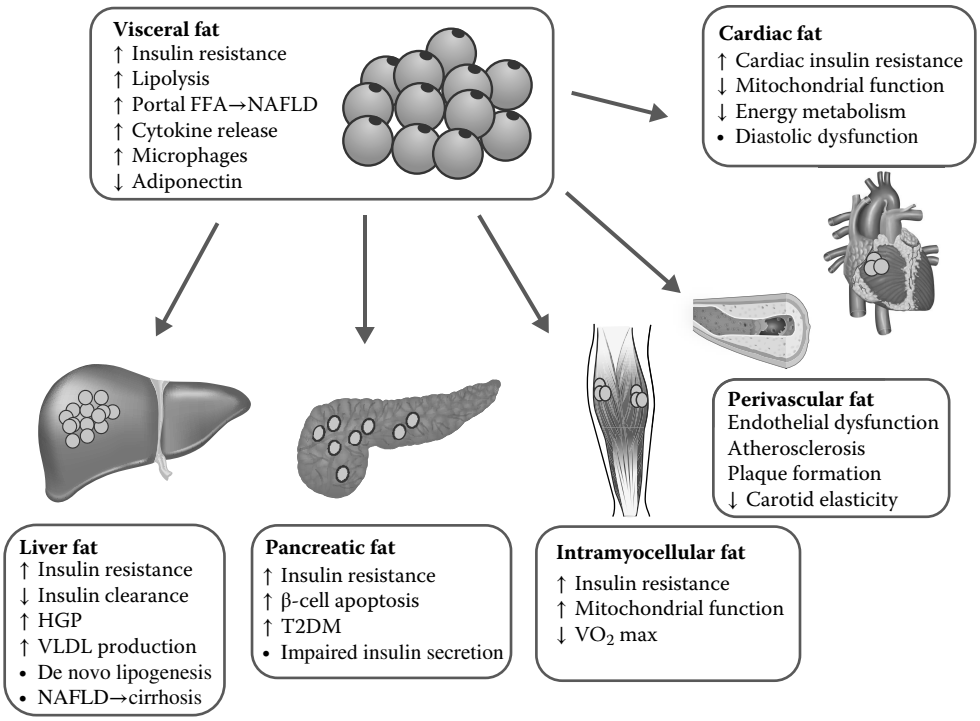

FIGURE 21.4 Accumulation of fat as visceral adipose tissue is related to the accumulation of fat in other organs, leading to lipotoxicity and metabolic dysfunction: HGP, hepatic glucose production; VO_2 max, maximal oxygen uptake.

However, the mechanisms by which abdominal obesity is causally related to the metabolic syndrome and impaired peripheral insulin sensitivity are not fully understood. Despite the strong association found between visceral fat and muscle insulin resistance, VAT does not seem to have a direct role in the development of peripheral insulin resistance.[12] In fact, despite visceral fat accounting for as much as 38% of total fat in some extreme cases (Table 21.1),[2,3] it is unlikely that FFAs released by VAT are responsible for increased intramyocellular lipid (IMCL) content. On the other hand, adipokines secreted by VAT can impair muscle insulin signaling and thus increase the risk of muscle insulin resistance.

Studies employing magnetic resonance spectroscopy have highlighted the fact that obese subjects also have ectopic accumulation as intra- and intermuscle triglycerides.[2] Triglycerides stored within muscle fibers were found to be strongly correlated with the severity of insulin resistance,[77] and it was further observed that IMCL was related to muscle lipotoxicity, mitochondrial dysfunction,[78] and impaired glucose metabolism.[77,79] IMCL is differently distributed among muscles and, in general, is higher in soleus muscle than in tibialis muscle[2] (Table 21.1). In healthy subjects, it was shown that acute changes in plasma FFAs (i.e., 4 hours of infusion of intralipid during euglycemic hyperinsulinemic clamp) were accompanied by corresponding changes in IMCL and the development of insulin resistance.[51] However, increased IMCL has also been observed in insulin-sensitive athletes in whom the lipid droplets likely serve as a readily mobilized energy substrate during exercise.[80] The explanation for this paradox is probably the difference in mitochondrial density and/or function that could balance fatty acid uptake and oxidation. The reduced adaptation of fuel oxidation to altered nutrient availability is termed "metabolic inflexibility" and has been associated with the accumulation of lipids within muscle cells and with insulin resistance.[44] Indeed, it was shown that a physiological increase in plasma FFA concentrations reduced insulin-stimulated muscle ATP synthase flux in parallel with the induction of insulin resistance.[52]

Another potential explanation for this paradox could be in the site of IMCL droplets. Morphological analyses have shown different contents of lipids, glycogen, and mitochondria in the subsarcolemmal and intermyofibrillar regions of muscle fibers.[81] Patients with T2DM had higher lipid deposition in the subsarcolemma compared with obese controls and endurance-trained subjects, whereas no difference was found in intermyofibrillar lipids or in volume, density, and localization of mitochondria and glycogen.[82] However, the amount of subsarcolemma lipids correlated negatively with muscle insulin sensitivity and, after training, subsarcolemma mitochondria and subsarcolemma glycogen increased while subsarcolemma lipids decreased in parallel with the improvement in insulin sensitivity.[82] These findings are in agreement with previous studies that showed the content of subsarcolemma mitochondria increased more than that of intermyofibrillar mitochondria following endurance training.[83]

21.5 VISCERAL AND INTRATHORACIC FAT

21.5.1 Epicardial, Mediastinal, and Visceral Fat

In the thoracic area, adipose tissue can significantly accumulate around the heart, that is, within the pericardial sac (named epicardial adipose tissue) or outside the pericardium (named

mediastinal or extra-pericardial adipose tissue)[6,23] (Figure 21.1). Epicardial fat is located over both ventricles and accounts for approximately 20% of the total ventricular mass[84] (Table 21.1). As the amount of epicardial fat increases, it progressively fills the space between the ventricles, sometimes covering the entire epicardial surface. No structures resembling a fascia (as found on skeletal muscle) separate the adipose and myocardial layers, but rather the epicardial fat covers the adventitia of the coronary artery branches. Although the left ventricular fat mass far exceeds the mass of the right ventricle, the absolute amount of fat tissue was similar in the right and left ventricles.[84] Overall, there appears to be a close functional and anatomic relationship between the adipose and muscular components of the heart that share the same coronary blood supply.[85]

Both epicardial and extra-pericardial adipose tissue are correlated with visceral fat accumulation[4,6,33] and have been proposed as markers of visceral fat accumulation.[85] As for VAT, a positive correlation was found for both epicardial and extra-pericardial adipose tissue with insulin resistance, increased triglyceride and blood pressure, and in general metabolic syndrome.[6,32,33] However, the parallel increase in epicardial adipose tissue and VAT is just an indication of the increase in fat accumulation, while a cause–effect relationship between epicardial adipose tissue and VAT is unlikely. Initially, such a relationship was proposed since epicardial adipose tissue and VAT share the same embryonic origin.[23] However, human coronary adipocytes are smaller and more irregularly shaped compared with adipocytes derived from subcutaneous and visceral (perirenal) adipose depots and exhibit a reduced state of adipocyte differentiation.[86] Epicardial adipocytes secrete lower levels of adiponectin and higher levels of proinflammatory cytokines IL-8 and IL-6.[33] Moreover, although intrathoracic fat, in particular epicardial adipose tissue, could play a significant role in cardiac metabolism because of its anatomical position, it is unlikely that visceral fat could directly influence heart metabolism or ectopic cardiac deposition. In intervention studies, that is, studies on weight loss and weight gain, after weight loss due to a very-low-calorie diet a parallel decrease was seen in both epicardial and visceral fat, but after weight regain visceral fat returned to previous levels while the reduction in epicardial adipose tissue was maintained[87]; this indicates that the two depots have different turnovers.

Experimental and clinical observations suggest both unfavorable and favorable effects of epicardial and perivascular adipose tissue. The close anatomical relationship between epicardial adipose tissue and the adjacent myocardium should readily allow local paracrine interactions between these tissues. Since epicardial fat covers the adventitia of coronary arteries, it is likely that adipokines and other factors are released into the cardiac bloodstream, participating also in the mechanism of contraction and relaxation of these vessels. Cardiac fat, in particular epicardial fat, has been associated with coronary calcification measured by computed tomography.[4,88,89] It has been suggested that epicardial fat could locally modulate the morphology and function of the heart.[9,90] During the hypertrophic process, the ventricular fat and the underlying myocardium show a parallel and correlated increase in their masses,[84] with a constant ratio of fat to muscle in each ventricle. And this is not influenced by the presence of ischemia.[84] Overall, these studies indicate that cardiac adiposity may play an important role in the development of an unfavorable cardiovascular risk profile and be implicated in the development of coronary artery disease.

21.5.2 Intramyocardial Fat, Visceral Fat, and Cardiac Metabolism and Dysfunction

Subjects with insulin resistance have increased fat deposition not only around the heart (epicardial + intrathoracic fat) but also in intramyocardial cells.[5,9,20,91] As subjects become more obese, fat accumulates not only around the heart but also as intramyocardial triglyceride, although in limited amounts.[24,25] However, most of the studies on cardiac fat measure epicardial and/or extra-pericardial adipose tissue[92] using imaging techniques such as ultrasound, computed tomography, and MRI, whereas the measurement of intramyocardial triglyceride requires magnetic resonance spectroscopy, which is not commonly available. Increased intramyocardial triglyceride accumulation has been found to be associated with increased intrathoracic and visceral fat[34] as well as with cardiac dysfunction.[24,25,35] Intramyocardial triglyceride accumulation is quite fast, and it may occur within 6 hours in the presence of combined hyperglycemia and hyperinsulinemia.[93] In healthy subjects intramyocardial triglyceride is not fixed but varies depending on nutritional conditions, whereas in patients with T2DM and heart failure intramyocardial triglyceride is often increased.[24,35] Metabolic interventions can change fat distribution, as well as act on cardiac function. For instance, short-term caloric restriction dose dependently increases myocardial triglyceride content with a parallel decrease in left ventricular function,[92] whereas a single high-fat meal does not affect myocardial triglyceride stores.[25,92] Whether cardiac steatosis plays a direct role in heart disease in human beings still remains an unanswered question. Animal models have shown that fatty acid overload results in intramyocardial triglyceride accumulation, cellular lipotoxicity, and impairment in cardiac energy metabolism.[94] In particular, in animal models abnormalities in cardiomyocyte mitochondrial energetics appear to contribute substantially to the development of cardiac dysfunction.

The available studies do not imply causality but suggest that accumulation of myocardial triglyceride may be at least an indirect marker of early cardiac dysfunction. We cannot exclude the possibility that cardiac fat is simply a consequence of fatty acid overload, progressing more rapidly after saturation of the cardiac muscle oxidative capacity. Indeed, in patients with dilated cardiomyopathy there is a preferential utilization of carbohydrates, probably due to an impairment in fatty acid oxidation, a reduced blood flow, a lower oxygen consumption at rest, and an impaired ability to increase glucose uptake during stress.[95] Under these circumstances, triglyceride accumulation may be seen as a maladaptive defense response, initially serving as a fatty acid sink to circumscribe the formation of toxic lipid species.[24]

21.5.3 Visceral Fat and Perivascular Fat

Perivascular adipose tissue (i.e., fat accumulation around blood vessels) is another site of adipose tissue accumulation, although small in proportion to total adipose tissue, and is elevated with obesity.[96] Perivascular adipose tissue is a thin sheet of adipose tissue, which consists of adipocytes and stromal cells including fibroblasts, leukocytes, stem cells, and capillaries present in different but significant amounts around blood vessels. Known locations of perivascular adipose tissue include the aorta (periaortic adipose tissue) and the microvascular beds of the mesentery, muscle, kidney, and adipose tissue.[97] Given its close anatomical position to coronary vessels,[84] epicardial fat could also be considered a sort of perivascular fat.

For a long time, perivascular fat was considered to provide mechanical support for any blood vessel it surrounds. Recent studies, however, have clearly shown that these adipocytes are an important source of adipocytokines as well as typical inflammatory cytokines, which regulate vascular function.[96,98,99] Perivascular adipose tissue may affect vascular function in a paracrine manner, as perivascular fat cells secrete vascular relaxing factors, proatherogenic cytokines, and smooth muscle cell growth factors.[86,99] Recent studies have confirmed the inhibitory action of perivascular fat on aortic and mesenteric contractile responses to a variety of vasoconstrictors, and the anticontractile effect is directly dependent on the amount of adipose tissue.[100]

Some of the paracrine factors released from perivascular adipose tissue such as adiponectin have been identified as novel vascular relaxing factors derived from the adipose tissue, which could thus act protectively against hypertension and other vascular-related disorders.[86,96,100] The exact mechanisms of vasorelaxant actions of adiponectin are incompletely understood. It was recently proposed that the role of perivascular fat in the regulation of vascular function might be mediated by the central nervous system, which regulates adipose tissue metabolism and adipocytokine release.[100] In fact, sympathetic nervous system endings are present not only in VAT but also, even more abundantly, in perivascular fat.

21.6 SUMMARY

From a metabolic standpoint, fat accumulation has double-edged consequences. On the positive side, it provides a safe repository for excess calories and glucose. On the negative side, it impairs the ability of body tissues to respond to insulin and can lead to mitochondrial dysfunction and impairment in energy production. The balance between the two sides may differ among subjects, but is influenced by age, gender, and ethnicity, thereby influencing individual disease risk. Furthermore, beyond some limit, the body reacts to excess fat as a foreign body, and fat deposition in undesirable sites (VAT and intrathoracic adipose tissue, liver, heart, pancreas, and muscle triglycerides) translates into a risk level well beyond the amount of fat itself (Figure 21.4). These relationships are still incompletely understood and need further research. Thus, there is now a compelling need to quantify ectopic fat accumulation not only for diagnostic purposes but also for therapeutic interventions with weight reduction, drugs, or pharmaceuticals targeted to adipose tissue, as well as antiobesity medications.

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22 Skeletal Muscle Metabolism and Obesity

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CONTENTS

22.1 INTRODUCTION

With obesity, there are multiple and complex aberrations in cellular metabolism that lead to increased health risk. In the reference male (75 kg), approximately 40% of body mass is skeletal muscle, whereas in the reference female (58 kg), this tissue contributes approximately 29% of total body mass. Even with severe obesity, muscle contributes approximately 25% of total body weight. Skeletal muscle, by virtue of its predominance and capacities for energy production and storage, can therefore dramatically influence whole-body metabolism. This chapter describes alterations in protein, carbohydrate, and lipid metabolism that are evident in skeletal muscle with obesity. It also discusses how muscle in and of itself sends signals through myokines that can influence substrate utilization and storage.

22.2 PROTEIN METABOLISM AND OBESITY

Skeletal muscle is a major component of resting energy expenditure. The energy cost of protein synthesis, which scales with muscle mass, is estimated to range from 485 kcal/day in a young male to 120 kcal/day in an elderly woman.[1] Additionally, protein degradation, particularly by the proteasome, consumes a large amount of energy.[2] While the exact amount of ATP required during degradation will vary, more than 300 ATP molecules may be required per molecule of protein degraded.[3] Taken together, skeletal muscle is a major energy-consuming tissue.

22.2.1 Relationship between Fat Mass and Lean Mass

The greater body mass of obese individuals is composed of additional fat and lean mass.[4] However, these increases are not directly proportional. In a classic study by Forbes, the amount of lean body mass plotted against fat mass formed a logarithmic curve,[5] meaning that as fat mass increased, lean mass increased in smaller and smaller increments. One possible explanation for this relationship is that the increased body mass associated with obesity places a greater load on skeletal muscle and therefore imparts a training effect (analogous to resistance training) to increase muscle mass and strength. Evidence in support of this is that maximal leg and trunk strength, but not handgrip and arm strength, has been shown to be greater in obese than in lean individuals.[6,7]

However, not all obese individuals have increased amounts of muscle mass. In fact, 5%–10% of the elderly are both obese and have low levels of muscle mass,[8,9] a condition referred to as sarcopenic obesity. These individuals are at much greater risk for disability[10] and mortality.[11,12]

Unfortunately, individuals with sarcopenic obesity are not easily identified because they may have normal or near-normal body mass.[13] The triggers that induce the accumulation of body fat but the loss of muscle mass are not understood.

22.2.2 Muscle Protein Metabolism and Obesity

Evidence is mounting that protein metabolism is altered with obesity. As skeletal muscle is the major reservoir of amino acids (AA), plasma AA concentrations are a general indicator of muscle protein metabolism. In humans, plasma AA, especially branched-chain AA, have been shown to be increased in obese compared to lean individuals,[14–16] indicating that AA are released from muscle at a greater rate (through protein degradation) and/or AA are taken into muscle at a slower rate (through slower protein synthesis).[15] Such a mechanism may be fostered, at least in part, by a change in the activity of enzymes that metabolize AA.[17]

Numerous studies have measured whole-body protein turnover more directly, but results are inconsistent. As recently summarized by Katsanos and Mandarino,[18] whole-body protein turnover in the basal/postabsorptive state in obese individuals is either elevated[14,19] or the same[20–22] as in lean individuals. The reason for the differences between studies is not clear but may be related to how data are normalized, as protein kinetics on an absolute whole-body basis are always greater with obesity.[18]

In agreement with the inconsistent findings on whole-body protein turnover, measures of protein synthesis have also been discordant. Under insulin-stimulated conditions, whole-body protein synthesis has been shown to be decreased with obesity[14,21] or the same.[20] However, some of these findings may be complicated by the higher levels of plasma AA in obese individuals, which by themselves stimulate protein synthesis.[23] After clamping plasma branched-chain AA concentration in one study, it became clear that obese subjects were resistant to insulin's actions to induce protein synthesis.[14]

Whole-body protein degradation during insulin-stimulated conditions follows a similar pattern to that of protein synthesis. In obese individuals, whole-body protein degradation rate has been found to be the same[14,20,24,25] or higher.[20,26] As insulin typically depresses the rate of protein degradation, the higher rate found in those with obesity is consistent with their muscle being resistant to insulin's actions. Unfortunately, direct measures of muscle-specific protein degradation are lacking.

With these findings, it is tempting to conclude that the skeletal muscle of obese individuals cannot respond to physiological cues to modify rates of protein metabolism. In support of this, Patterson et al. demonstrated that the rate of protein degradation during fasting (when protein degradation is greatly accelerated) was much slower in those with obesity.[22] Furthermore, studies in rodents have shown that obesity blunts the increases in mass,[27] protein synthesis,[28] and protein degradation[28] associated with the mechanical overload of skeletal muscle. This lack of "metabolic flexibility," which is defined as appropriately altering energy utilization in response to changes in fuel availability,[29] is akin to conditions seen in both carbohydrate (i.e., insulin resistance) and lipid (fatty acid oxidation [FAO]) metabolism with obesity (discussed in Sections 22.3 and 22.4).

22.3 CARBOHYDRATE METABOLISM AND OBESITY

22.3.1 Insulin Signal Transduction is Depressed with Obesity

Approximately 75% of the carbohydrate in a meal goes to skeletal muscle for disposal, making this tissue essential for the maintenance of postprandial glucose homeostasis. Insulin action in muscle starts with binding of insulin and subsequent activation of intrinsic tyrosine kinase in the beta subunit of the insulin receptor (Figure 22.1). The insulin receptor phosphorylates a number of intracellular proteins on tyrosine residues to initiate the signaling process. Insulin receptor substrate 1 (IRS-1), when tyrosine phosphorylated, becomes a docking protein for phosphatidylinositol 3-kinase (PI3K), leading to the formation of phosporylated inositol, which in turn activates phosphoinositide-dependent protein kinase (PDK) and subsequently Akt (a serine/threonine-specific protein kinase also known as protein kinase B) and atypical protein kinase C zeta (aPKCζ). Activation of this pathway stimulates the movement of insulin-sensitive glucose transporters (GLUT4, glucose transporter type 4) to the cell surface membrane, with a subsequent increase in glucose transport (Figure 22.1).

To investigate mechanisms of insulin resistance, a strip preparation was developed in rectus abdominus muscle removed during elective surgery.[30] Metabolic processes, such as glucose transport, glycolysis, and glycogen synthesis, were then studied under controlled conditions in the presence and absence of insulin. Using this in vitro system, it was confirmed that insulin stimulation of glucose uptake, glycolysis, glucose oxidation, and glycogen synthesis are depressed in muscle of obese individuals,[30,31] as had been reported for in vivo metabolism. Insulin stimulation of insulin receptor tyrosine phosphorylation, IRS-1 tyrosine phosphorylation, PI3K activity, and Akt activity was depressed[32,33] in muscle from obese patients. Likewise, the tyrosine kinase activity of partially purified insulin receptor was depressed in muscle with obesity.[34]

Further studies were conducted to establish that depressed insulin signal transduction is the cause of muscle insulin resistance. In a manner similar to insulin, muscle contraction and hypoxia stimulate glucose transport by stimulating the translocation of GLUT4 to the cell membrane. When insulin-resistant muscles were stimulated by the contraction/hypoxia pathway, the response of glucose transport was completely normal,[35–37] demonstrating that the mechanisms for GLUT4 translocation were not defective in insulin-resistant muscle. It was concluded that insulin resistance is a result of depressed insulin signal transduction.

Insulin action also has been investigated in human skeletal muscle cells raised in culture (HSkMC). Muscle biopsies from lean and obese subjects are treated with collagenase for the separation of satellite cells, which are then cultured so

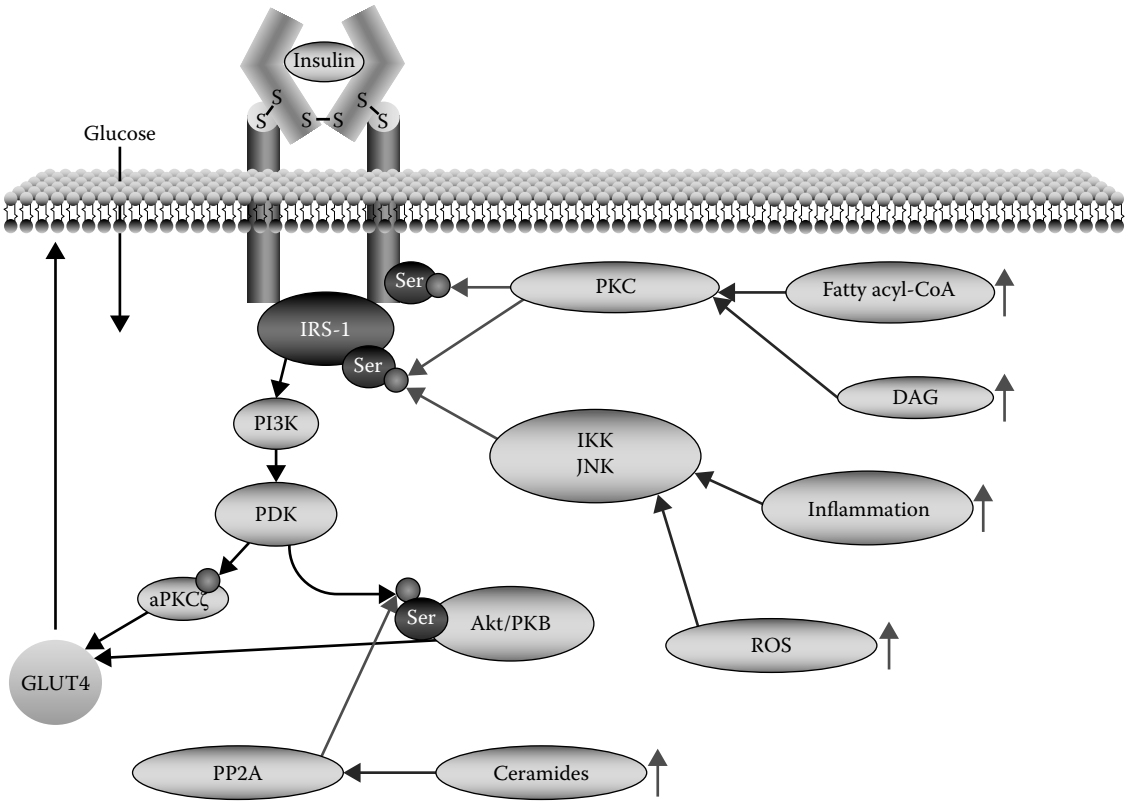

FIGURE 22.1 (**See color insert.**) Mechanism(s) of insulin resistance in muscle of obese individuals. Insulin stimulates glucose transport by first binding to its receptor, with activation of a kinase that tyrosine phosporylates IRS-1. Activated IRS-1 in turn activates PI3K and PDK. PDK activates aPKCζ and Akt through serine/threonine phosphorylation, which leads to the translocation and activation of the insulin-sensitive glucose transporter (GLUT4). The result is insulin resistance in muscle of obese individuals due to the accumulation of lipids (fatty acyl-CoA, DAG, and ceramides), inflammation, and/or the production of reactive oxygen species (ROS). These lead to the activation of kinases (PKC, IKK, and JNK) or phosphatases (PP2A). Insulin signal transduction is reduced when the insulin receptor and IRS-1 become serine phosphorylated (PKC, IKK, and/or JNK) and Akt is dephosphorylated (PP2A). Akt/PKB, protein kinase B; aPKCζ, atypical protein kinase C zeta; DAG, diacylglycerol; IKK, nuclear factor kappa-B kinase; IRS-1, insulin receptor substrate 1; JNK, c-Jun NH2-terminal kinase; PDK, phosphoinositide-dependent protein kinase; PI3K, phosphatidylinositol 3-kinase; PP2A, serine/threonine-protein phosphatase 2A activator.

that they proliferate. Myoblasts are then put into a medium that induces differentiation to myotubes (elongated, multinucleated cells with many characteristics of mature muscle tissue). HSkMC from obese subjects have been shown to have a depressed stimulation of insulin signal transduction (IRS-1 tyrosine phosphorylation and Akt phosphorylation) compared to those from lean subjects.[38,39] The fact that insulin resistance is maintained in HSkMC after several cycles of cell division and differentiation suggests that there are genetic or epigenetic changes that produce an "obesity metabolic program,"[40] which, in combination with the cellular environment (see Section 2.4), induces insulin resistance in muscle.

22.3.2 Insulin Receptor and IRS-1 Are Serine/Threonine Phosphorylated with Obesity

Because all of the steps of the insulin signaling pathway are depressed in muscle of obese individuals, it was speculated that the most proximal step might be the point where control is exerted. This was confirmed by decreased activity of partially purified muscle insulin receptors from obese people.[34,41] Serine/threonine phosphorylation of insulin receptors causes tyrosine kinase activity to be decreased; thus, receptors from obese patients were treated with a phosphatase to remove phosphate. This treatment restored receptor activity to normal.[41] This finding was interpreted as evidence that a muscle serine/threonine kinase is activated in obese subjects to phosphorylate and inactivate the insulin receptor.

Several research groups have shown that serine phosphorylation of IRS-1 may also be responsible for depressed insulin signal transduction. When serine/threonine is phosphorylated, IRS-1 has a lower affinity for its downstream binding partners, which decreases their activation by insulin. In an investigation of serine/threonine phosphorylation of IRS-1, it was found that serine-312 had significantly elevated phosphorylation in muscle of obese patients.[42] This seems to suggest that excessive serine phosphorylation of the insulin receptor and IRS-1 is a mechanism causing insulin resistance.

22.3.3 Serine/Threonine Kinases and Phosphatases

As the insulin receptor and IRS-1 are hyperphosphorylated in muscle of obese individuals (Figure 22.1), the question is, which kinase(s) and/or phosphatase(s) is/are responsible?

IRS-1 contains a large number of serine/threonine phosphorylation sites, and those have been reviewed.[43] Of the kinases that phosphorylate IRS-1, several are activated by insulin, including PKCζ, ribosomal protein S6 kinase, and mitogen-activated protein (MAP) kinase. Activation of these kinases may be the mechanism that terminates the insulin signal and also causes insulin resistance during long periods of high fasting insulin, that is, hyperinsulinemia. There is a direct relationship between hyperinsulinemia and insulin resistance, but a cause-and-effect relationship has not been established.

Kinases in signaling pathways other than insulin also demonstrate activity toward IRS-1. These include PKC, inhibitor of nuclear factor kappa-B kinase (IKK), and c-Jun NH2-terminal kinase (JNK)[43] (Figure 22.1). Research has been conducted to determine whether higher activities of the isoforms of muscle PKC may correlate with insulin resistance. In obese rats, PKCθ activity was elevated,[44] while in obese humans, PKCβ protein and activity were elevated.[41] We also investigated the role of PKC in insulin resistance with activators and inhibitors. Activation of PKC produced insulin resistance in muscle from lean patients, while inhibition of PKC enhanced insulin signal transduction in muscle of obese patients.[45] These data are consistent with PKC playing a role in muscle insulin resistance.

As several kinases can phosphorylate IRS-1, the question then becomes, what activates these kinases in insulin-resistant muscle? One molecule that activates PKC is diacylglycerol (DAG), which is a precursor of triacylglycerol. This is of interest because muscle triacylglycerol content recently has been shown to be elevated in obese individuals and to be a strong predictor of insulin resistance.[46] A cause-and-effect relationship between intracellular lipid accumulation and insulin resistance has been implied by studies in rodents and humans, in which Intralipid®/heparin was infused and the accumulation of fatty acyl-coenzyme A (acyl-CoA) and DAG was directly related to activation of PKC, serine phosphorylation of IRS-1, and impaired glucose uptake[44] (Figure 22.1).

Obesity produces a tonic, low-grade activation of the immune system, which has been proposed as a mechanism that causes insulin resistance. Inflammation is accompanied by the expression of several cytokines, including tumor necrosis factor alpha (TNFα), which may emanate from activated macrophages. TNFα binding to its receptor can lead to activation of the MAP kinase pathway and subsequently JNK1 and IKK. Activation of these kinases may cause insulin resistance and depressed insulin signal transduction through serine phosphorylation of IRS-1[44] (Figure 22.1).

Chronic overnutrition and physical inactivity, which are factors in obesity, are associated with increased production of reactive oxygen species (ROS), and these also are believed to cause insulin resistance. The link between ROS production and insulin resistance may be redox-sensitive sensor proteins containing thiol groups, which activate stress-sensitive kinases such as IKK and JNK.[47] This in turn leads to serine phosphorylation of IRS-1 and depressed insulin signal transduction (Figure 22.1).

22.3.4 Weight Loss and Exercise

This discussion of muscle carbohydrate metabolism underscores the dangers of obesity, but it is encouraging that weight loss or exercise can induce positive changes that will improve health. To investigate the effect of weight loss on insulin sensitivity, we[42] studied patients having bariatric surgery. Approximately 18 months after gastric bypass, patients were weight stable after losing approximately 50 kg. However, they were still overweight/obese with body mass index (BMI) values of approximately 30 kg/m^2. After weight loss, the patients had insulin sensitivity values approximately fourfold higher than before surgery. Interestingly, insulin sensitivity after weight loss was even higher than in weight-matched controls who were never severely obese. Loss of weight and recovery of insulin sensitivity were accompanied by decreased phosphorylation on serine 312 of IRS-1 and reduced activity of IKK.[42] Consistent with storage of intracellular fat being associated with insulin resistance, the muscle content of fatty acyl-CoAs has been shown to be reduced with weight loss.[48]

Exercise training has long been established as producing health benefits, including improved insulin sensitivity. Sedentary overweight/obese individuals were randomly assigned to 6-month exercise trials at low volume/moderate intensity, low volume/high intensity, and high volume/high intensity. All groups had improvements in insulin sensitivity, but, interestingly, the low-volume/high-intensity group had significantly less improvement than the other two groups. Changes in muscle triglycerides correlated with improvement in insulin sensitivity.[49]

22.4 LIPID METABOLISM

22.4.1 Lipid Oxidation with Obesity

An impairment in the ability to utilize lipid may contribute to weight gain and obesity. For example, individuals who exhibited a low rate of FAO, as determined from a 24-hour respiratory exchange ratio obtained in a metabolic chamber, were predisposed to subsequent weight gain.[50] Similarly, a reduced rate of whole-body FAO was predictive of weight gain in initially nonobese women during a 6-year follow-up[51] and in nonobese Caucasian men in the Baltimore Longitudinal Study of Aging.[52] A dampened ability to oxidize fatty acids was also associated with a propensity for weight regain after weight loss.[53] These and other findings[54–56] suggest that an impaired ability to utilize fatty acids to produce energy may contribute, at least in part, to positive lipid balance and ectopic lipid storage in both adipose tissue and skeletal muscle.

During fasting (postabsorptive) conditions, up to 90% of energy requirements for skeletal muscle are obtained from oxidation of fatty acids.[57] Skeletal muscle is therefore a metabolically active tissue that contributes substantially to whole-body lipid utilization. Studies utilizing a variety of techniques have reported an impaired ability for FAO in the skeletal muscle of obese subjects. In the fasted condition, obese individuals had an elevated respiratory exchange ratio and reduced

rate of FAO in muscle as determined in vivo with the leg balance technique.[58] Impairments in the ability of obese individuals to utilize plasma free fatty acids in skeletal muscle have also been reported during the fasting condition and with β-adrenergic stimulation.[59,60] With obesity, there was a decline in whole-muscle palmitate oxidation in muscle biopsy samples.[61] However, not all studies are supportive of a reduction in FAO with obesity, as equivalent or even an elevated use of lipid has recently been reported.[62,63]

The discrepancies between studies concerning lipid utilization could be due to the degree of obesity examined. Hulver et al. observed no decline in labeled palmitate oxidation in muscle strips obtained during abdominal surgery in moderately obese individuals (BMI ~ 30 kg/m^2), but a significant reduction was observed in patients with severe obesity (BMI ≥ 40 kg/m^2).[64] As indicated in Figure 22.2, the heterogeneity at the lower ranges of overweight/obesity (BMI 28–32 kg/m^2) could be interpreted to indicate that individuals with an impairment in FAO are prone to progressing to severe obesity, while a higher FAO could be protective against additional weight gain. The reduction in FAO with obesity may thus be consistent only if higher ranges of the condition are examined. In support, in severely obese individuals, declines in FAO were reported in both the rectus abdominis[64] and vastus lateralis,[65] which are two muscle groups with distinctly different locations and functions (postural vs. locomotion, respectively). FAO was also reduced with severe obesity as determined in vivo with labeled palmitate.[66] In HSkMC, a reduction in lipid oxidation was observed, which implies a relatively resilient trait with severe obesity.[38,67,68] Figure 22.3 summarizes these findings of reduced FAO with severe obesity.

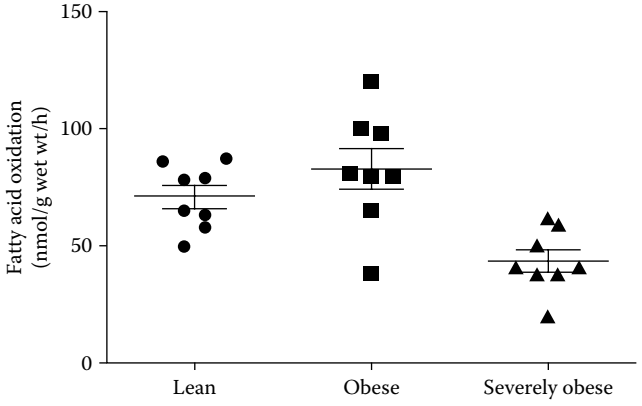

FIGURE 22.2 Relationship between body mass and fatty acid oxidation determined in muscle strips (rectus abdominus) from lean (BMI 23.8 ± 0.6 kg/m^2), obese/overweight (BMI 30.2 ± 0.8 kg/m^2), and severely obese (BMI 53.8 ± 3.5 kg/m^2) subjects. Fatty acid oxidation was significantly lower ($p < .05$) in the severely obese versus the other groups. Data are presented as individual data points with lines representing mean ± SE. The rate of palmitate oxidation is expressed in nmol/g wet weight of muscle per hour.

22.4.2 Mitochondrial Mass and FAO with Obesity

The reduction in the oxidation of fatty acids with obesity/severe obesity could be the result of fewer mitochondria, impaired mitochondrial function, or a combination of both.[69] Several pieces of data suggest that a reduction in mitochondrial content is the major factor responsible for the decrement in FAO with obesity. Studies have reported reductions in enzyme activities representative of mitochondrial content and FAO at both moderate[70,71] and higher ranges[61,65] of obesity. Holloway et al.[61] reported declines in enzymatic markers of mitochondrial content and a decline in calculated whole-muscle FAO in obese individuals. However in isolated mitochondria, FAO was not depressed, indicating that mitochondrial function was not compromised and that the decline in FAO was solely due to reduced organelle mass.[61,69] In HSkMC, indices of mitochondrial content and FAO were reduced in cells from severely obese donors.[68] When normalized to mitochondrial content, FAO was equivalent between lean and severely obese subjects, again implicating that function is normal and the reduction in FAO with severe obesity is due to lowered mitochondrial content.[68]

Skeletal muscle is a heterogeneous tissue consisting of different fiber types that are categorized by their contractile characteristics (i.e., myosin ATPase activity and myosin

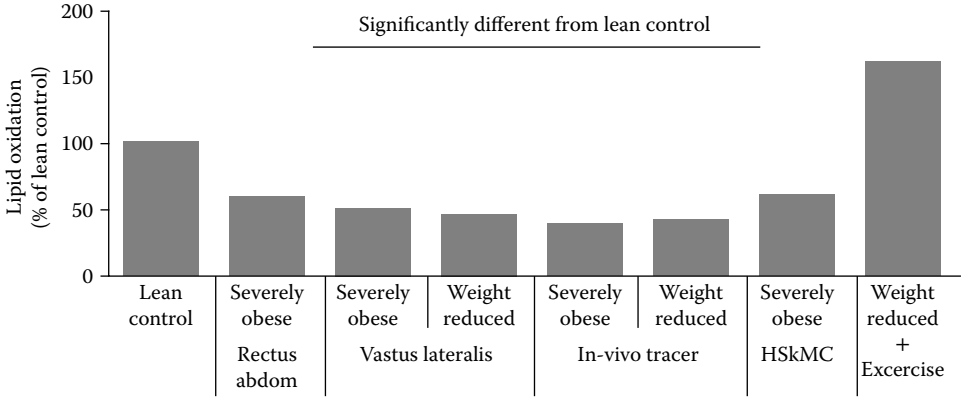

FIGURE 22.3 Decrements in lipid oxidation with severe obesity, determined using various methodologies, and inability of weight loss (weight reduced columns) to restore lipid oxidation. Only exercise training in severely obese individuals who have lost weight appears to be effective for increasing FAO (last column). HSkMC, human skeletal muscle cells raised in culture; rectus abdom, rectus abdominus muscle.

heavy chain composition). Type I, or red, muscle fibers favor oxidative metabolism, compared to type II (white) muscle fibers, because of elevated mitochondrial content. It would thus be logical to hypothesize that the reduced rate of FAO seen in obese individuals is due to an increased proportion of type II muscle fibers. However, findings are not consistent, with some studies indicating a relationship between muscle fiber type and adiposity[72–74] while others have not.[75,76] It is generally recognized that factors other than fiber type must be involved, as skeletal muscles with similar enzyme activities exhibit large differences in fiber type distribution, and interventions such as endurance training can profoundly influence enzymatic activities but not alter type I fiber distribution.[77]

22.4.3 Metabolic Flexibility

The capacity to adjust appropriately to changes in fuel availability, or "metabolic flexibility," is an important trait, as failure to increase FAO in response to elevation of dietary lipid could result in positive lipid balance and weight gain.[56] For example, in lean individuals, an isocaloric high-fat diet (HFD) was accompanied by a relatively rapid increase in FAO indicative of metabolic flexibility; in contrast, this rapid increase in FAO with an HFD was not evident with obesity and produced positive lipid balance.[56] To examine metabolic flexibility, HSkMC from lean and severely obese subjects were incubated for 24 hours with lipid, and FAO was determined with high-resolution respirometry.[78] State 3 (ADP-stimulated) respiration with palmitate as the substrate increased in HSkMC from lean subjects, indicating metabolic flexibility in response to increased lipid availability; this increase in FAO was accompanied by an elevation in mitochondrial DNA, suggesting that mitochondrial content also increased.[78] In contrast, there were no comparable responses in cells from severely obese subjects.[78] Similarly, after an HFD, the expression of genes linked with lipid oxidation and mitochondrial content such as peroxisome proliferator-activated receptor alpha and peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (*PGC-1α*, also known as *PPARGC1A*) increased in lean subjects; however, there were no concomitant changes in muscle of the severely obese.[79]

The lack of metabolic flexibility may be an underlying defect contributing to the lower FAO and mitochondrial mass evident with severe obesity, as muscle is constantly subjected to elevated lipid concentrations during conditions such as an overnight fast and dietary fat consumption. To test this premise, we overexpressed *PPARGC1A* in HSkMC and observed that FAO and indices of mitochondrial content increased in cultures from severely obese and lean donors.[68] However, both FAO and mitochondrial content remained depressed in HSkMC from the severely obese compared to the lean subjects at comparable levels of PPARGC1A, indicating an impairment in the ability to appropriately induce mitochondrial biogenesis.[68] Such data have led us to postulate that with severe obesity there is an inherent metabolic program in skeletal muscle that produces a phenotype conducive to positive lipid balance and insulin resistance.[40]

22.4.4 Weight Loss and Exercise

Studies have found that in severely obese individuals, the impairment in FAO in skeletal muscle is retained after bariatric surgery despite the pronounced decrease in body mass (~50 kg) (Figure 22.3, weight reduced bars).[66,80,81] Such data indicate not only the resilience of the impairment in FAO but also that the decrement in FAO may be a preexisting condition evident before the expression of the severely obese state. With more subtle obesity, weight loss can reduce the amount of energy derived from fat, which can render these individuals susceptible to positive lipid balance and weight regain.[55]

In lean individuals, endurance-oriented exercise training has been shown to increase FAO; however, in obese individuals, findings are discordant.[54,55] We examined severely obese individuals who had undergone gastric bypass surgery and exhibited the reduction in FAO in skeletal muscle[81] (Figure 22.3). After 10 consecutive days of endurance-oriented exercise training, FAO determined in muscle biopsy samples increased to the same extent in these previously severely obese subjects as in lean individuals performing identical training. These data indicate that endurance-oriented exercise is an effective intervention for overcoming the deficit in FAO and perhaps mitochondrial content evident with obesity/severe obesity.

22.5 MUSCLE AS AN ENDOCRINE ORGAN

Recent work has identified cytokines that are secreted from skeletal muscle, which are collectively classified as myokines. Interleukin-6 (IL-6) is a multifunctional myokine that is elevated twofold to threefold in obese individuals.[82] Surprisingly, it has been found that exercise results in a >10-fold increase in plasma IL-6, but this increase is transient.[83] These high levels may be protective against obesity, as increases in circulating levels of IL-6 resulted in an increase in lipolysis.[84] Consistent with the lipolytic nature of IL-6 is that in mice, chronic, high levels of IL-6 led to loss of fat mass[85] and loss of IL-6 led to obesity.[86] In contrast, both high and low levels of IL-6 led to insulin resistance.[85,86] Taken together, the specific role of IL-6 in whole-body metabolism and obesity is not clear.

Circulating levels of the myokine IL-15 have been shown to be lower in those with obesity and negatively correlated with BMI and fat mass.[87] IL-15 has direct effects on muscle protein metabolism, that is, high levels of IL-15 led to muscle hypertrophy.[88] High levels of IL-15 by transgenic overexpression[89] or injection of recombinant protein[90] in mice reduced fat mass and prevented the increase in fat in response to an HFD. Furthermore, the lack of IL-15 in transgenic mice led to more body fat.[90] These effects of circulating IL-15 seem to be, at least partly, due to direct actions on adipose tissue, as IL-15 can stimulate lipolysis[91] and inhibit lipid deposition[90] in adipocytes.

Myostatin (also known as growth/differentiation factor 8) is best known for its autocrine actions as a negative regulator of muscle mass.[92] However, it is becoming accepted that myostatin also has a role in obesity and overall metabolism.[93] Research has demonstrated that myostatin mRNA and

protein content are elevated in obese humans[94] and decreased with weight loss.[95] Although it is not clear what drives these changes, the high myostatin persisted in HSkMC,[94] suggesting a genetic or epigenetic origin. In mice, when myostatin was inactivated, muscle mass increased, and the animals were resistant to HFD-induced obesity.[96] Allen et al. found that both skeletal muscle and adipocytes express the myostatin receptor in mice[97]; thus, one might expect myostatin to directly control adipocyte size. However, mice with a muscle-specific inhibition of the myostatin receptor (ActRIIb) had more muscle and were resistant to HFD-induced obesity, but animals with an adipose-specific inhibition of ActRIIb had control-level amounts of muscle and gained weight in response to an HFD at the same rate as wild-type mice.[98] Therefore, it appears that the effects of myostatin on obesity are mediated, at least in large part, by the ability of myostatin to control muscle mass.

Finally, two recently discovered myokines warrant mention for their ability to affect fat cell metabolism. First, myonectin is predominantly expressed in skeletal muscle, and Seldin et al. demonstrated that its expression is suppressed by fasting and diet-induced obesity and increased by exercise.[99] Importantly, administration of myonectin to mice reduced circulating free fatty acid levels, in part by increasing fatty acid uptake into adipocytes and hepatocytes.[99] A second newly identified myokine is irisin.[100] Irisin is secreted from skeletal muscle in both mice and humans in response to exercise and is able to stimulate expression of uncoupling protein 1 and other genes in white fat cells that lead to a brown-fat phenotype. This leads to increased whole-body energy expenditure with no changes in movement or food intake. Elevated irisin is then able to improve glucose tolerance and obesity in response to an HFD.

22.6 SUMMARY

In summary, obesity influences many facets of energy metabolism in skeletal muscle. Although muscle mass is increased in obese individuals, the muscle is less responsive to insulin and other stimuli that typically alter protein metabolism. In relation to carbohydrate metabolism, obesity causes muscle insulin resistance, which is characterized by depressed insulin stimulation of glucose uptake, oxidation, and storage. This is most likely due to depressed insulin signal transduction in response to activation of several kinases that serine phosphorylate the insulin receptor and IRS-1. Weight loss and exercise may reverse insulin resistance by restoring normal activities of kinases that phosphorylate the insulin receptor and IRS-1. In respect to fat metabolism, there is evidence that FAO is depressed with obesity and particularly with severe obesity. This decrement could be due to a reduced number of skeletal muscle mitochondria and ultimately contribute to positive lipid balance and weight gain. Myokines, proteins made by and secreted from muscle, are able to alter adipocyte and whole-body metabolism. As such, myokines can have a profound effect on obesity. In conclusion, skeletal muscle appears to be intimately involved in a multifaceted and complex manner with many of the metabolic aberrations evident with obesity.

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23 Mitochondrial Bioenergetic Aspects of Obesity and Weight Loss

Mary-Ellen Harper, Robert Dent, and Ruth McPherson

CONTENTS

23.1 INTRODUCTION

The concept that some people metabolize energy sources more efficiently than others is controversial. Many debates have focused on the question is a dietary kilocalorie for one person the same for another? Relevant to this question is the fact that research in the last 20 years has shown that the efficiency of the conversion of energy substrates to useful forms of cellular energy can vary greatly.[1] The molecular origins of variable efficiency in energy transduction in the context of obesity and successful weight loss are the subject of this chapter. Our research over the last decade has identified processes in the mitochondria that may explain some of the heterogeneity in obesity risk and in the response to hypocaloric diets.

23.2 CELLULAR FUEL OXIDATION

Mitochondria are referred to as the "powerhouses" of cells, where the reducing equivalents from fuel substrate oxidation reactions are harnessed for the synthesis of adenosine 5′-triphospate (ATP). ATP is a high-energy phosphagen that is used throughout the body to support processes such as the synthesis of proteins, DNA, and RNA and to support the maintenance of ion gradients across membranes. Although ATP is not the only high-energy phosphagen in cells (e.g., others include phosphocreatine, guanosine triphosphate, and phosphoenolpyruvate), ATP is the most commonly used phosphagen, and for this reason it is called the "common energy currency of cells." Most ATP is produced in mitochondria through a process referred to as oxidative phosphorylation. ATP is also produced by substrate-level phosphorylation in the cytoplasm (by glycolysis) and in mitochondria (by the citric acid cycle), but when oxygen is available to a cell by far most of the ATP is produced by mitochondrial oxidative phosphorylation.

During the cellular oxidation of carbohydrates (mainly glucose, from dietary starches), fatty acids (from dietary fats), and to lesser extents amino acids and ethanol, reducing equivalents are extracted during oxidative processes in the cytoplasm and mitochondria. The reducing equivalents are then transferred mainly to coenzymes nicotinamide adenine dinucleotide (NAD+) and flavin adenine dinucleotide (FAD), reducing the latter to NADH and $FADH_2$, respectively. The reducing equivalents from the various oxidized fuels are ultimately funneled into the mitochondrial electron transport chain, which is located in the mitochondrial inner membrane. There, electrons are shuttled through a series of stepwise redox reactions in which the final electron acceptor is oxygen. While electron transfer within the inner membrane indirectly supports ATP synthesis, proton transfer across the inner membrane directly supports ATP synthesis. This is because the energy from electron transfer is used at three steps in the electron transport chain to pump protons out from the matrix (interior) of the mitochondrion, thus creating a protonmotive force that is subsequently used to drive ATP synthase. Specifically, protons move through ATP synthase from a high concentration outside to a low concentration inside the matrix. Thus, oxygen is consumed and ATP is produced. Accordingly, the overall process is referred to as oxidative phosphorylation.[2]

Oxidative phosphorylation, in comparison with substrate-level phosphorylation, can be a very efficient means of cellular ATP synthesis. However, research in the last 20 years has demonstrated clearly that the efficiency of oxidative phosphorylation is variable.[3] When ATP needs are high the efficiency of ATP production is high, and when needs are low the efficiency is very low.[4] This variable efficiency of oxidative phosphorylation is due to the variable extent of proton leak, that is, the return of protons to the mitochondrial matrix through a route other than ATP synthase.[3] Recent research

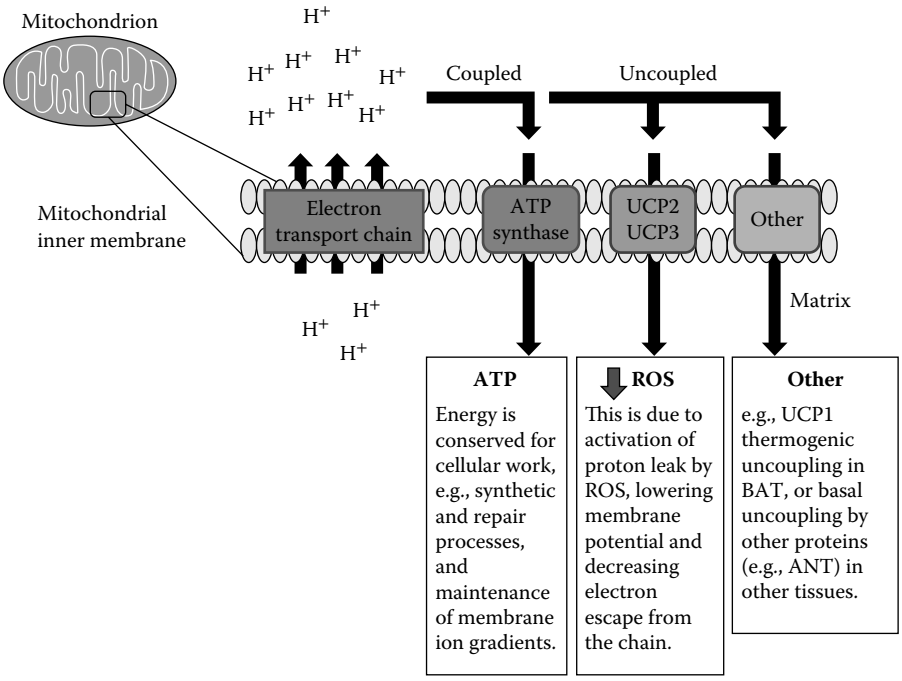

FIGURE 23.1 (**See color insert.**) Coupled and uncoupled oxidative phosphorylation: mitochondria transduce energy, ultimately from dietary sources, to adenosine 5′-triphospate (ATP). Most of a cell's ATP is produced through the process of oxidative phosphorylation, which takes place in the mitochondria of cells. ATP is produced when protons return to the mitochondrial matrix, down their concentration gradient, through ATP synthase. The proton gradient is part of the electrochemical gradient across the mitochondrial inner membrane that is used to drive ATP synthase. ATP is then used to support cellular work. When the need for ATP is low (e.g., when a muscle cell is resting), or when there is a need for thermogenesis in brown adipose tissue (BAT), or when reactive oxygen species trigger uncoupling protein 2 (UCP2) and uncoupling protein 3 (UCP3) proton leaks, protons return to the matrix bypassing ATP synthase. Thus, through uncoupling the energy in the proton gradient is not captured in a form of energy that can be used by cells, and the efficiency of energy transduction from dietary energy to cellular ATP is decreased.

has shown that there are various ways by which protons can leak back into the matrix and thus short-circuit the oxidative phosphorylation process.[5] Regardless of the mechanism, proton leak causes fuel substrates to be oxidized and oxygen to be consumed, without any synthesis of ATP.

Thus, the potential energy of fuels is wasted; the energy is simply released as heat. In this situation, when protons bypass ATP synthase, oxidative phosphorylation is said to be "uncoupled" (Figure 23.1). As discussed in Section 23.7, our research studies have shown that obese individuals in a clinical weight loss program who lose weight much more slowly than others have lower "energy wastage" though proton leak uncoupling in their muscles and have very different oxidative phosphorylation gene expression profiles than those obese individuals who lose weight very quickly.

23.3 MITOCHONDRIAL UNCOUPLING IN BROWN FAT

Before discussing the proton leak uncoupling mechanisms in muscle and other tissues, the classical mitochondrial uncoupling in brown adipose tissue (BAT) should first be reviewed, as the differences in mitochondrial uncoupling between BAT and skeletal muscle are profound. The physiological function of BAT is widely recognized as thermogenesis for the purpose of thermoregulation. In humans, there are substantial amounts of BAT in newborns[6,7] and this is thought to be necessary for adaptation to environmental temperatures colder than those in the womb. BAT undergoes atrophy in childhood, but recent research has unequivocally demonstrated that active BAT remains in adults.[8–12] Although levels of active BAT are lower in those having a higher body mass index (BMI) than in those with a lower BMI,[10,11] it is as yet unknown if this is a cause or a consequence (i.e., of the insulation capacity of body fat) of obesity. In rodents and various other small mammals, BAT remains active throughout life unless they are in a thermoneutral environment.

At the tissue level, BAT is capable of remarkable levels of oxygen consumption and heat production. This is due to the very high amounts of mitochondria and uncoupling protein 1 (UCP1) therein.[13] UCP1 is essential for BAT thermogenesis; mice deficient in UCP1 are cold intolerant and are more susceptible to obesity when housed at thermoneutrality.[14,15] BAT thermogenesis is acutely activated by the sympathetic nervous system; UCP1 is activated by fatty acids and is inhibited by purine nucleotides (see the study by Azzu and Brand[16]). When UCP1 is activated, it allows protons to leak at a very high rate into the mitochondrial matrix, prompting subsequent increases in the oxidation of fatty acids to support the very

high rates of electron transport chain activity. Claessens-van Ooijen et al.[17] estimate that about 11% of metabolic rate could be due to active BAT in adults during cold exposure. Although the overall (whole-body) contribution of normal and abnormal BAT thermogenesis to heterogeneity in obesity susceptibility has yet to be determined, recent studies of the UCP1-3826 A/G variant have revealed lower resting energy expenditure in G-allele carriers and lower thermoregulatory sympathetic nervous system activity for the G/G genotype, consistent with the conclusion that lower UCP1-linked thermogenesis can affect the regulation of energy balance.[18]

23.4 MITOCHONDRIAL UNCOUPLING IN OTHER TISSUES

Compared to that in BAT, the extent of uncoupled oxidative phosphorylation in other tissues is far less. This is due in part to the fact that the other uncoupling proteins in other tissues are expressed at levels hundreds of times lower than the extremely high levels of UCP1 in BAT. However, small changes in the extent of uncoupling in tissues that make up a much greater proportion of body mass than BAT, such as skeletal muscle, could contribute substantially to total body energy expenditure and could modulate susceptibility for obesity. The latter has been demonstrated, for example, in the uncoupling protein 3 (UCP3) transgenic mouse[19,20] and in the UCP1 transgenic mouse models in which UCP1 is ectopically expressed in skeletal muscle.[21,22] These studies (21, 22) and others demonstrate overall that increases in mitochondrial uncoupling in skeletal muscle may be an effective means to treat obesity. That we have observed lower levels of proton leak and UCP3 expression in the rectus femoris muscle of obese individuals who lose weight more slowly than matched individuals who lose weight much more quickly[23] is relevant in this regard (more discussion in Section 23.7).

There are different types of proton leak uncoupling: basal and inducible. Both forms apparently occur in most tissues. Proton leak was first characterized in liver mitochondria when ATP synthesis was absent (adenosine diphosphate [ADP] limited) or inhibited.[3] It has been studied also in mitochondria isolated from other major oxygen-consuming tissues including kidney, brain, and skeletal muscles of the rat.[24] Initially, it was thought that proton leak was an artifact of damaged mitochondria (i.e., during their isolation for experiments) instead of a physiological process. However, in intact hepatocytes it was found to be substantial (i.e., responsible for 25%–30% of resting cellular energy expenditure).[25,26] In addition, Rolfe and Brand[4] showed that mitochondrial proton leak was responsible for about 50% of the resting respiration rate in skeletal muscles of the rat and remains significant (~35%) even when ATP turnover and respiration are increased in muscles.[27] At least in rats, it has been estimated that proton leak accounts for about 20% of resting metabolic rate.[4,27,28] The remarkable studies of the association between proton leak and metabolic rate in mammals of greatly divergent body masses in which Porter and Brand[29] showed a direct relationship between leak and mass-specific metabolic rate are also of relevance. Clues regarding the mechanism were few and far between until the identification of the novel uncoupling proteins 2–5 in the late 1990s.

23.5 NOVEL UNCOUPLING PROTEINS

Uncoupling protein 2 (UCP2) and UCP3 were identified in many mammalian tissues.[30–33] UCP2 mRNA is very widely expressed in tissues, with the highest levels in lung, spleen, and brain and lower levels in most tissues. UCP2 protein expression is at very low levels or is undetectable in many tissues.[30,34] UCP3 mRNA and protein are exclusively expressed in skeletal muscle and BAT, with some expression also in the heart.[31,32,35]

In mice and humans, UCP2 and UCP3 have an approximate 59% amino acid sequence homology to UCP1; between UCP2 and UCP3, there is an approximate 72% homology.[36] The function of UCP2 and UCP3 was originally proposed to be adaptive thermogenesis, akin to UCP1 in BAT. However, unlike UCP1, it has been shown that UCP2 and UCP3 are not involved in adaptive thermogenesis. As mentioned, the tissue levels of UCP2 and UCP3 are much lower compared to UCP1 (0.01%–0.1% compared to levels of UCP1 in BAT).[37] The fact that UCP3 mRNA and protein levels increase in muscles of starved rats when thermogenesis decreases is also notable.[38] However, UCP3 expression is upregulated after short-term cold exposure. Prolonged cold exposure leads to a decrease in UCP3 mRNA expression, indicating that UCP3 does not have a major role in adaptive thermogenesis.[39] As well, UCP3 knockout mice have normal responses to cold exposure.[40,41] These findings, along with the discoveries of uncoupling proteins in ectothermic fish and in plants, further indicated that UCP2 and UCP3 have different functions than UCP1.[37]

Shortly after the identification of UCP2 and UCP3, many human studies sought to determine if sequence variants were associated with metabolic rate and obesity, the preponderance of which indeed support some metabolic implications and risk for metabolic disease. It is not possible to review all these studies here and readers are referred to reviews, which describe associations of the promoter region, coding region, and 3′UTR region variants of these proteins with diabetes, obesity, and lipid metabolism and with altered UCP2 or UCP3 mRNA levels (e.g., the study by Jia et al.[42]). Given the degree of proton leak in skeletal muscle and the highly selective expression of UCP3 there, there is much interest in skeletal muscle. One of the first studies linked a UCP3 polymorphism in the proximal promoter region of UCP3 with increased expression of UCP3 in the skeletal muscle of nondiabetic male Pima Indians, indicating that low UCP3 mRNA expression may contribute to a low sleeping metabolic rate, a predisposing factor for weight loss failure.[43] Argyropoulos et al.[44] showed that a missense mutation in exon 4 (C427T) and two polymorphisms in exon 3 (Val102Ile) and 6 (Ggt-Gat at the exon 6–splice donor junction) in the *UCP3* gene were identified in two severely obese probands. In addition, basal fat oxidation rates were reduced

by 50% and respiratory quotient was significantly increased in exon 6 splice donor heterozygotes compared with control lean individuals, indicating a role for UCP3 in metabolic fuel partitioning. However, Chung et al.[45] were not able to confirm the latter findings in a separate population.

23.6 REACTIVE OXYGEN SPECIES AND THE ACTIVATION OF UNCOUPLING PROTEINS AND PROTON LEAK

In the context of uncoupling proteins, it is highly relevant to also discuss reactive oxygen species (ROS). Cellular ROS are important for a wide variety of signaling processes, but they can, if not maintained within tolerable limits, cause oxidative stress.[46] In most cell types, mitochondria are the major cellular sites of ROS production. The addition of one electron (e^-) to molecular oxygen (O_2) results in superoxide anion ($O_2^{\cdot-}$) formation.

During oxidative phosphorylation, electrons are transferred from NADH to complex I (NADH dehydrogenase) and then to coenzyme Q; electrons can also originate from succinate and the electron transfer flavoprotein to be transferred subsequently to coenzyme Q. Electrons funneling into coenzyme Q are then transported to complex III, cytochrome *c*, and then to complex IV, where oxygen is reduced to form water. Evidence gathered to date is consistent with the conclusion that complexes I and III are the most significant sites of superoxide generation.[47,48] Complex I–dependent superoxide is released on the matrix side of the mitochondrial inner membrane, whereas superoxide from complex III is released to both sides of the membrane.[48,49] Additional ROS, created by dismutases and other enzymes, include hydrogen peroxide (H_2O_2), nitric oxide ($NO^{\cdot}$), peroxyl radicals ($ROO^{\cdot}$), and the hydroxyl radical ($^{\cdot}OH$). H_2O_2 can easily traverse cellular membranes and has a longer half-life than $O_2^{\cdot-}$ and is thought to be an important signaling molecule in cells.[50]

Excessive ROS and oxidative stress are associated with insulin resistance.[51,52] Lefort and colleagues[53] demonstrated that skeletal muscle mitochondria from obese individuals maintained higher ATP levels at low rates of metabolic flux compared with lean controls, which may underlie the higher ROS production rate. The inflammatory environment caused by excessive supplies of glucose and fatty acids is thought to contribute to abnormal ROS production and impaired signaling in muscle cells.[54,55] Consistent with this, high-fat diets can induce mitochondrial ROS emission in both rodents and humans.[52] The increased expression of UCP3 in rat L6 myotubes led to enhanced fatty acid oxidation and decreased ROS levels.[56]

Under normal cellular conditions, mitochondrial ROS play an important role in the modulation of numerous cell functions. However, uncontrolled ROS production is associated with cell damage or death. The main enzyme involved in the dismutation of $O_2^{\cdot-}$ to H_2O_2 is superoxide dismutase (SOD). There are three known mammalian forms of SOD: the cytoplasmic Cu/Zn SOD (SOD1), the mitochondrial MnSOD (SOD2), and the extracellular Cu/Zn SOD (SOD3). SOD1 knockout mice have extensive oxidative damage in the cytoplasm, whereas SOD2 knockout mice have a lethal phenotype.[57,58] After the dismutation of $O_2^{\cdot-}$ to H_2O_2, the H_2O_2 is able to oxidize thiol residues on proteins and low molecular weight thiolating agents such as glutathione (GSH). As mentioned, H_2O_2 is more stable than $O_2^{\cdot-}$, can easily traverse membranes, and is important in cell signaling. However, if present at high levels, H_2O_2 can still damage cells by generating highly reactive hydroxyl radicals through Fenton reactions (the iron-dependent conversion of H_2O_2 to hydroxyl radical).[59,60] To prevent the generation of hydroxyl radicals, H_2O_2 can be reduced to H_2O by glutathione peroxidases, and/or peroxiredoxins.

By uncoupling oxidative phosphorylation, UCP2 and UCP3 are now thought to attenuate mitochondrial ROS production; they therefore are thought to play roles in redox and ROS signaling and protection against oxidative damage.[60,61] In other words, this type of signaling and protection comes at the cost of energetic efficiency. The first evidence was provided by Nègre-Salvayre et al.,[62] who showed that UCP2 inhibition by guanosine diphosphate increased mitochondrial ROS production in hepatocytes. Echtay and colleagues[63] demonstrated that the activation of uncoupling proteins 1–3 by superoxide decreased protonmotive force, resulting in lower ROS levels and protection against ROS-related cellular damage. Thereafter, they extended their findings to show that the lipidic ROS by-product 4-hydroxy-2-nonenal (4-HNE) activated uncoupling proteins 1–3.[64] It was proposed that 4-HNE produced from superoxide-induced lipid peroxidation induces UCP activity and therefore decreases mitochondrial ROS production. As elaborated on in section 23.7, our more recent studies support the idea that the activating species are ROS rather than 4-HNE.[61]

It must be noted, however, that the role of UCP1 in mitigating ROS production is controversial; the absence of UCP1 in BAT mitochondria of UCP1 knockout mice has no effect on superoxide production.[65] Shabalina et al.[66] showed that the effects of 4-HNE are independent of UCP1. Very recent findings support the idea that reversible glutathionylation regulates ROS-induced mitochondrial proton leak through UCP2 and UCP3, but not UCP1.[61] Also, glutaredoxin-1 was shown to covalently conjugate GSH to purified UCP3 in vitro, consistent with the idea that glutathionylation of UCPs may be enzymatic. Recently, thioredoxin-2 was shown to interact with UCP3 and inhibit UCP3, consistent with our findings that the activation of UCP3 is regulated by cellular redox states.[67] In addition, the ROS-mediated activation of UCP3 was reversed by glutathionylation. The deglutathionylation of UCP3 is required to decrease ROS emissions from skeletal muscle mitochondria through a proton leak mechanism.[61] Moreover, UCP3 deglutathionylation that was induced by dithiothreitol or by small increases in ROS was needed to control mitochondrial ROS production in energized mitochondria.[68] Overall, therefore there is good evidence that uncoupling proteins 2 and 3 are activated by low levels of ROS in a negative feedback loop, playing a role in ROS signaling; for a more in-depth discussion of the role of these uncoupling proteins in ROS and redox signaling, recent reviews are available.[60,69]

Another protein in the mitochondrial inner membrane that should at least briefly be considered in the context of mitochondrial uncoupling is adenine nucleotide translocase (ANT), which normally catalyzes the exchange of mitochondrial ATP for cytosolic ADP. The latter is one of the most abundant proteins in the mitochondrial inner membrane, accounting for nearly 10% of proteins in cardiac mitochondria, for example.[70] It has been shown that adenosine monophosphate can activate a proton leak associated with ANT, which can be inhibited by carboxyatractyloside.[71] Moreover, Nadtochiy et al.[72] demonstrated that changes in ANT-mediated proton leak were due to the covalent modification of ANT cysteine residues and that high levels of ROS activate this leak. Therefore, cells are well equipped with many enzymes and processes for the detoxification of ROS; mitochondrial proton leak through UCP2 and UCP3 (and perhaps also ANT) is one such process, and it comes with the cost of decreased energy conversion efficiency in mitochondria.

23.7 MUSCLE MITOCHONDRIAL PROTON LEAK AND GENE EXPRESSION IN WEIGHT LOSS RESISTANCE

Given that about 50% of muscle energy expenditure is attributable to mitochondrial proton leak[4] and that proton leak is estimated to account overall for about 20% of resting metabolic rate,[27] we have been exploring proton leak uncoupling in the muscle of patients in the Ottawa Hospital Weight Management Program for over a decade. Specifically, we have focused on the issue of variability in weight loss.

The clinical diet intervention program is intensively supervised and uses a hypocaloric total meal replacement regimen for the first 6 or 12 weeks. Subjects then continue to be given intensive diet and lifestyle counseling and return weekly for 26 weeks and again at 52 weeks and on an annual basis thereafter. Patients are excluded from research studies based on a detailed set of compliance measures and medical conditions (for further description, see the studies by Harper et al.[23] and Ghosh et al.[73]). Weight loss is evaluated on the basis of three repeat measures prior to and at the end of the first 6 weeks of meal replacement. During the initial 6 week phase of meal replacement, weight loss varies by more than twofold after correction for age, sex, and initial body weight. Subjects in the highest quintile (greatest weight loss) are considered "diet sensitive" (or obese diet sensitive [ODS]), whereas those in the lowest quintile (least weight loss) are considered "diet resistant" (or obese diet resistant [ODR]).

We have reported differences in muscle mitochondrial proton leak between obese individuals exhibiting high versus low weight loss success (i.e., ODS vs. ODR).[23] Rectus femoris mitochondria from female ODS subjects had a proton leak rate that was 50% greater than that from ODR subjects, and mRNA expression of UCP3 was significantly higher in ODS than ODR subjects. UCP3 sequence variants were screened, but no differences were identified between groups.[23] We then extended findings by demonstrating distinct differences in skeletal muscle gene expression profiles, notably in the oxidative phosphorylation pathway, and we also found differences in structural and metabolic characteristics (oxidative vs. glycolytic fibers).[74] Between ODS and ODR groups, physical activity energy expenditure was minimal and comparable. Gene expression analysis of rectus femoris and vastus lateralis biopsies (taken after program completion, when subjects were in a weight stable state) revealed upregulation of genes and gene sets involved in oxidative phosphorylation and the metabolism of glucose and fatty acids in ODS compared with ODR. In vastus lateralis biopsies, there was a higher proportion of oxidative (type I) fibers in ODS compared with ODR women and lean controls, as well as fiber hypertrophy in ODS compared with ODR women and lean controls, and lower succinate dehydrogenase in oxidative and oxidative-glycolytic fibers in all obese compared with lean subjects. Intramuscular lipid levels were generally higher in obese versus lean women and, in particular, higher in ODS versus lean women.

More recently, to determine early predictors of weight loss success we compared whole blood gene expression profiles of obese subjects prior to the initiation of energy restriction. Again, pathway enrichment analysis of gene expression profiles by multiple applications converged on the oxidative phosphorylation pathway as being statistically significantly upregulated in ODS compared to ODR individuals.[75] The finding of increased oxidative phosphorylation genes is consistent with earlier observations of increased proton leak, increased expression of oxidative phosphorylation genes, and increased oxidative muscle fibers in skeletal muscle of ODS versus ODR subjects. Moreover, the study highlighted the use of blood as a sentinel tissue reflecting systemic states and identified a potential modality to predict future weight loss success.

Therefore, skeletal muscle of ODR subjects appears to have a dysregulated oxidative phosphorylation system, including proton leak. Given the estimates that muscle energy expenditure could account for about 20% of resting metabolic rate and that proton leak could be responsible for about 50% of resting muscle energy expenditure,[4,28] the 50% higher proton leak in ODS compared with ODR subjects[23] could mean that resting metabolic rate is approximately 5% lower in ODR subjects. Whether such a difference in resting metabolic rate is detectable (e.g., by indirect calorimetry), even after normalization to muscle mass, is unknown; but relevant studies are under way in our group. Moreover, given our recent findings that glutathionylation of UCP3 plays a very important role in regulating ROS-induced UCP3 proton leak in muscle,[61] studies are also under way to test for differences in ROS-induced proton leaks in muscle of our clinical populations. Therefore, ROS activation of UCP3 in muscle from ODS and ODR individuals needs to be further studied. Overall, there is as yet much to learn about the regulation of oxidative phosphorylation and its variable efficiency. The integration of findings with clinical phenotype will hopefully lead to new insights into novel obesity treatment strategies.

23.8 SUMMARY

Thus, extensive research has demonstrated that the efficiency of energy conversion in oxidative phosphorylation is not perfect. Moreover, the efficiency of mitochondrial ATP production substantially varies depending largely on the degree of ATP demand. Recent studies, especially those that have involved the study of mitochondria in situ (i.e., in intact cells or tissues) rather than the study of preparations of isolated mitochondria, have shown that the novel uncoupling proteins decrease ATP production efficiency through the induction of proton leaks. There are other types of proton leaks beyond those caused by UCP2 and UCP3, such as the leak associated with ANT. Mechanisms that activate and inhibit proton leaks require further study. Although it is clear that UCP2- and UCP3-mediated proton leaks act in a negative feedback loop in which ROS activate proton leaks and subsequently decrease mitochondrial ROS production, there is controversy as to whether UCP1 is similarly controlled. In skeletal muscle at rest (when ATP synthase activity is low), roughly 50% of oxygen consumption is due to proton leak. Many research studies have examined the association of single-nucleotide polymorphisms and mutations in uncoupling protein genes with obesity. Our research has shown that leaking in skeletal muscle is lower in obese women who lose weight more slowly than in those who lose weight quickly and that patterns of oxidative phosphorylation gene expression and muscle fiber composition differ between these groups. Research in various types of mice has shown that slight increases in proton leaks, specifically in skeletal muscle, protect against the development of obesity with no discernible detrimental effects. Further research is needed for a better understanding of proton leak control mechanisms so that therapeutic approaches can possibly be developed in the future.

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24 Resting Metabolic Rate, Thermic Effect of Food, and Obesity

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CONTENTS

24.1 METHODS OF MEASURING ENERGY EXPENDITURE IN RESTING AND FREE-LIVING CONDITIONS

24.1.1 Introduction

A review of the major methods used in human experimental studies is important since some components of energy expenditure (EE) are relatively small and cannot be measured with all methods, for example, the thermic effect of food (TEF).

The complex studies of the regulation of energy metabolism and nutrient utilization in humans at rest and during exercise have recently raised a great deal of interest thanks to advances in the construction of open-circuit ventilated hood indirect calorimeters and comfortable respiration chambers, the latter having also largely benefited from the inconspicuous assessment of EE in free-living conditions by nonradioactive stable isotopes ("heavy" water labeled with deuterium and oxygen [O_2] 18; method called "doubly labeled water").

Several methods are used to assess EE in humans: [1] "indirect calorimetry," which measures total heat production from the quantification of respiratory gas exchange, that is, O_2 consumption ($\dot{V}O_2$) and carbon dioxide "(CO_2)" production ($\dot{V}CO_2$); [2] "direct calorimetry," which measures total heat losses; and [3] the "doubly labeled water technique," which assesses total CO_2 production. The first two methods can assess EE over short periods of time (typically minutes), whereas the third method requires a long time constant (1 week or more). These methods are based on different principles and do not measure the same parameter.

This partition is important since the reasons for an abnormal 24-hour EE can be ascribed to a combination of abnormal subcomponents.

Indirect calorimetry is the method of choice to measure resting EE, TEF (postprandial thermogenesis), and the energy expended for physical activity. It has the great advantage of being relatively simple; it can be used with either a ventilated hood system (for a resting subject) or a face mask typically during exercise, using a light portable system attached to the trunk, or finally with a whole-body respiration chamber, when a 24-hour measurement is needed under strictly controlled environmental, nutritional, and physical activity conditions. The first advantage of indirect calorimetry is the ability to measure short-term $\dot{V}O_2$, which is related to the O_2 consumption of tissues and organs, as they have negligible O_2 stores. A second advantage of indirect calorimetry in comparison with other methods is the possibility to assess macronutrient oxidation rates when $\dot{V}O_2$, CO_2 production, and urinary nitrogen excretion are measured simultaneously.

The term indirect calorimetry stems from the fact that the heat released by chemical processes within the body can be indirectly calculated from the rate of O_2 uptake. The main reason for the tight relationship between energy metabolism

and O_2 consumption is that the oxidative phosphorylation in the respiratory chain is coupled with a continuous synthesis of adenosine triphosphate (ATP).

The energy expended within the body is essential to maintain cell structure and functions in homeostasis; electrochemical gradients (e.g., Na+, K+, or Ca^2+ gradients); biosynthetic processes (protein synthesis and degradation); macromolecules turnover; RNA and DNA turnover; muscle tone and muscular contractions; and biochemical transformations such as gluconeogenesis, lipogenesis, synthesis of urea, fuel cycling, cellular signaling, and many other biochemical processes that require ATP. Almost all chemical processes requiring energy depend on ATP hydrolysis. It is the rate of ATP utilization that determines the overall rate of substrate oxidation and therefore utilization of O_2. With the exception of anaerobic glycolysis, ATP synthesis is coupled with substrate oxidation. Because there is proportionality between $\dot{V}O_2$ and ATP synthesis, and because each mole of ATP synthesized is accompanied by the production of a given amount of heat, this is a clear rationale for using $\dot{V}O_2$ measurement to calculate heat production within the body [1].

Direct calorimetry is the method of choice for studies aimed at assessing thermoregulatory responses. The number of studies using this complex system remains rather limited.

The method consists of measuring heat losses rather than heat production. In many non-steady-state conditions, heat losses differ from heat production and there is a net change in heat stored. For instance, after a meal heat production begins to increase 20–30 minutes after the onset of eating, whereas heat loss increases only later on. The consequence of the different time courses of heat production and heat loss resulting in a heat "imbalance" is a small change in internal body temperature.

The method of direct calorimetry consists of the measurement of heat dissipated by the body by radiation, convection, conduction, and evaporation. Under conditions of thermal equilibrium in a subject at rest and in postabsorptive conditions, heat production measured by indirect calorimetry is almost identical to heat dissipation measured by direct calorimetry. This is an obvious confirmation of the first law of thermodynamics, that is, the energy released by oxidative processes is ultimately transformed into heat (and external work during exercise). In steady-state conditions, the identity between heat production and heat loss in a resting subject corroborates the validity (for the whole body) of the method of indirect calorimetry.

The doubly labeled water technique is the third method and is based on the difference in the rates of turnover of ^2H_2O and $H_2{}^{18}O$ in body water. The subject is given a single oral dose of $^2H_2{}^{18}O$ to label body water with both isotopes ^2H and ^{18}O. A rapid exchange of ^{18}O occurs between water and CO_2 owing to the action of carbonic anhydrase. As a result, after equilibrium of $^2H_2{}^{18}O$ in the water pool and equilibrium of ^{18}O with CO_2, ^{18}O is lost both as $H_2{}^{18}O$ and $CO^{18}O$, whereas ^2H is lost only as ^2H_2O. The difference in the rates of turnover of $H_2{}^{18}O$ and ^2H_2O is an estimate of CO_2 production rate. To calculate the subject's EE, the mean respiratory quotient (RQ) must also be known. EE is obtained by multiplying $\dot{V}CO_2$ by the energy equivalent of CO_2 production. Unfortunately, the latter varies substantially from 21.0 to 27.7 kJ/L CO_2 (i.e., as much as 30% difference) at extreme ranges of RQs of 1.0 (100% carbohydrate oxidation) and 0.7 (100% fat oxidation), respectively. The disappearance rates of the isotopes can be measured in urine, blood, or saliva for a period equivalent to two to three biologic half-lives. This corresponds to approximately 14 days in adult subjects. Thus, the method provides a mean value of EE for a 1- to 2-week period. Note that it is not possible to calculate the day-to-day variation in EE with the doubly labeled water technique, in contrast to the respiration chamber.

24.1.2 Methodological Aspects of Measuring Energy Expenditure by Indirect Calorimetry

With the measurement of $\dot{V}O_2$ (in liters of O_2 per minute) at STPD conditions (standard temperature [0°C], pressure [760 mmHg], and gas dry), the metabolic rate (M), which corresponds to heat production, can be calculated (in kilojoules per minute) as follows:

$$M = 20.3 \times \dot{V}O_2 \tag{24.1}$$

The number 20.3 is a mean value (in kilojoules per liter) of the energy equivalent for the consumption of 1 L (STPD) O_2. The value of the energy equivalent of O_2 depends on the composition of the fuel mixture oxidized (Table 24.1). The error in using Equation 24.1 instead of an equation that takes into account the type of fuels oxidized (Equations 24.2 and 24.3) is not greater than ±2%.

The heat released by the oxidation of each of the three macronutrients (carbohydrates, fats, and proteins) can be calculated from three measurements: O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), and urinary nitrogen excretion (N).

Simple equations for computing metabolic rate (or EE) from these three determinations are written in the following form:

$$M = a\dot{V}O_2 + b\dot{V}CO_2 - cN \tag{24.2}$$

The factors a, b, and c depend on the respective constants for the amount of O_2 used and the amount of CO_2 produced during oxidation of the three classes of nutrients (Table 24.1). An example of such a formula is given as follows:

$$M = 16.18\dot{V}O_2 + 5.02\dot{V}CO_2 - 5.99N \tag{24.3}$$

where M is in kilojoules per unit of time, $\dot{V}O_2$ and $\dot{V}CO_2$ are in liters STPD per unit of time, and N is in grams per unit of time. Slightly different factors for the amounts of O_2 used and of CO_2 produced during oxidation of the nutrients are used by other authors, and the values for the factors a,

TABLE 24.1
O_2 Consumed, CO_2 Produced, and Heat Released from Oxidation of Substrates

						Energy Equivalent (per Liter STPD) of			
				Heat Released (per Gram)		$\dot{V}O_2$		$\dot{V}CO_2$	
Nutrients	O_2 Consumed[a]	CO_2 Produced[a]	RQ	(kJ/g)	(kcal/g)	(kJ/L)	(kcal/L)	(kJ/L)	(kcal/L)
Starch	0.829	0.829	1.00	17.6	4.20	21.2	5.06	21.2	5.06
Saccharose	0.786	0.786	1.00	16.6	3.96	21.1	5.04	21.1	5.04
Glucose	0.746	0.746	1.00	15.6	3.74	21.0	5.01	21.0	5.01
Lipid	2.019	1.427	0.71	39.6	9.46	19.6	4.69	27.7	6.63
Protein	1.010	0.844	0.83	19.7	4.70	19.5	4.66	23.3	5.58
Lactic acid	0.746	0.746	1.00	15.1	3.62	20.3	4.85	20.3	4.85

Source: Schutz, Y., and E. Jéquier, *Handbook of Obesity: Etiology and Pathophysiology*, 2nd edition, Marcel Dekker, Inc., New York, 2004.
Note: $RQ = \dot{V}CO_2/\dot{V}O_2$.
[a] In liters per gram of substrate oxidized.

b, and *c* are modified accordingly. The difference in EE calculated by the various formulae is not greater than 3%. Detailed information about these calculations is given elsewhere in the literature [2–4].

24.2 RESTING AND BASAL METABOLIC RATES

There is an arbitrary distinction between basal metabolic rate (BMR) and resting metabolic rate (RMR) in the literature. BMR is measured supine under strict standardized conditions 10–12 hours after the last meal; without prior exercise; under thermoneutrality; without any movements; awake without drowsiness and sleep; under mental relaxation but without meditation; without excess noise; and by avoiding exogenous stimuli (investigator's effect). Both BMR and RMR are measured in immobile conditions, explaining why the terms are often interchanged. Whereas BMR is highly standardized, the measurement of RMR is less so; it can be made in the postprandial or interprandial phase (a few hours after a nonstandardized meal), with prior physical activity, explaining why RMR is generally slightly higher than BMR.

24.2.1 Whole-Body, Organ, and Tissue Metabolic Rates

Elia [5] has written an excellent classical review of the contribution of organs and tissue to metabolic rate. As shown in Figure 24.1, the major part of whole-body RMR (60%) stems

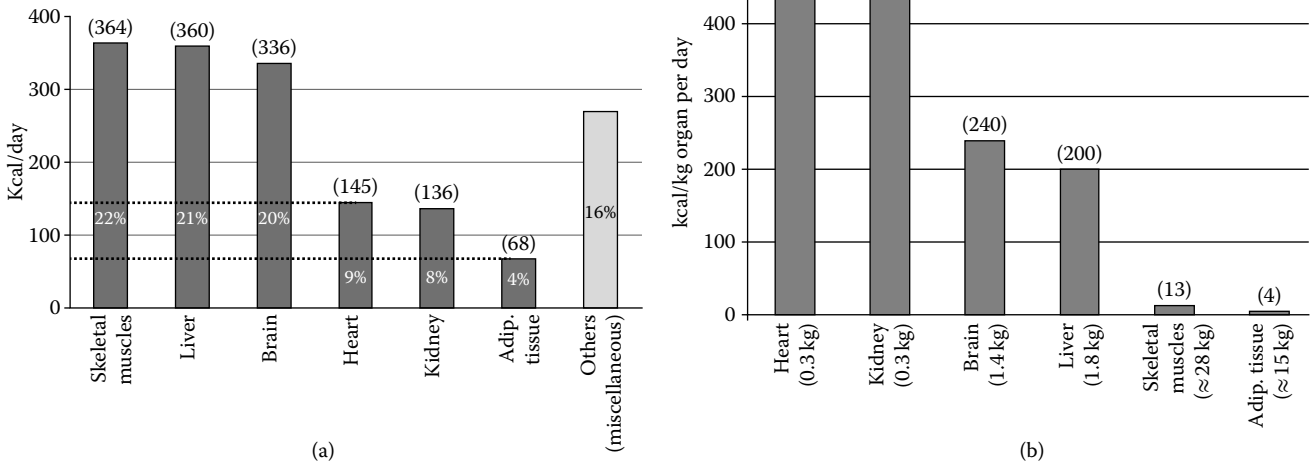

FIGURE 24.1 Contribution of different organs and tissues to resting metabolic rate (RMR)/basal metabolic rate (BMR) in an average nonoverweight man of 70 kg with an RMR/BMR of 1680 kcal/day expressed in absolute terms (a) or adjusted for body weight (b): the sum of major organs explains 84% of the BMR/RMR, 16% remaining for miscellaneous tissues and/or unexplained. Note the large diversity in both absolute and specific organ metabolic rates per unit of organ weight in adults. (Drawing based on Elia M., *Energy Metabolism. Tissue Determinants and Cellular Corollaries*, Raven Press, New York, 1992.)

from organs with high metabolic activity such as liver, kidneys, brain, and heart, although these account for only a small proportion of the total body weight (5%); this contrasts with skeletal muscle, which makes up between 35% and 50% of body weight but contributes to only 20%–25% of RMR. The "residual" metabolic rate (16%) not explained by the aforementioned tissues and organs can be accounted for by skin (a large protein depot) and the gastrointestinal tract, in particular the intestines (which have a relatively large protein mass and protein turnover), as well as bones and lungs.

Per unit body weight, the kidneys and heart have a metabolic rate more than twice as high as that of the liver and the brain (Figure 24.1). In contrast, the metabolic rate of muscle per unit body weight is nearly 35 times lower than that of the heart and kidneys. Since the proportion of muscle to nonmuscle changes with age from birth to adulthood, the RMR per unit body weight is not constant with age; the younger the children, the higher the relative value [6].

The tissue with the lowest metabolic activity per unit body weight is adipose tissue, which accounts for only about 4% of the whole-body RMR in nonobese subjects. This value can increase substantially (10% of RMR or more) in obese subjects with a large excess in body fat (Y. Schutz, unpublished data).

New technologies, such as magnetic resonance imaging, have been used to reevaluate organ and tissue dimensions and thus allow a better characterization of the differences in BMR among individuals. According to recent findings, the specific metabolic rate of major organs and tissues expressed per unit body weight (Figure 24.1) is overestimated by 2% in obese adults [7]. These values were also validated across adulthood, although age adjustment was found to be appropriate for specific applications [8].

24.2.2 Effect of Fat-Free Mass and Fat Mass on Resting (Basal) Metabolic Rate

The excess body weight of the obese is primarily constituted by adipose tissue, and also a small component of associated lean tissue, which includes muscles. Although the exact composition of extra lean tissue in obesity is largely unknown, it seems logical to expect a greater absolute RMR in obese adults [9,10] compared to their lean counterparts, the former characterized by a large excess of adipose tissue, with very low metabolic activity, and a smaller increase in fat-free tissue, with three to four times higher metabolic activity (Figure 24.1).

Numerous studies conducted over the past two decades have demonstrated [11] that the most powerful factor explaining the variation in RMR between individuals of different genders, ages, and body weights is fat-free mass (FFM), which accounts for two-thirds of the interindividual variance in BMR [12].

FFM is a heterogeneous component that can be partitioned into two simple subcomponents: about half is skeletal muscle mass and the other half nonmuscle mass (organs and other tissues) in nonobese individuals. There is no simple and accurate way to assess these two subcomponents, although the rate of urinary creatinine excretion measured over 24 hours or more (with no source of exogenous creatine fed, such as meat) can constitute a rough index of absolute muscle mass [13,14].

Owing to the much larger interindividual variability in fat mass, compared to FFM, and because, in grossly obese women, fat mass can represent a nonnegligible component of total RMR (10% or more), the prediction models for RMR that include both FFM and fat mass significantly explain more variance in RMR than FFM alone [11]. Age, sex, and family membership (the latter as a surrogate for genetic factors) are additional factors that should be taken into account. FFM, fat mass, and age account for over 70% of the RMR (BMR) variance in humans [12]. The fraction of the variance in RMR unexplained by the aforementioned factors (about 30% or more) could be attributed to the following: (1) statistical considerations (magnitude of spreading of x axis vs. y axis), (2) methodological considerations (measurement errors of both variables), and (3) "philosophical" factors. This means that 100% variance explained in a real-life physiological process in humans is expected to be an extremely rare phenomenon in experimental studies, even with the best methods used.

24.2.3 Prediction of Resting (Basal) Metabolic Rate in Normal-Weight/Overweight Individuals

In overweight and obese subjects, the best approach is to measure the resting component by indirect calorimetry. When this is not possible, predictive equations either based on simple anthropometry (body weight and height combined with sex and age) or based on body composition can be used for clinical work.

A few equations have proved to be more appropriate for obese individuals, but they remain controversial [15–18]. Table 24.2 lists the most used equations based on anthropometry appropriate for normal-weight, overweight, and obese individuals. Several prediction equations were identified as the most commonly used ones in clinical practice (e.g., equations by Harris-Benedict [18] and Mifflin–St. Jeor [16]). Of these equations, the Mifflin–St. Jeor equation [16] was found to be the most reliable, predicting RMR within 10% of measured values in nonobese and obese individuals. A recent study has claimed that in obesity anthropometric predictors of BMR are as accurate as body composition if the latter is estimated by bioelectrical impedance [19].

24.3 THERMIC EFFECT OF FOOD IN HUMANS

The acute rise in RMR consecutive to the ingestion of food or a meal, which persists several hours after taking the meal, is called TEF or the thermic effect of a meal. During this phase, macronutrients are stored temporarily for subsequent use. TEF mainly depends on the energy costs of processing and/or storing the macronutrients (carbohydrates, fats, and proteins). Other important factors influencing TEF are summarized in Table 24.3.

TABLE 24.2
Commonly Used Prediction Equations for RMR

I. Predicted from Weight + Height + Age + Gender	**Practical Results in Two Obese Individuals: 100 kg, 1.70 m**
30-year-old obese women and men	
a. Equation of Harris and Benedict [18]	
Women: RMR (kcal/day) = 956 × weight (kg) + 185 × height (m) – 468 × age (year) + 655	1785 kcal/day
Men: MR (kcal/day) = 1375 × weight (kg) + 500 × height (m) – 676 × age (year) + 66	2088 kcal/day
b. Equation of Mifflin [16]:	
Women (kcal/day) 10 × weight (kg) + 6.25 × height (cm) – 5 × age (year) – 161	1757 kcal/day
Men (kcal/day) 10 × weight (kg) + 6.25 × height (cm) – 5 × age (year) + 5	1918 kcal/day
c. Equations of the Institute of Medicine, the United States [17]	
Women: RMR (kcal/day) = 860 × weight (kg) + 402 × height (m) – 267 × age (year) + 247	1710 kcal/day
Men: RMR (kcal/day) = 101 × weight (kg) + 456 × height (m) – 38 × age (year) + 293	1995 kcal/day
II. Equation Based on Two Compartments Body Composition [11]	
MR (kcal/J) = 302 + 22.3 × fat-free mass (kg)	Example with fat-free mass = 55 kg in women and 70 kg in men Women: 1529 kcal/day, men: 1863 kcal/day

Note: No clear consensus exists about the most valid equation for obesity. Two typical obese subjects are given as examples for visualizing the differences in resting metabolic rate (RMR) obtained when different equations are used: maximum difference (see equations a to c) is on the order of 8% in men and 4% in women. Equations based on anthropometry give systematically higher values than those based on body composition.

TABLE 24.3
Key Factors Influencing TEF

Factors	**Basic Findings**
Gender	Little effect of gender particularly when difference in body composition is accounted for
Menstrual cycle	Blunted TEF during the luteal phase or no changes observed
Aging	Glucose induced thermogenesis negatively correlated with age; corrected for the fat-free mass, both young and elderly subjects have similar values
Nutritional status	Malnourished individuals show high TEF response during recovery from malnutrition in children and adults
Body composition	TEF has been shown to be inversely related to relative body fat
Obesity	Low TEF has been observed in some obese individuals with insulin resistance
Familial and genetic effect	About one-third of the TEF is explained by genetic factors

Source: Schutz, Y., and E. Jéquier, *Handbook of Obesity: Etiology and Pathophysiology*, 2nd Edition, Marcel Dekker, Inc., New York, 2004.

TEF is generally expressed as a percentage of the energy content of food, since the greater the food energy load, the higher the total response. Values of TEF average 5%–8% for carbohydrates, 2%–3% for fat, and 20%–30% for protein [1]. Ethanol has a high thermogenic capacity, on the order of 22% [20].

The most adequate technique to assess the thermic effect of a meal is to measure the RMR following meal ingestion during 3–6 hours and to compare the values with a control test during the same period of time after a zero-energy drink or a caloric control meal is given. Alternatively, the usual method is to measure RMR during 1 hour or so before giving the load in the postabsorptive state (10–12 hours after the previous meal), to get a stable premeal baseline. Thereafter, a meal is given to the subject and EE is continuously measured with a ventilated hood system for 3–6 hours. The area under the curve of RMR versus time over the extrapolated baseline value (considered to be a constant) represents the absolute thermic effect of the meal. It is important that the period of measurement is of sufficient duration so as to include the entire thermogenic response. Figure 24.2 represents the thermic effect of glucose measured in a nonobese group of subjects ($n = 10$) for 8 hours. For a 50 g load, glucose-induced thermogenesis (GIT) averaged 5% of the load energy value; it increased to 8.8% with a 100 g load and reached 11% with a 150 g load.

The TEF component is difficult to measure in practice [21] because of numerous constraints, both technical constraints (relatively small rise of EE compared to the effect of physical activity and poor reproducibility when expressed as the coefficient of variation [CV] [CV% = standard deviation/mean × 100]) and

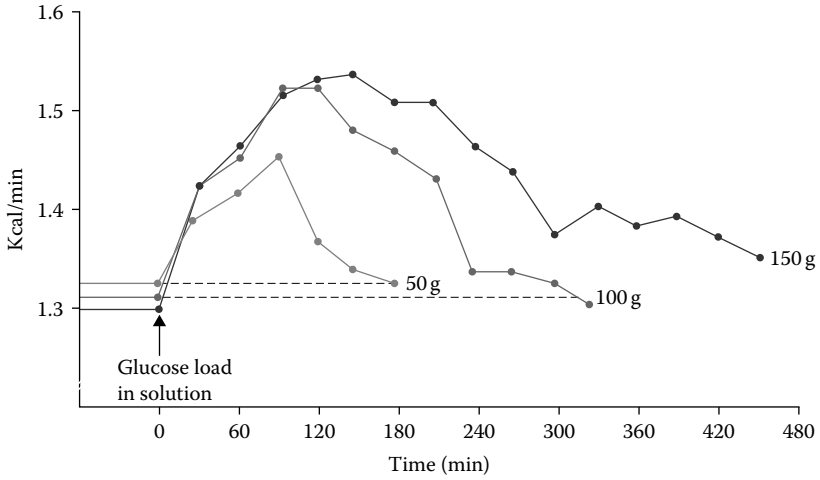

FIGURE 24.2 Thermic effect of glucose measured in a nonobese group of subjects ($n = 10$): note that the steep upward phase (first hour) up to the peak thermogenic response depends less on the size of the load energy value than the descending phase up to the time the premeal baseline is recovered. The glycemic peaks were almost identical with all three doses with a rise to between 141 and 147 mg/dL at 60 minutes. The total thermogenic response was essentially completed within 3 hours, 6 hours, and 8 hours for 50 g, 100 g, and 150 g glucose loads, respectively. For the 50 g load glucose-induced thermogenesis was 5% of the load energy value, which increased to 8.8% with the 100 g load and reached 11% with the 150 g glucose load. The glucose storage, calculated over 180 minutes (for comparison purposes), increased with the size of the glucose load, amounting to 20 ± 1 g (i.e., 40% of load), 60 ± 1 g (i.e., 60% of load), and 110 ± 1 g glucose (i.e., 73% of the load) after the 50 g, 100 g, and 150 g glucose loads, respectively. The higher the size of the glucose load, the greater the net glucose storage and the higher the glucose-induced thermogenesis. A factor that plays a role in the increased glucose-induced thermogenesis with the size of the load is enhanced de novo lipogenesis (transformation of exogenous glucose into fat). (From Schutz, unpublished.)

TABLE 24.4
Confounding Factors Thought to Explain the Intrinsic and Extrinsic Difficulties in Identifying Clear, Consistent Differences in Thermogenic Response (Measured by Indirect Calorimetry) among Investigators between Obese Individuals and Their Lean Counterparts

Factors	Potential Effects
1. Heterogeneity of obesity phenotypes	Large interindividual variability of thermogenic response
2. Difference in antecedent diets obese versus nonobese Failure to stabilize RQ during baseline	Difference in RQs
3. Nonfasting conditions at study outset	Underestimation of postprandial response
4. Duration of chewing/masticating food load	Confounding effect in initial response[a]
5. Assumption of identical absorption of food load	Difference in substrate availability among subjects for oxidation and storage[a]
6. Nonstable premeal baseline	Underestimation of thermogenic response
7. Low energy load (e.g., 200 kcal)	May not sufficiently discriminate differences in TEF among groups
8. Poor (unstable) indirect calorimeter	Will increase TEF random variability. Excellent precision (reproducibility) is the factor of importance
9. Measured response is discontinued	Underestimation of thermogenic response
10. Gastric symptoms during measurements	Discomfort may perturb the smooth response; diarrhea will wash out substrates underestimating TEF
11. Personality/behavioral types	Fidgeting versus drowsiness differences among groups during the TEF test
12. Utilization of "sensitive" videos during TEF	"Thermogenic movies": different emotional responses to stimuli in some individuals

[a] Some factors may be considered as purely academic.

constraints related to the subject's behavior (importance of total immobility, lack of stress, no drowsiness, and no sleep).

The reproducibility of TEF is rather poor because it is a difference (Δ) derived from two values close to each other. The total thermogenic response can rarely be measured integrally in practice—in particular with a high food energy load—as it requires a very long measurement period (6–8 hours), a difficult situation for the subject who has to remain totally immobile and awake during the period.

Table 24.4 outlines several confounding factors that contribute to the variations observed in the accuracy and precision of TEF among different studies investigating similar subjects.

24.3.1 Why Is There So Much Difference in Thermic Effect of Food among Different Substrates?

The thermic effect of dietary fat is very small; an increase of only 2% of its energy content has been described during the infusion of an emulsion of triglyceride. This slight increase in EE is explained by the ATP consumption in the process of free fatty acid reesterification to triglyceride. As a consequence, the energy of exogenous fat is used and stored very efficiently. The thermic effect of proteins is the highest of all nutrients (20%–30% of the energy content of proteins). Ingested proteins are degraded in the gut into amino acids. After absorption, amino acids are deaminated, their amino group is transferred to urea, and their carbon skeleton is converted to glucose. These biochemical processes require the consumption of energy amounting to approximately 25% of the energy content of amino acids. The second pathway of amino acid metabolism is protein synthesis. The energy expended for the synthesis of the peptide bonds also represents approximately 25% of the energy content of amino acids. Therefore, irrespective of their metabolic pathway, the thermogenesis induced after the absorption of amino acids represents approximately 25% of their energy content. The thermic effect of ethanol constitutes a special case since it is not stored as such. The thermogenesis of ethanol amounts to approximately 22% of its energy content [20]. The acute effects of ethanol ingestion include a decrease in the plasma-free fatty acids level and a change in the cellular redox state in the liver cells, with an inhibition of lipid oxidation.

Past studies have attempted to partition TEF into two subcomponents: (1) an "obligatory" component, which is attributed to the energy costs of digesting, absorbing, processing, and storing the nutrients and obtained using stoichiometrically balanced biochemical equations; and (2) a "nonobligatory" or facultative (regulatory) component, which is explained by sympathetic nervous system (SNS) activity stimulation [22]. This facultative component is calculated by the difference between the total thermogenic response measured experimentally and the obligatory component. For example, GIT results from the cost of glycogen synthesis and substrate cycling. Glucose storage as glycogen requires 2 mol of ATP per mole of glucose absorbed. Since 38 mol of ATP are produced when glucose is fully oxidized into CO_2 and water, the theoretical energy cost of glucose storage as glycogen corresponds to 5% (or 2/38) of the energy content of glucose stored (obligatory thermogenesis); this assumes negligible energy-requiring processes (which could increase the thermic effect of glucose) during the postprandial phase such as substrate-cycling processes (e.g., between glucose to glucose-6-phosphate, between glucose-1-phosphate and fructose-1,6-diphosphate, or between glucose and lactate).

The most important factor at rest that stimulates thermogenesis in daily life is food intake, although bioactive ingredients (caffeine and nicotine) and psychological–behavioral factors also stimulate RMR [23,24]. Cold exposure does not play a significant role in stimulating EE under usual life conditions [25], since humans adapt their clothing to the thermal conditions of the environment.

The total TEF measured over 24 hours (or during daytime to avoid the confounding effect of sleep) represents about 10% (range 5%–15%) of the total energy expenditure (TEE) in sedentary subjects. This overall response (typically integrating three meals or more) is generally called diet-induced thermogenesis (DIT), to distinguish it from the immediate postprandial response of a single meal. This component can be estimated inconspicuously over daytime (typically 15 hours or more) in an indirect calorimetric respiration chamber using an original approach [26], provided the effect of spontaneous physical activity, which superimposes the effect of resting, can be totally offset. In practice, this means that a fixed radar system is required [27], which can be adequately combined with accelerometers on the moving subject to decrease the random error of measurement [28]. The radar system provides an accurate assessment of the duration of any spontaneous physical activity, whereas accelerometry gives an estimate of both duration and intensity of the activity, that is, of the "volume" (product of the two) of overall physical activity over daytime. Using an individual regression line approach, the overall thermogenic component can be calculated from the difference between the postprandial/interprandial EE at zero physical activity and the basal EE measured 10 hours after the meal [26,28]. However, the accuracy of DIT assessment is poorer than the classical method using a hood method partly because of the large volume (and hence slow response time) of the chamber.

24.3.2 Thermic Effect of Food in Obesity

Good reviews on the effect of obesity on the magnitude of TEF were published more than a decade ago [29–31]. No consensus exists in the literature regarding whether or not TEF is reduced in obesity.

One review examined 50 studies from the mid-1970s that have investigated TEF in obesity and highlighted the differences in the nature of experimental factors, the differences in protocol design, as well as the control of subjects during TEF studies [30]. The authors pointed out that these factors could influence postprandial EE response and the calculation of TEF.

Although several studies have reported that TEF was reduced in obesity, about half of the studies have reported no reduction of TEF among obese individuals. In our opinion, this is not surprising since obesity is a very heterogeneous syndrome with various etiologies and body fat distribution. For example, body fat distribution plays a role [32]; after weight loss, TEF has been shown to be increased in gluteal-femoral-obese women but not in abdominal-obese women [33].

In another comprehensive review, De Jonge and Bray [29] have concluded that when reduction in TEF in obese individuals was present it could be due to a reduced sympathetic response to feeding resulting from insulin resistance. Indeed, in previous studies from our group claiming that thermogenesis was blunted in many obese individuals [1] the reduction in postprandial thermogenesis observed in some obese individuals was related to the degree of insulin resistance, which may influence (or be influenced by) a low sympathetic

activity. Evidence of a role for the activation of SNS after glucose infusion could be derived from the demonstration of a reduced glucose-induced thermogenic response after β-adrenergic blockade with propranolol [1].

Does the reduced TEF observed in subgroups of obese individuals contribute to obesity or is it normalized after weight loss [34] and hence represents a consequence of obesity? Does a blunted thermogenic response to food contribute to the weight regain after cessation of dietary therapy? In other words, does a lowered TEF predispose obese individuals to relapse after weight loss? To address these questions, we have attempted to assess TEF, using a longitudinal design, in 10 obese women under four rigorous conditions (Y. Schutz, unpublished data) as follows: (1) before weight loss; (2) during the dynamic phase of weight loss; (3) after weight loss, following a period of weight maintenance for 2 months (maintenance diet); and (4) following an ad libitum diet, in which weight-gain relapse may spontaneously occur after a year or more.

The results show that TEF averaged 7.7%, 11.7%, 8.9%, and 8.6% for the four conditions (range of standard deviation was 2.5%–3.8%, nonsignificant across conditions). The reproducibility of TEF within the same subject was excellent and, interestingly, there was a significant inverse relationship ($r = 0.85$, $p = 0.01$) between the magnitude of TEF and the weight regained, suggesting that a blunted TEF may play a role in the degree of weight relapse. Note that to avoid a fixed energy load at any body mass index (BMI), which would mean that during slimming and after weight loss the subjects would receive an excessive energy load compared to their new energy requirements, it was fundamental that the test meal size be tailored to each individual's resting postabsorptive EE baseline. Therefore, for each individual one-third of his or her total resting EE value, calculated over 24 hours, was fed as a single meal to avoid this problem.

Several important issues can be highlighted regarding defective TEF in obesity and its comparison with a control group:

- In most experimental studies, the thermogenic response to a mixed meal (or a glucose load) should include the total response, typically about 4 to 5 hours measured minute by minute by indirect calorimetry, to avoid an underestimation of the TEF response. As shown in Figure 24.2, 3 hours of measurement are sufficient with a 50 g glucose load (200 kcal); but at least 8 hours are required for a three times larger load (150 g, 600 kcal), confirming the importance of adapting the duration of a TEF study to the meal size (energy level) as well as the composition of the load (high relative protein content will increase the total response). A previous report [35] suggested a minimum of 5 hours.
- From a physiological and energetic standpoint the reduction of TEF in obesity can be viewed as an improved metabolic efficiency of energy utilization, but its magnitude is only about 3%–5% of the energy value of food. This indicates that the interpretation of TEF should focus not only on "energy-saving" capacity but also on changes in functional and metabolic capacities to manage an energy load.
- The quantitative importance of a defect in TEF in the etiology of obesity should be considered: in absolute terms, the magnitude of difference in TEF observed when it is blunted in the obese remains relatively small. The daily saving in energy cannot explain the development of obesity per se but just a few kilograms of weight gain over several years. Quantitatively, it is more likely that a defect in the control of food intake plays a more important role in the development of obesity (or in the relapse of body-weight gain) than a blunted thermogenesis.
- The difference in TEF in the obese has been claimed by some to be an experimental artifact, mostly related to the problem of defining the equivalent energy load in the test meal given to subjects of very different body weights [31].

24.3.3 Adaptive Thermogenesis During Overfeeding in the Resting Energy Expenditure Component

When the plane of nutrition is changed by prolonged overfeeding (surfeit energy for several days/weeks, i.e., semichronic), the natural response is a change in body weight and body composition, which, in itself, is an expected effect resulting from the prolonged positive energy balance. These changes represent an expansion of tissue mass (fat mass and FFM) and tissue redistribution. The putative changes in tissue metabolic activity can be ascribed to an adaptive thermogenesis process in response to a dislocation of energy or substrate balance. It is operating within a few days or weeks after the onset of overfeeding or underfeeding. Its role is to dampen the initial "nutritional insult" in a direction that will minimize the initial perturbation and moderate its final effect up to the time when a new steady state is reached. Adaptive thermogenesis also exists for cold (and less for warm) temperatures, but it concerns primarily thermoregulatory response consecutive to a cold stimulus. In contrast to adaptive thermogenesis in response to the plane of nutrition, postprandial thermogenesis or TEF is an acute response that persists for several hours after the meal. During this phase, macronutrients are stored temporally for subsequent use. During the early and late postabsorptive phase, substrates are mobilized so that over a 24-hour period (or more) an energy balance equilibrium is reached.

When adaptive thermogenesis is fully operating, the weight change measured will be smaller than that predicted from the magnitude of excess energy during overfeeding (or energy deficit during weight loss). As a result, large differences in weight gain and changes in body composition among subjects (characterized in overfeeding conditions as obesity-prone subjects or high gainers vs. obesity-resistant subjects or low gainers) constitute indirect evidence of various magnitudes of adaptive thermogenesis. However, to be qualified as adaptive thermogenesis these differences, which may be marked in the two aforementioned extreme categories, should be corroborated

more directly by measuring the components of TEE, that is, BMR or RMR, TEF or DIT, and physical activity. Ideally, when a metabolic chamber is used one can also measure 24-hour substrate balance for a quantitative assessment of the changes in the nature of tissue stored, which is below the level of detection of the body composition methods available today.

The concept of adaptive thermogenesis remains somehow obscure and hotly debated among most investigators, mostly because it has not been clearly mathematically defined (ideally by a straight equation). It is presented somehow differently by different investigators. For some [36], adaptive thermogenesis is EE to produce heat beyond that which is proportional to the amount of overfeeding associated with the theoretical costs of an increased body size and a larger food intake. Therefore, if there is no adaptive thermogenesis during overfeeding then weight gain will be considerable and fully comparable with the expected value predicted from the excess energy consumed. In contrast, those who are obese resistant tend to increase their EE with increased energy intake beyond the obligatory costs of the additional weight gain. For others, "adaptive thermogenesis is a mechanism explaining interindividual differences in weight gain on the same overfeeding regimen. Increases in EE during overfeeding are explained by the energy cost of weight gain (for storing macronutrients) and the energy cost of maintenance of a larger body weight" [37]. Changes in EE above these obligatory costs are considered to be adaptive thermogenesis. Note that the unexplained value includes not only the error of measurement but also adequacy of the algorithm to predict changes in EE, errors in assumptions made, and day-to-day differences in physical activity, the latter being assumed to be unchanged [38].

In summary, adaptive thermogenesis in response to overfeeding can be considered as a compensatory mechanism to limit excess weight gain and ultimately obesity, explained by various metabolic efficiencies among individuals. The changes in RMR (BMR) consecutive to short-term overfeeding (or underfeeding), which occur beyond those predicted from changes in body weight and body composition, reflect part of the phenomenon of adaptive thermogenesis. For example, if a change in EE at rest is measured as +200 kcal/day during overfeeding and 80% of this change is explained by weight gain, that is, FFM and fat mass gains, this means that adaptive thermogenesis is assumed to be 20%. This is only true if we hypothesize that 100% of the variance can be explained, which assumes no error of measurements.

The concept of adaptive thermogenesis remains somehow obscure and hotly debated among many investigators [38], mostly because it has not been clearly mathematically defined (ideally by a straight equation).

24.3.4 Basal or Resting Metabolic Rate as a Predictor of Total Energy Expenditure

In absolute terms, the TEE of the obese has been shown to be greater than that of lean individuals, both in the confinement of a respiration chamber [9] and in free-living conditions [10], despite the fact that some may have a blunted thermogenesis (see Section 24.3.2). However, in some circumstances the assessment of TEE is not feasible in practice (e.g., low budget and technical complexity of ^2H_2O measurement), despite the wide availability of objective methods to track it [39].

As mentioned in Section 24.1.1, it has been customary to partition TEE into BMR, TEF (postprandial thermogenesis), and physical activity subcomponents. Physical activity is the most variable, and hence the least predictable, component of TEE, since, in contrast to the other components, it can be voluntarily altered from day to day by the spontaneous or voluntary behavior of the subject. Based on the observation that half (in case of very high "physical activity level" [PAL]) to two-thirds (in case of low activity level) of the TEE is due to RMR (BMR), a so-called "factorial method" can be used to predict TEE.

One common factorial approach [38] specifies that TEE can be expressed as a multiple of baseline RMR or BMR (Figure 24.3). This is a ratio, without unit, defined as the physical activity level (PAL). It can be expressed in a simple

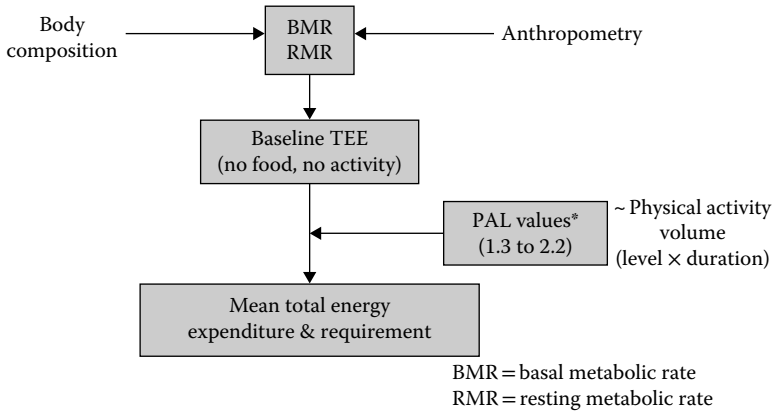

FIGURE 24.3 Simplified procedure used to estimate food energy needs from the measurement of total energy expenditure (TEE) as from resting metabolic rate (RMR) and physical activity level (PAL) in subjects of different body weights. RMR (basal metabolic rate [BMR]) is well predicted from body weight, age, and gender, whereas PAL can be considered as an overall descriptor of lifestyle activity and/or behavior. A PAL of 1.4 (sedentary lifestyle) indicates an increase in TEE of 40% above baseline RMR. If such calculations are applied to individuals rather than to groups, a much greater error of prediction is expected.

equation: PAL = TEE/BMR (kilocalories per kilocalories or kilojoules per kilojoules); hence, TEE is equal to BMR × PAL.

However, this global index of physical activity is telling nothing about the nature of physical activity and is somehow confounded by the varying contribution of TEF when RMR is used as the denominator rather than BMR.

Note that PAL is always calculated over a 24-hour period, although it has been proposed to assess PAL also during daytime (PALday) to avoid the confounding effect of sleeping duration on PAL24 hour [39]. PAL is never calculated for a specific activity (e.g., structured activity lasting minutes/hours during sports exercise). In the latter case, the ratio representing the relative intensity of work is called METs (an acronym for multiples of resting/sitting metabolic rate) and the equation is as follows: METs = energy cost of activity/BMR (kilocalories per kilocalories or kilojoules per kilojoules).

24.3.5 Magnitude of Physical Activity Level

The overall range of PAL for individuals maintaining body weight has been found to range from 1.30 for the most sedentary individuals to 2.5 for the most active ones [18]. Values on the order of 1.30 represent a "maintenance" level just compatible with healthy life in terms of energy requirement (intake). This value is based on the measurement of TEE in a respiration chamber with spontaneous movements but without structured exercise prescription [9]. Substantially increasing the PAL value in a sedentary subject requires a reasonable duration and intensity of physical activity (i.e., a certain volume): for example, an additional 30 minutes of moderate activity five times a week (such as brisk walking) assigned to a sedentary subject will increase PAL by about 10% only, that is, from 1.30 to about 1.45.

Note that PAL values of 3–4.7 can be sustained for limited periods of time in elite endurance athletes [18], but the PAL values that can be sustained for a long period of time in free-living adult populations fall in the range of 1.30–2.40. It is thought that the values that will reduce the probability of becoming obese and that would prevent the risk factors associated with obesity are on the order of 1.70.

24.3.5.1 How Is Physical Activity Level Classified?

Individuals with PAL values between 1.30 and 1.69 correspond to a sedentary or "light activity" lifestyle, whereas PAL values between 1.70 and 1.99 correspond to an active or "moderately active" lifestyle. A "vigorously active" lifestyle (very rare in occupational real life today) corresponds to PAL values between 2.00 and 2.40. The PAL approach is widely used today for calculating the total energy requirement of groups of individuals displaying various physical activities [17–18]. Figure 24.3 schematically shows the two steps required from the baseline BMR value (measured or predicted) to obtain TEE and hence total energy requirement in individuals or populations.

24.3.5.2 Physical Activity Level in Obesity

Since both RMR (BMR) and TEE of obese subjects are greater in absolute value for the same activity level, it seems of interest to briefly discuss whether or not PAL is substantially biased in terms of classifying physical activity in obese individuals of various BMIs. Recall that EE, expressed in absolute value, for a weight-bearing activity is proportional to body weight based on biomechanical considerations. The net efficiency of work also plays a minor role. As a result, the absolute EE during daily physical activity involving mostly the displacement of body weight (dynamic work) will be essentially linearly related to body weight. This is not the case for measurement in resting static conditions (RMR or BMR), which are associated more closely with FFM than body weight. The PAL index adjusts for body weight and body composition (denominator); but it is not necessarily independent of body weight or FFM, particularly in weight-bearing activities of moderate to vigorous intensity. The issue is whether obese individuals may have a slightly inflated PAL, not because of a higher level of physical activity but as a result of their larger body mass per se. Is it worth making a PAL correction for obese individuals? Using regression analysis, the influence of PAL on BMI was recently reported in a comprehensive, well-documented British expert report [18]. It showed a nonsignificant effect, suggesting that TEE can be calculated from PAL without considering BMI levels.

To summarize, TEE can be reasonably well predicted from BMR (RMR) in obesity using an appropriate PAL value as a function of the level of physical activity. PAL can be considered as an overall but rough index of lifestyle and physical activity behavior of individuals of various body weights.

Early studies have explored the PAL value in individuals of increasing body weight or BMI.

Compilations of total daily EE assessed by the doubly labeled water technique in individuals of various body weights and genders have been made by Schulz and Schoeller [40]. It was found that the increased weight of men (but not of women) was associated with a tendency for the PAL to be lower, indicating that obesity tends to depress physical activity in obese men, thereby confirming our previous results in the respiration chamber [9]. Subsequently, Prentice et al. [41], who used doubly labeled water measurements, showed an overall average value for PAL of 1.60 (range 1.55–1.65) for both men and women living a relatively sedentary lifestyle in affluent societies. The effect of gender and different body-weight classes on RMR, TEE, and PAL is shown in Figure 24.4. Globally considered, there is some evidence that the level of physical activity is generally lower in very (massive) obese individuals compared to lean ones, although this trend obviously masks the large variations among individuals.

In conclusion, absolute RMR is greater in obese than in lean individuals, in view of a much larger tissue mass. The excess adipose tissue with relatively low specific metabolic activity (compared to organs such as liver and kidney) is associated with additional lean tissues, including muscles (of higher metabolic activity) in a variable proportion, which adds to the difficulty of accurately predicting RMR in obesity. Even if some obese

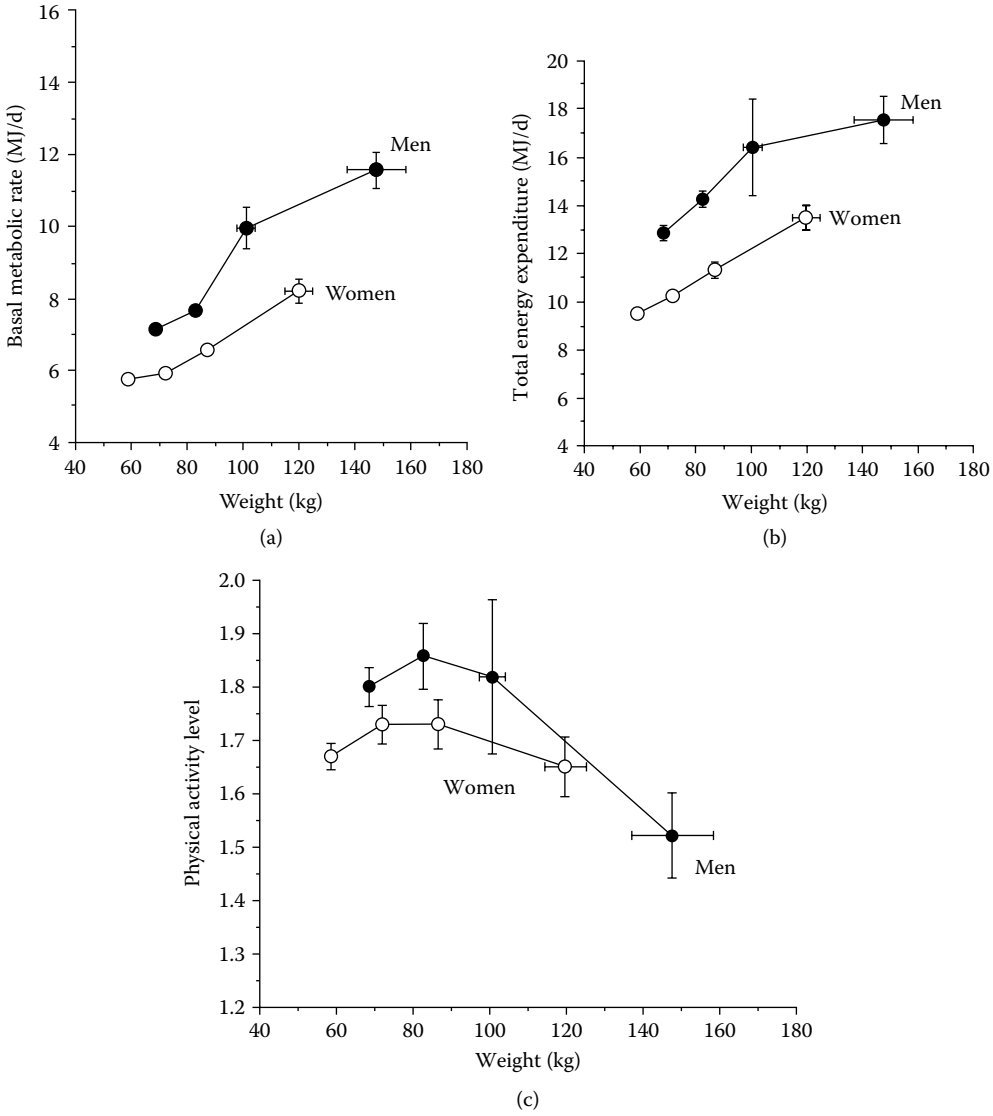

FIGURE 24.4 Effect of body weight and gender on resting energy expenditure (basal metabolic rate [BMR]/resting metabolic rate [RMR]) (a), on total energy expenditure (TEE) (b), and on physical activity level (PAL = TEE/BMR) (c) in free-living subjects: note the powerful effect of body weight on BMR and TEE and the higher energy expenditure at the same body weight in men compared to women. PAL sharply decreased on average in obese men with more than 100 kg (no differences in obese women below 120 kg, on average). The range of PAL was 1.52–1.73 in the pooled obese individuals and slightly higher in nonobese subjects (1.67 to 1.80). (From Prentice et al., *Eur J Clin Nutr*, 50, 93–7, 1996.)

seem to be penalized by a blunted postprandial thermogenesis (i.e., a low TEF) or DIT, this represents more a "metabolic tag" than an etiological factor of great importance for explaining a major disruption of daily energy balance and hence obesity.

24.4 MECHANISMS OF THERMOGENESIS

Ever since studies on the mechanisms of DIT started in the 1960s, the focus of attention on the neurohormonal control of thermogenesis has been (and still is) on the pivotal role played by the SNS, which, via its neurotransmitter norepinephrine (NE), acts on α- and β-adrenoceptors to influence heat production [42]. But it was not until the demonstration that SNS activity in a variety of tissues is increased during overfeeding (a state of enhanced energy dissipation) and decreased during starvation (a state of energy conservation) that SNS was considered as a pivotal efferent system linking diet and thermogenesis [43]. The subsequent demonstration that mice lacking genes coding for all β-adrenoceptors (β_1AR, β_2AR, and β_3AR) showed impaired DIT and developed obesity further underscored the key role of SNS in the control of DIT [44].

Many hormones are also known to modulate thermogenesis, notably thyroid hormones, leptin, insulin, glucagon, and glucocorticoids, as well as the human corticotrophin-releasing hormone. However, they are thought to exert a more permissive or facilitatory role in SNS-mediated thermogenesis, either by altering peripheral adrenergic responsiveness to the thermogenic effects of NE or by acting as peripheral signals for

central control of SNS activity to peripheral tissues. Indeed, studies in mice suggest that some of these peripheral signals (insulin, leptin, and ghrelin) act on the same hypothalamic neuronal circuitry that controls feeding behavior and satiety to exert influence over SNS-induced activation of thermogenesis [45]. In humans, evidence in support of a role for the leptin–SNS axis in the control of thermogenesis comes from the studies showing that in obese and never-obese humans who were maintaining body weight after a 10% weight loss the adaptations that occurred—lower mass-adjusted EE, associated with decreased circulating levels of NE, leptin, and thyroid hormones (T4 and T3)—all returned to pre-weight-loss levels following leptin replacement therapy, and the subjects lost more body weight and body fat [46].

Of particular interest for SNS-mediated thermogenesis is the potential control by NE over biochemical mechanisms whose activation leads either to an increased use of ATP (e.g., ion pumping and substrate cycling) or to a high rate of mitochondrial oxidation with poor coupling of ATP synthesis—the net result is an increase in heat production. To date, however, the only established molecular effector system for SNS control of DIT is the mitochondrial protein uncoupling protein 1 (UCP1), which uncouples oxidative phosphorylation in brown adipose tissue (BAT). The central importance of this SNS–BAT–UCP1 axis in the control of thermogenesis in response to diet or cold is well established in small mammals. But the organs and tissues that contribute importantly to DIT in humans are uncertain, despite decades-old controversies about the importance of skeletal muscle as a major site of sympathomimetically mediated thermogenesis and about the amount and functionality of BAT in humans. In recent years, the hypothesis of a role for BAT in the control of thermogenesis in adult humans has been revitalized by investigations using positron emission tomography coupled with computed tomography scanning. These have revealed the presence of substantial amounts of BAT in the neck and shoulder region that become apparent by relatively short exposure to mild cold through increased sympathetic activity [47]. Whether or not BAT has physiological relevance to human DIT, the search for pharmaceutical and nutraceutical products that may increase its amount and/or activity is an appealing strategy for the management of human obesity via stimulation of thermogenesis in a tissue whose primary function is to produce heat [48].

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25 Energy Cost of Exercise, Postexercise Metabolic Rates, and Obesity

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CONTENTS

25.1 INTRODUCTION

Basic laws of thermodynamics in humans determine that if total daily energy expenditure (EE) exceeds daily energy intake (EI), a negative energy balance ensues and obesity reduction will follow. Of the three major components of EE ([1] resting metabolic rate, [2] the thermal effect of feeding, and [3] the thermal effect of physical activity [PA]), the thermal effect of PA is the most variable component of daily EE and can constitute from 15% to 30% of 24-hour EE.[1] Indeed, a large portion of the marked variability of 24-hour EE among individuals, independent of differences in body size, is due to variability in the degree of daily PA.[2] Thus, variation in daily PA and/or exercise will have a notable effect on daily EE and reinforces its importance as a primary determinant of energy balance and, hence, obesity.

Although the exercise-induced negative energy balance prescribed in early studies was extremely modest, subsequent investigations employed designs wherein the negative energy balance was substantial, and hence a marked reduction in body weight and adiposity was observed in response to exercise.[3] Our prior review suggested that a positive dose–response relationship exists between exercise and obesity reduction but that major gaps in knowledge remained to determine whether a dose–response relationship existed between exercise and abdominal obesity.[3] In this report, we discuss the dose–response relationship between exercise and reduction in total and abdominal obesity. We also consider whether for a given volume of exercise, the intensity of exercise influences the reduction in fat and whether alterations in postexercise oxygen consumption may explain associations observed between exercise-induced increases in EE and reduction in body fat.

25.2 METHODOLOGY

We performed a MEDLINE search between the years 1966 and April 2012. The search was performed using the following key words: "exercise," "weight loss," "waist circumference (WC)," "body fat," "energy metabolism," and "oxygen consumption." The reference lists of those studies identified were then reviewed for additional studies. Studies were found suitable if they met the following inclusion criteria:

1. The participants in the study were asked to maintain their diet while changing their exercise routine.
2. EE or maximal oxygen consumption (VO_2 max) was reported.
3. The modality of exercise was aerobic in nature.
4. One of the following variables was provided: body weight or fat mass.
5. Subjects were 18 years or older.

Studies meeting these five inclusion criteria were subsequently divided into different groups according to study design. Initially, studies were divided according to whether it was a randomized controlled trial (RCT) or a non-RCT. Further analysis subdivided the RCT and non-RCT studies according to whether the exercise was supervised or not supervised. Supervised studies were studies wherein exercise (EE) was supervised and diet (EI) was monitored. Exercise was considered supervised if monitored for at least 90% of the time, whereas diet was considered supervised if monitored by self-reported food records for at least 3 days preintervention and postintervention. Unsupervised studies were studies wherein exercise was not supervised (exercise supervision was less than 75%) and dietary intake was not monitored (i.e., daily self-reported food records were not required; however, subjects were asked to maintain diet).

25.3 DERIVATION OF EXERCISE-INDUCED ENERGY BALANCE: LIMITATIONS AND ASSUMPTIONS

Derivation of exercise-induced EE in the majority of studies required that we make a number of assumptions. The principal assumption was that the exercise-induced EE derived from the prescribed or structured exercise performed was not masked by alterations in 24-hour PA and/or EI. Since no study reported data on 24-hour EE and/or measured daily PA levels (e.g., nonstructured PA) using objective measures such as accelerometry, we assumed that subjects' nonstructured PA remained unaltered during the intervention. Without exception, the studies reviewed reported EI values derived from self-report diet records, the validity of which is questionable.[4]

In addition to these limitations, several assumptions were required to derive exercise-induced EE for those studies wherein EE was not reported (26 studies). EE was calculated using the following variables: average weight and VO_2 max at baseline and at study completion, exercise duration (e.g., weeks), exercise frequency per week, and exercise intensity. Results from Polak et al.[5] are used to illustrate the method employed to estimate EE. In this study, subjects were asked to exercise for 45 minutes, 5 times a week for 12 weeks. Intensity increased every 3 weeks starting from 50% VO_2 max in the first week to 65% VO_2 max at the end of the intervention. Initial VO_2 max was 24.6 and 27.7 mL × kg^{-1} × min^{-1} at completion. Average VO_2 max and intensity for 12 weeks were calculated. To determine EE per 1 minute of exercise, average VO_2 max was multiplied by average intensity and by the energetic cost of oxygen (5 kcal/L). EE for one session and for a full week was then calculated using session duration and number of sessions per week. When intensity was determined using HRmax instead of VO_2max, we used the equation by Swain et al.[6] to determine EE. EE derived using these calculations assumed that changes in VO_2 max throughout the intervention were linear.

25.4 IS EXERCISE ASSOCIATED WITH REDUCTION IN BODY WEIGHT AND TOTAL ADIPOSITY IN A DOSE–RESPONSE MANNER?

A total of 39 studies met the inclusion criteria (Tables 25.1 and 25.2). Upon inspection of Tables 25.1 and 25.2, a specific pattern of response was observed. On average, studies with longer duration reported smaller weight loss for a given EE, whereas shorter duration studies reported greater weight loss. Based on this observation, short-term studies were identified as having a duration of less than 26 weeks, whereas long-term studies were identified as having a duration of more than 26 weeks (Table 25.1 and 25.2). This observation is consistent with our previous review.[3]

Short-term RCT and non-RCT studies were characterized by higher average weight loss (0.14 and 0.13 kg × week^{-1}, respectively, Table 25.1) than long-term RCT and non-RCT studies (0.02 and 0.04 kg × week^{-1}, respectively, Table 25.2). Paradoxically, weight loss remained greater in the short-term non-RCT trials despite reported EEs that were lower than long-term trials (~1393 and ~1557 kcal × week^{-1}, respectively).

Not surprisingly the exercise-induced changes in fat mass revealed a similar pattern to that observed for weight loss. Short-term RCTs and non-RCTs exhibited a greater average reduction in fat mass (0.23 and 0.14 kg × week^{-1}, respectively) than long-term RCT and non-RCTs (0.02 and 0.04 kg × week^{-1}, respectively).

We observed a dose–response relationship between exercise[3] and the reduction in body weight and fat mass. A positive linear association between EE, weight loss, and fat mass reduction was found in the short-term studies (Figure 25.1a); as EE increased, a greater weight loss and fat mass reduction were observed. A linear relationship was also evident in the long-term studies; however, for a given increase in EE, the magnitude of the reduction in weight loss and fat mass across studies was minimal (Figure 25.1b).

Differences in study design between the short- and long-term studies may provide insight into why, for a given EE prescribed, the decrease in body weight and fat loss differed substantively. The exercise prescribed within the majority of long-term studies was unsupervised whereas the exercise prescribed within the majority of short-term trials was performed under direct supervision. Consequently, by comparison to long-term trials, it is more likely that the participants in short-term studies adhered better to the exercise regimen prescribed, thus achieving the expected weight and/or fat loss. Long-term trials relied on subjects properly adhering to the prescription of exercise while performing the exercise on their own (e.g., unsupervised). It is also possible that adherence to dietary intake instructions was more readily adhered to in short-term as opposed to long-term trials. Indeed, the frequency of self-reporting dietary intake in short-term trials was generally increased by comparison to long-term trials. Together, these observations suggest that in short-term trials, adherence to the exercise and diet interventions prescribed was likely increased by comparison to long-term trials.

TABLE 25.1
Influence of Energy Expenditure on Changes in Body Weight, Total Body Fat, Waist Circumference, Abdominal Adipose Tissue, Abdominal Subcutaneous Adipose Tissue, and Visceral Adipose Tissue in Short-Term Studies (<26 Weeks)

Supervision	Reference	Subjects	BMI (kg × m^{-2})	% Fat	Group	Study Duration (weeks)	Energy Expenditure (kcal × week^{-1})	Prescribed Exercise Duration (min × week^{-1})	Expected Weight Loss (kg × week^{-1})*	Actual Δ Weight (kg × week^{-1})	Δ Body Fat (kg × week^{-1})	Δ WC (cm × week^{-1})	ABAT (% × week^{-1})	ΔASAT (% × week^{-1})	ΔVAT (%× week^{-1})
							RCT								
US	Mourier et al.[7]	11 diabetics	30		Control	8				−0.02	−0.15				
		10 diabetics	30		Exercise		959	112	−0.12	−0.19	−0.07	−0.13	−5.79	−1.51	−6.06
S	Sopko et al.[8]	6 men		28	Control	12				NS	NS				
		6 men		31	Exercise		3500	300	−0.46	−0.52	−0.64				
S	Ross et al.[9]	8 men	31		Control	12				0.01	−0.60	−0.01			0.00
		16 men	32		Exercise		4900	455	−0.63	−0.63	−0.51	−0.58			−2.35
S	Ross et al.[10]	17 obese women			Exercise	14	3668	448	−0.48	−0.44	−0.48	−0.47	0.00	0.14	−2.17
		10 obese women			Control					0.04	0.06	0.08	−1.63	−1.41	−0.31
US	Cuff et al.[11]	9 diabetic women			Exercise	16	914	225	−0.12	−0.08	NR		−0.17	−0.13	−0.26
		9 diabetic women			Control					0.13	NR		0.13	0.20	−0.01
US	Van Aggel-Leijssen et al.[12]	8 obese men			Exercise	12	1050	171	−0.14	0.03	−0.03				
		8 obese men			Exercise		1050	98	−0.15	−0.03	0.05				
		8 obese men			Control					−0.06	−0.01				
US	Coker et al.[13]	3 men, 6 women	32	39	Exercise	12	2250		−0.29	−0.42	−0.37		−1.56	−1.03	−2.51
		3 men, 5 women	31	40	control					0.17	0.14		−0.03	−0.22	0.30
S	Nordby et al.[14]	12 men		31.3	Exercise	12	4200	360	−0.55	−0.49	−0.64	−0.33	−2.35	−2.10	−2.60
		12 men		31.1	Control					0.09	0.00	0.00	−0.02	0.14	−0.12
S	Davidson et al.[15]	10 older men, 14 older women	30.4		Control	24				0.01	−0.06	−0.01	−0.02	−0.03	0.03
		13 older men, 17 older women	29.5		Exercise		115	150	−0.15	−0.13	−0.37	−0.21	−0.43	−0.36	−0.51
							Non-RCT								
S	Goran and Poehlman[16]	11 older adults		30	Exercise	8	675	86	−0.09	0.00	−0.11				
S	Hagan et al.[17]	12 men		25	Exercise	12	1772	150	−0.23	−0.02	0.02				
		12 women		35	Exercise		1002	150	−0.13	−0.05	−0.12				
S	Grediagin et al.[18]	6 women	24		Hi Ex	12	1200	133	−0.16	−0.06	−0.19	−0.10			
		6 women	26		Li Ex		1200	212	−0.16	−0.27	−0.19	−0.16			
S	Wilund et al.[19]	6 men, 10 women CETP genotype (B1B1)		38	Exercise	12	974	120	−0.11	−0.07	−0.09		−0.61	−0.30	−0.91
		8 men, 6 women CETP genotype (B1B2)		34	Exercise		974	120	−0.11	−0.10	−0.09		−0.48	0.03	−1.24
S	Kim et al.[20]	24 obese men	30.7		Exercise	12	1124	180	−0.15	−0.30	−0.23	−0.38			−1.33
S	Bouchard et al.[21]	14 young men		24	Exercise	13	3999	357	−0.57	−0.38	−0.38	−0.46	−2.24	−2.10	−2.75

(*Continued*)

TABLE 25.1 (*Continued*)
Influence of Energy Expenditure on Changes in Body Weight, Total Body Fat, Waist Circumference, Abdominal Adipose Tissue, Abdominal Subcutaneous Adipose Tissue, and Visceral Adipose Tissue in Short-Term Studies (<26 Weeks)

Supervision	Reference	Subjects	BMI ($kg \times m^{-2}$)	% Fat	Group	Study Duration (weeks)	Energy Expenditure ($kcal \times week^{-1}$)	Prescribed Exercise Duration ($min \times week^{-1}$)	Expected Weight Loss ($kg \times week^{-1}$)*	Actual Δ Weight ($kg \times week^{-1}$)	Δ Body Fat ($kg \times week^{-1}$)	Δ WC ($cm \times week^{-1}$)	ABAT ($\% \times week^{-1}$)	ΔASAT ($\% \times week^{-1}$)	ΔVAT ($\% \times week^{-1}$)
S	Houmard et al.[22]	13 men	30		Exercise	14	1545	153	−0.20	−0.14	−0.20	−0.31			
S	Smutok et al.[23]	10 men	29		Control	20				0.04	0.01				
		13 men	28		Exercise		808	90	−0.10	−0.02	−0.07				
US	Farrel and Barboriak[24]	7 men	28		Exercise	8	1566	105	−0.20	−0.25	−0.21				
		9 women	24		Exercise		888.32	105	−0.12	−0.06	−0.11				
US	Giannopoulou et al.[25]	11 diabetic women			Exercise	14	1030	150	−0.13	−0.12	−0.19	−0.21			−0.73
US	Halverstadt et al.[26]	34 men, 49 women		36	Exercise	24	902	134	−0.12	−0.05	−0.06		−0.14	0.00	−0.47
US	Gordon et al.[27]	14 hypertensive adults	34		Exercise	12	996	147	−0.17	−0.08	−0.07				
US	Polak et al.[5]	25 premenopausal women	32.2		Exercise	12	1450	225	−0.19	−0.43	−0.34	−0.30			
US	Green et al.[28]	30 postmenopausal women	29.3		Exercise	20	790	129	−0.10	0.01	−0.02	−0.05	−0.08	−0.06	−0.16
S	Crampes et al.[29]	11 overweight men	27.7	22.8	Exercise	16	3219	300	−0.42	−0.12	−0.09				
S	O'Leary et al.[30]	5 men, 11 women	33.2	36.5	Exercise	12	1734	275	−0.22	−0.27	−0.28		1.45	−1.11	−1.87

Notes: ABAT, abdominal adipose tissue; ASAT, abdominal subcutaneous adipose tissue; CETP, cholesteryl ester transfer protein; Hi Ex, high-intensity exercise; Li Ex, low-intensity exercise; RCT, randomized controlled trial; S, supervised exercise; US, unsupervised exercise; VAT, visceral adipose tissue; WC, waist circumference.

[a] Expected change in weight on the basis of weekly caloric expenditure (7700 kcal = 1 kg).

TABLE 25.2
Influence of Energy Expenditure on Changes in Body Weight, Total Body Fat, Waist Circumference, Abdominal Adipose Tissue, Abdominal Subcutaneous Adipose Tissue, and Visceral Adipose Tissue in Long-Term Studies (≥26 Weeks)

Supervision	Reference	Subjects	BMI (kg × m^{-2})	% Fat	Group	Study Duration (weeks)	Energy Expenditure (kcal × week^{-1})	Prescribed Exercise Duration (min × week^{-1})	Expected Weight Loss (kg × week^{-1})[a]	Actual Δ Weight (kg × week^{-1})	Δ Body Fat (kg × week^{-1})	Δ Waist Circumference (cm × week^{-1})	ABAT (% × week^{-1})	ΔASAT (% × week^{-1})	ΔVAT (% × week^{-1})
								RCT							
S	Donnelly et al.[31]	16 men			Exercise	64	2710	225	−0.35	−0.08	−0.07		−0.28	−0.25	−0.36
		15 men			Control					0.00	0.01		−0.06	−0.09	−0.11
		25 women			Exercise		1880	225	−0.24	0.01	−0.01		−0.28	−0.02	−0.09
		18 women			Control					0.05	0.03		−0.06	0.20	0.08
US	Dipietro et al.[32]	9 older women			Exercise	36	1200	260	−0.16			−0.04			
		9 older women			Exercise		1200	220	−0.16			−0.07			
		7 older women			Control			180				−0.06			
US	Ready et al.[33]	10 postmenopausal women	32		Control	26				0.02	0.01	0.00			
		15 postmenopausal women	29		Exercise		1522	266	−0.20	−0.07	−0.05	−0.10			
US	Kohrt et al.[34]	12 postmenopausal women	27		Control	39				0.01	0.01				
		14 postmenopausal women	27		Exercise		599	145	−0.08	−0.07	−0.08				
US	Irwin et al.[35]	87 women			Exercise	48	632	176	−0.08	−0.03	−0.03	−0.02	−0.12	−0.11	−0.12
		86 women			Control						0.00	0.00	0.03	0.04	0.00
S	Watkins et al.[36]	11 obese men			Exercise	26	1583	119	−0.21	−0.08	−0.04				
		11 obese men			Control					0.04	0.04				
US	Campbell et al.[37]	85 post-menopausal women	30	47.4	Control	48				0.00					
		83 postmenopausal women	30	47.5	Exercise		1173	171	−0.20	−0.03					

(*Continued*)

TABLE 25.2 (*Continued*)
Influence of Energy Expenditure on Changes in Body Weight, Total Body Fat, Waist Circumference, Abdominal Adipose Tissue, Abdominal Subcutaneous Adipose Tissue, and Visceral Adipose Tissue in Long-Term Studies (≥26 Weeks)

Supervision	Reference	Subjects	BMI (kg × m^{-2})	% Fat	Group	Study Duration (weeks)	Energy Expenditure (kcal × week^{-1})	Prescribed Exercise Duration (min × week^{-1})	Expected Weight Loss (kg × week^{-1})[a]	Actual Δ Weight (kg × week^{-1})	Δ Body Fat (kg × week^{-1})	Δ Waist Circumference (cm × week^{-1})	ABAT (% × week^{-1})	ΔASAT (% × week^{-1})	ΔVAT (% × week^{-1})
								Non-RCT							
S	Kohrt et al.[38]	16 older men	25		Control	45				0.00	-0.01	0.01			
		47 older men	27		Exercise		1879	184	−0.24	−0.12	−0.06	−0.09			
		13 older women	24		Control					0.03	0.02	0.00			
		46 older women	25		Exercise		1106	184	−0.14	−0.04	−0.04	−0.06			
US	Poirier et al.[39]	11 diabetic men		27	Exercise	26	1470	170	−0.24	−0.03	−0.02				
US	Coggan et al.[40]	12 older men		28	Exercise	43	1515	172	−0.20	−0.08	−0.08				
		11 older women		36	Exercise		1515	172	−0.20	−0.05	−0.06				
US	Lamarch et al.[41]	31 women	34		Exercise	26	2589	405	−0.33	−0.03	−0.03				
US	Frey-Hewitt et al.[42]	44 men		27	Exercise	46	1786	173	−0.23	−0.09	−0.09				
US	Despres et al.[43]	13 women	34		Exercise	60	2623	405	−0.34	−0.06	−0.08		−0.16	−0.18	−0.05
S	Donnelly et al.[44]	11 women		41.8	Continuous	72	640	90	−0.08	−0.02	−0.03	−0.03			
		11 women		42.6	Intermittent		446	150	−0.06	−0.01	−0.01	0.00			

Notes: ABAT, abdominal adipose tissue; ASAT, abdominal subcutaneous adipose tissue; RCT, randomized controlled trial; S, supervised exercise; US, unsupervised exercise; VAT, visceral adipose tissue; WC, Waist Circumference.

[a] Expected change in weight on the basis of weekly caloric expenditure (7700 kcal = 1 kg).

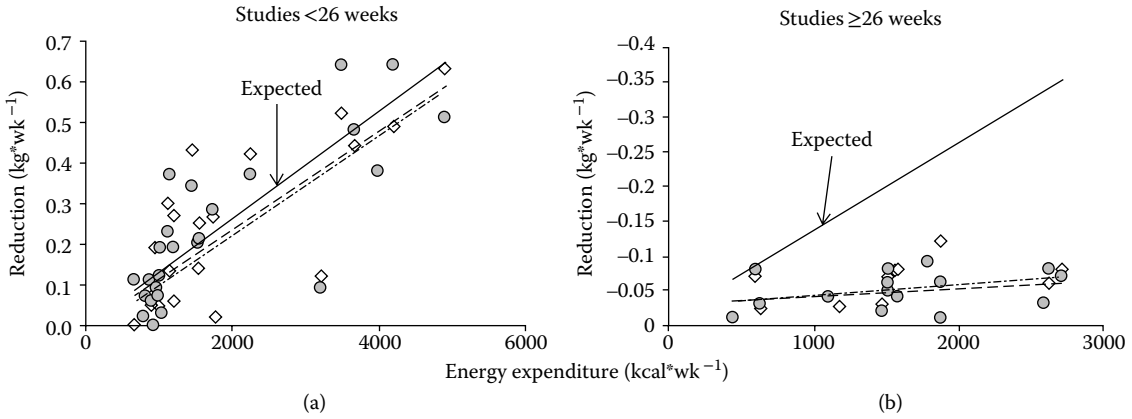

FIGURE 25.1 (a) The relationship between energy expenditure and actual weight reduction ($N = 25$) versus expected reduction in weight ($N = 25$) and fat mass ($N = 24$) in short-term randomized controlled trial (RCT) and non-RCT (Table 25.1). (b) The relationship between energy expenditure and weight reduction ($N = 13$), expected reduction in weight and fat mass ($N = 12$) in long-term RCT and non-RCT (Table 25.2). Diamonds (◇) represent weight loss. Circles (◯) represent fat loss. Expected weight loss is demonstrated by a solid line, while -.-.-.- demonstrates weight loss, and – – – – – demonstrates fat loss. The data plotted in the figure are group means for the studies cited in Tables 25.1 and 25.2.

25.5 IS EXERCISE ASSOCIATED WITH A REDUCTION IN ABDOMINAL OBESITY IN A DOSE–RESPONSE MANNER?

25.5.1 Abdominal Adipose Tissue

Reduction in total abdominal adipose tissue as measured using radiographic methods (e.g., CT or MRI) in response to short-term RCTs approximated 1.1%/week whereas the corresponding reduction in long-term RCTs and non-RCTs was 0.1%/week (Tables 25.1 and 25.2). A positive dose–response relationship was observed between EE and reduction in abdominal adipose tissue for short-term studies (Figure 25.2). It is apparent from Figure 25.2 that additional long-term, well-controlled studies are required to determine whether a dose–response relationship truly exists between EE and abdominal adipose tissue.

25.5.2 Abdominal Subcutaneous Adipose Tissue

Short-term RCT and non-RCT studies suggest a 0.6% reduction in abdominal subcutaneous adipose tissue per week, whereas long-term RCT and non-RCT revealed a modest 0.1% loss in abdominal subcutaneous adipose tissue per week (Tables 25.1 and 25.2). A positive dose–response association was observed between EE and reduction in abdominal subcutaneous adipose tissue for short-term studies (Figure 25.2).

25.5.3 Visceral Adipose Tissue

The changes in visceral adipose tissue (VAT) in response to exercise revealed that short-term RCT and non-RCT showed a 1.3% and 1.2% reduction in VAT per week, whereas examination of long-term RCT and non-RCT studies revealed together a 0.1% loss in VAT per week (Tables 25.1 and 25.2). A positive association was observed between EE and reduction in VAT for both short-and long-term studies (Figure 25.2). For the short-term studies, a single outlier, Mourier et al.[7] report a disproportionately large reduction in VAT following 8 weeks of exercise in men and women of modest EE. Other than errors in self-report of EI (e.g., diet), this observation is not readily explained.

25.5.4 Waist Circumference

Consistent with observations using imaging methods, short-term RCT and non-RCT studies report reductions in WC (0.18 and 0.24 cm × week^{-1}, respectively) compared to the long-term RCTs and non-RCTs (0.04 and 0.03 cm × week^{-1}, respectively). A positive dose–response association between EE and the reduction in WC was observed for both short- and long-term studies (Figure 25.3). However, it is noteworthy that the reduction in WC across the short-term studies was more than four times greater than long-term studies.

25.6 IS EXERCISE INTENSITY ASSOCIATED WITH A REDUCTION IN BODY FAT IN A DOSE–RESPONSE MANNER?

Whether a dose–response relation exists between exercise intensity and reduction in body fat is unclear. In other words, if exercise volume is held constant, is high-intensity exercise associated with an increase in the mobilization of total or regional fat compared to moderate or low-intensity exercise? Few studies have examined this question and those that have are characterized by small sample sizes and relatively short-term exercise durations. Tjønna et al.[45] randomized subjects with the metabolic syndrome to one of two groups: continuous moderate-intensity exercise (70% HRmax) and aerobic interval training (90% HRmax). The volume (kcal) of exercise was equalized between groups over the 16-week intervention. Interestingly, despite a modest reduction in body weight that was not different between groups, WC decreased to a greater extent in response to moderate- compared to high-intensity

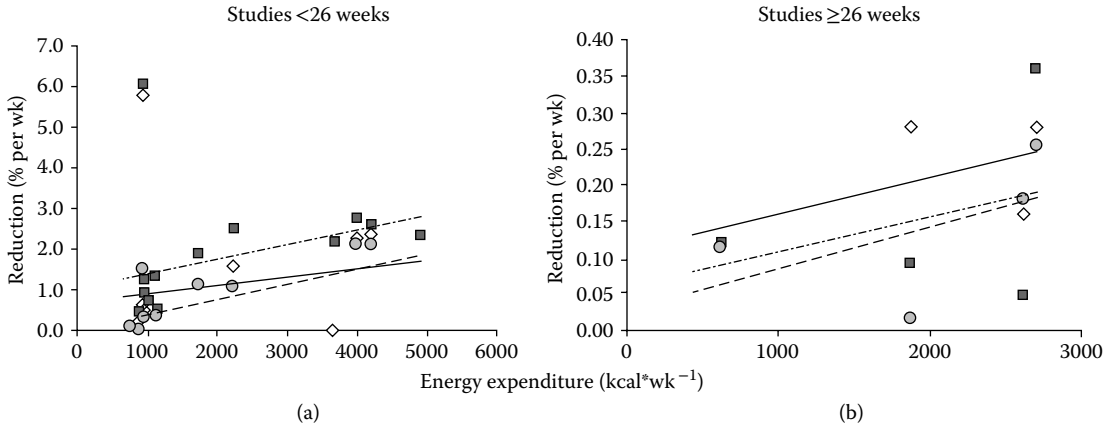

FIGURE 25.2 The relationship between energy expenditure and total abdominal adiposity reduction ($N = 12$), abdominal subcutaneous adipose tissue reduction ($N = 12$), and visceral adipose tissue (VAT) reduction ($N = 15$) in (a) short-term randomized controlled trial (RCT) and non-RCT ($N = 14$, Table 25.1) and in (b) long-term RCT and non-RCT ($N = 3$, Table 25.2). Diamonds (◇) represent total abdominal adiposity loss. Circles (◯) represent subcutaneous adipose tissue loss. Squares (□) represent VAT loss. Total abdominal adiposity loss represented by a solid line, while _ _ _ _ _ represents abdominal subcutaneous adipose tissue loss and -.-.-.- represents VAT loss. The data plotted in the figure are group means for the studies cited in Tables 25.1 and 25.2.

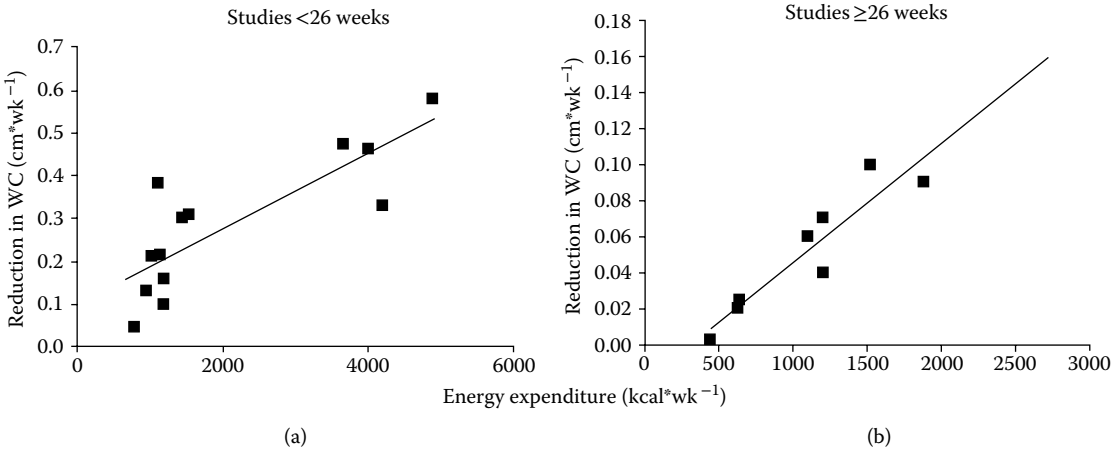

FIGURE 25.3 The relationship between energy expenditure and waist circumference (WC) reduction in (a) short-term randomized controlled trial (RCT) and non-RCT ($N = 12$, Table 25.1) and in (b) long-term RCT and non-RCT ($N = 5$, Table 25.2). Squares (□) represent WC reduction. The data plotted in the figure are group means for the studies cited in Tables 25.1 and 25.2.

exercise. This observation contrasts with those of Trapp et al.[46] who randomized obese subjects into one of three groups: high-intensity intermittent exercise (relative intensity not indicated), steady-state exercise (60% VO_2max), and control. Exercise volume was equalized over the 15-week intervention. In contrast to Tjønna et al.,[45] the high-intensity group reduced total and abdominal fat compared to the steady-state or moderate-intensity exercise group. Mougios et al.[47] randomized a small sample of nonobese women into one of two exercise groups: low intensity (45% VO_2max) and high intensity (72% VO_2max). Exercise volume was equalized between groups (370 kcal/session) over the duration of the 3-month intervention. Despite a greater decrease in body mass within the low-intensity group compared to the high-intensity group, the reduction in fat mass was not different between groups.

DiPietro et al.[32] randomized older subjects (>60 years) into one of three groups: high-intensity exercise (80% VO_2max), moderate-intensity exercise (65% VO_2max), and controls. Exercise groups expended 300 kcal/session, 4 days/week. No significant differences were observed either within or between groups for any body composition measure. Similar findings were reported by van Aggel-Leijssen[12] who examined the effects of high-intensity (70% VO_2max) and low-intensity exercises (40% VO_2max) on adiposity in men. The volume of exercise was equalized over 12 weeks. No effect on body weight and body composition was observed as a result of either intervention.

At present, it is unclear whether increasing exercise intensity when the volume of exercise is held constant is associated with an increase in the loss of total or regional adiposity. Given increasing evidence suggesting the benefits of high intensity compared to moderate intensity for reducing cardiometabolic risk factors,[48,49] further study is required to investigate whether a possible pathway that would explain

cardiometabolic benefit associated with higher-intensity exercise is mediated through an increased reduction in total or abdominal adiposity.

25.7 EXCESS POSTEXERCISE OXYGEN CONSUMPTION AND REDUCTION IN BODY FAT

The increase in oxygen uptake required to meet the energy needs during exercise does not return to resting levels immediately postexercise but rather may be elevated for extended periods. The term "excess postexercise oxygen consumption" (EPOC) was first introduced by Gasser and Brooks in 1984 as a means of capturing both the rapid and prolonged components of the observed increase in oxygen uptake postexercise.[50,51] A detailed description of the EPOC components and their associated mechanisms is beyond the scope of this chapter and the reader is referred to the review of Borsheim and Bahr[51] for details. The objective here is to consider whether exercise intensity and/or volume may influence the magnitude and duration of EPOC and more specifically whether the magnitude of EPOC may be of value with respect to obesity reduction.

25.8 EFFECTS OF INTENSITY AND DURATION OF EXERCISE ON EXCESS POSTEXERCISE OXYGEN CONSUMPTION

Two prior reviews have carefully considered current knowledge with respect to the separate influence of exercise intensity and duration on EPOC.[51,52] Consistent within the conclusions of these reviews is the notion that duration and intensity of exercise act synergistically to influence EPOC; however, it appears that, at least at exercise intensities above 50% of VO_2max, exercise intensity makes the greater contribution.[51] This observation is well illustrated by the work of Gore and Withers.[53] Their seminal study included nine experimental treatments ($N = 9$ trained men), each with different combinations of the following exercise durations: 20, 50, and 80 minutes, and intensities 30%, 50%, and 70% VO_2max. The authors observed a strong interaction between exercise duration and exercise intensity. With the exception of exercise performed at 30% VO_2max, the magnitude of the EPOC was elevated as exercise duration increased while exercise intensity was held constant. Although the magnitude of the EPOC also increased with increasing exercise intensity while duration was held constant, the authors noted that intensity contributed far more to the increase in EPOC (~45%) compared to exercise duration (7%). With a constant duration of 80 minutes, the lowest EPOC was only 1.0 L equivalent to 5.2 kcal at 30% VO_2max, while the highest EPOC was 14.6 L equivalent to 73 kcal at 70% VO_2max. EPOC was determined over 8 hours postexercise.

Although the vast majority of studies report that a synergistic relation exists between exercise intensity, duration, and EPOC, it is apparent that with increasing exercise duration, total EE is increased, thus confounding this interpretation. Thus, whether exercise intensity is positively associated with EPOC when exercise volume is held constant is still unclear. We examined four studies within which the investigators held exercise volume (kcal) constant while varying intensity.[54–57] Characteristic to this design, for a given exercise volume, the duration of higher-intensity exercise is *less than* lower-intensity exercise. Sedlock and colleagues[57] were one of the first to consider the separate effects of exercise intensity and volume on EPOC. Highly trained men exercised at (1) high (~75%) and low (~50%) intensities with caloric expenditure held constant (~300 kcal) and (2) equal exercise intensity with varying duration. The primary observation was that exercise intensity affected both the magnitude and the duration of the EPOC. Holding EE constant revealed a longer EPOC duration for the high-intensity group (33.3 minutes) compared to the low-intensity group (19.8 minutes) and a greater caloric expenditure during the EPOC rapid phase. This finding is consistent with Frey and colleagues[54] who examined trained and untrained women who exercised at high (~80%) and low (~65%) intensities with caloric expenditure held constant (~300 kcal/session). The authors also found that EPOC at high intensity was greater than at low intensity despite a shorter duration for the high intensity. Phelain and colleagues[55] observed similar results with trained women exercising at high (~75%) and low (~50%) intensities with constant caloric expenditure (~500 kcal). In contrast to these findings, Sedlock and colleagues[56] found no effect of exercise intensity and duration on EPOC magnitude. This study was also performed with trained women who exercised at high (~60%) and low (~40%) intensities with caloric expenditure held constant (~200 kcal). That exercise intensity did not affect the EPOC magnitude might be due to a lower exercise volume (200 kcal) as opposed to the other studies (300 kcal and above). In general, however, these findings support the notion that exercise intensity contributes substantially to the observed EPOC.

Whether the EPOC is of value with respect to reducing body fat will depend on whether the individual sustains exercise long term. Indeed, although EPOC appears to be modest in response to a single exercise session, the potential energy increase associated with EPOC may be substantial if exercise is sustained long term. Based on their comprehensive review, Borsheim and Bahr[51] report that for a single session of moderate-intensity (less than 1 hour at ~50% VO_2max) exercise, EPOC will approximate 12–24 kcal, equivalent to ~2800 kcal a year, which translates to a loss of 311 g fat (assuming exercise is performed 3 days/week). In response to vigorous exercise (at least 1 hour at a minimum of 70% VO_2max), EPOC will approximate 170 kcal/session or approximately 26,000 kcal/year, which translates to a loss of 3.0 kg fat. Clearly 1 hour of exercise performed at no less that 70% of VO_2max for many if not most overweight or obese persons will be difficult to sustain. Consequently, while from a physiological perspective EPOC consequent to sustained high-intensity exercise may be associated with a marked increase in fat reduction, whether overweight persons will adopt and sustain this regimen is uncertain.

25.9 SUMMARY

Our search strategy identified 39 studies having investigated the effects of exercise without alterations in dietary intake as a treatment strategy for obesity. Among these, only one study recruited entirely non-Caucasian subjects.[20] Given that the accumulation of adipose tissue for a given BMI varies substantially according to race,[58,59] it is not unreasonable to suggest that the mobilization of lipid (adipose tissue) may also differ according to race. Clearly, there is a need for additional well-controlled trials that consider the independent effects of exercise on obesity reduction.

Without exception, the contribution of 24-hour PA and/or EE was not reported and thus we must assume that the increase in structured, prescribed exercise is responsible for the negative energy balance. In this regard, the observations of Church and colleagues[60] are instructive as they report that the pedometer-measured PA patterns outside of that prescribed did not change in women who were randomized to one of three doses of exercise for 6 months. The inclusion of accelerometry as a relatively straightforward method for measuring daily PA EE would provide much needed insight into whether prescribed exercise is associated with corresponding changes (e.g., compensation) in 24-hour EE.

Few studies have included multiple exercise arms; thus, our interpretation of group mean data from independent studies with variations in exercise-induced negative energy balance should be taken with caution. There is a need for RCTs that are specifically designed to determine the dose–response associations between exercise and obesity reduction.

Notwithstanding these limitations, our observations extend prior reviews and confirm that a positive dose–response relationship exists between exercise and reduction in body fat. However, although exercise alone is associated with reductions in total and abdominal fat in a dose–response manner, gaps in knowledge persist. This is particularly true for short-term studies wherein the weekly EE induced by exercise is either very low or very high (Figure 25.1). Nevertheless, the dose–response relationship observed in the short-term studies indicates that to reduce bodyweight by about 0.25 kg/week, the required EE approximates 2700 kcal/week (Figure 25.1). Our observations suggest that EE of this magnitude will require exercising for about 50 minutes, five times a week at 70% VO_2max (83% of maximum heart rate). It is important to reinforce the observation that these calculations are derived from short-term studies alone. It is evident from Figure 25.1 that in long-term trials, despite the similarity in the EEs prescribed, that the corresponding reduction in both total and abdominal obesities is substantially less.

Taken together, the findings reported here underscore the notion that regular exercise combined with a healthful diet is associated with reductions in both total and abdominal obesities in a dose–response manner. Although the reduction in adiposity and/or bodyweight is relatively modest, it is repeatedly observed that substantial benefit occurs in response to modest weight and/or fat loss across a wide range of health outcomes.[61,62] Despite this positive observation, demonstration that the adoption of exercise alone as a treatment strategy for obesity reduction can be sustained long term remains a challenge.

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26 Energy Partitioning, Substrate Oxidation Rates, and Obesity

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CONTENTS

26.1 INTRODUCTION

The notion of energy partitioning is perceived by the authors of this chapter as the sharing of substrate energy between metabolic pathways and/or tissues depending on the homeostatic needs of the moment. Even if energy partitioning represents a concept that seems to be worthy of consideration in any issue pertaining to metabolic regulation, it is not systematically considered in obesity research. In this chapter, the energy partitioning concept is described to better understand the factors involved in the development of obesity taken as a whole. In addition, the clinical implications of emerging relevant topics are discussed.

26.2 ENERGY PARTITIONING AND MACRONUTRIENT BALANCE

26.2.1 Respiratory Quotient–Food Quotient Concept

The partitioning of body energy seems to be organized to promote homeostasis or at least to permit the best compromise in a context where some metabolic dysfunctions are present. One of the main conceptual models that have been proposed over the past few decades to describe in vivo metabolic regulation is the respiratory quotient (RQ)–food quotient (FQ) concept.[1] Basically, Flatt[1] demonstrated a high positive relationship between RQ-FQ ratio and energy balance, suggesting that the latter occurs when macronutrient balance is also reached. This phenomenon necessitates taking into account the particularities of each component of macronutrient balance, including specific nutrient partitioning, in the regulation of energy balance. As shown in Table 26.1, discussion on this topic includes consideration of different processes that influence the precision of the regulation of protein, carbohydrate, and lipid balances. In addition, even if alcohol cannot be viewed as a nutrient it is metabolized by the body with consequences on metabolic regulation that may induce important effects on energy balance and partitioning.

26.2.2 Protein Balance, Energy Partitioning, and Obesity

As previously described,[2] humans have the capacity to minimize protein losses even under conditions of severe food deprivation. Accordingly, small increases or decreases in the protein content of the diet are known to promote concordant adjustments of amino acid oxidation.[3] This can be done because of the energy partitioning opportunities that are accessible to protein metabolism via deamination and transamination. As indicated in Table 26.1, variations in protein intake and/or metabolism can also influence appetite control

TABLE 26.1
Characteristics of Components of Macronutrient Balance

	Components			
Characteristics	**Protein**	**Carbohydrate**	**Lipid**	**Alcohol**
• Can acutely promote its oxidation	Yes	Yes	No	Yes
• Can acutely influence appetite control	Yes	Yes	No	No?
• Can acutely transfer energy to another macronutrient component	Yes	Yes	No	Yes

Source: Tremblay A, Alméras N, *Int J Obes*, 19, 4, 597–S101, 1995.

and energy intake. To our knowledge, Mellinkoff et al.[4] were the first investigators to present evidence of this effect when they proposed an aminostatic theory of appetite control. The rationale underlying this theory seems to justify the use of high-protein diets to facilitate appetite and body weight control in obese individuals. Indeed, the use of a high-protein diet was found to accentuate the loss of body weight and fat in obese individuals[5] and to promote weight maintenance in weight-reduced obese subjects.[6] In addition, the appetite-facilitating effect of a high-protein diet and the protein–glucose metabolism connection have prompted clinical investigations combining high protein intake and low–glycemic index (GI) carbohydrate intake. In the study by Dumesnil et al.,[7] a high-protein, low-GI diet was found to induce a substantial decrease in daily energy intake compared to a low-fat diet typical of the recommendations of the American Heart Association. This is concordant with the recent results obtained in the Diogenes Study in which a high-protein, low-GI regimen was the best dietary intervention to promote body weight stability over time.[8]

The clinical implications of high protein intake also necessitate the evaluation of safety of this strategy, considering the ability of the kidney to take charge of the resulting demand for nitrogen clearance. In this regard, a recent review of relevant literature revealed that long-term daily protein intakes under 2.8 g/kg body weight per day have no negative effects on the renal function of athletes and that the concern regarding increased risk of complications in diabetics who could display diminished renal function should not be generalized to healthy individuals.[9]

26.2.3 Carbohydrate Balance, Energy Partitioning, and Obesity

Body carbohydrate stores in the form of glycogen vary between 200 and 500 g in adults[10] and correspond to approximately the total daily intake of this nutrient. Under normal feeding conditions carbohydrate utilization is dominant in macronutrient oxidation, which implies the presence of mechanisms allowing a precise adjustment from carbohydrate oxidation to carbohydrate availability.[1] This includes flexibility in glucose oxidation, which declines acutely under low-carbohydrate diet conditions and increases when carbohydrate intake increases.[3] Energy partitioning from gluconeogenesis is also important since it can significantly contribute to glucose oxidation when carbohydrate intake is low.[11] In addition, lipogenesis can accommodate excess carbohydrate intake when glycogen stores and glucose oxidation reach their maximal adaptability. As demonstrated by Acheson et al.,[12,13] this only happens under high-carbohydrate diet conditions.

As with protein, total body carbohydrate level/availability also has a significant impact on appetite control. This idea was proposed by Mayer,[14,15] who reported evidence suggesting that variations in glycemia and/or glucose availability may serve as afferent signals to induce compensations in energy intake. Accordingly, mild hypoglycemia was found to trigger eating episodes in animals[16] and to coincide with spontaneous eating in humans tested under free-living conditions.[17] In this regard, our clinical experience reveals that weight loss up to the occurrence of resistance to further fat loss favors hypoglycemia,[18] which is associated with weight regain over time.[19]

26.2.4 Alcohol, Energy Partitioning, and Obesity

Alcohol is not essential for body functioning and is thus not considered as a nutrient. In fact, it is rather occasionally perceived as a toxin. It is then not surprising to note that body metabolic processes, including energy partitioning, are oriented toward giving priority to clearing alcohol from the body. Alcohol drives its own oxidation,[20] and its thermic effect exceeds that of carbohydrate.[21] Alcohol clearance also benefits from energy partitioning since its oxidation has priority over fat oxidation. This has been investigated by Suter et al.,[22] who showed that the addition or the substitution of alcohol in the dietary regimen resulted in an immediate daytime reduction in fat oxidation of about 45 g/day.

With respect to the effect of alcohol on energy intake, it does not appear to have the potential to attenuate subsequent energy intake, at least under typical living conditions of low-to-moderate alcohol consumers. Rather, moderate alcohol consumption seems to result in long-term passive overconsumption.[23] Our own research experience agrees with this observation, since alcohol consumption in a context of free-food intake was found to significantly increase energy

intake.[24,25] In addition, a high alcohol intake was found to accentuate the risk of overweight, beyond what can be attributable to high-fat diet and low physical activity participation alone.[26] This agrees with the evidence reported by Suter[27] in a review of relevant literature. In summary, available literature suggests that under conditions of low-to-moderate alcohol consumption the maintenance of a "zero body alcohol balance" is mostly ensured by a metabolic switch giving priority to alcohol utilization over lipid oxidation. From a clinical standpoint, this provides support to the estimates made by some nutritionists who consider that dietary units of alcohol consumption are equivalent to units of fat intake.

26.2.5 Fat Balance, Energy Partitioning, and Obesity

One of the main features of the RQ-FQ concept is that variations in energy balance are equivalent to those in fat balance under free-living conditions.[1] In fact, considering the earlier sections (26.2.2, 26.2.3, 26.2.4) emphasizing the rigorous regulation of protein, carbohydrate, and alcohol balance, the corollary necessarily becomes that any significant deviation in energy balance represents a deviation in fat balance. As summarized in Table 26.1, fat (lipid) balance is the vulnerable component within an obesogenic environment. First, fat intake does not acutely promote fat oxidation. This was specifically demonstrated by Flatt et al.,[28] who found no increase in postprandial lipid oxidation in response to a fat-supplemented meal. Rather, as subsequently documented, fat oxidation adapts, on a long-term basis, to variations in body fat.[29,30] Second, there is no metabolic pathway that promotes the metabolism of excess fat intake. In this regard, fat storage appears to accommodate excess fat intake and also permit excess intake from other energy substrates. Third, fat represents a low-satiety substrate,[31] which means that overfeeding is likely to occur with a high-fat diet before spontaneous interruption of feeding.[32] Fourth, the fat storage compartment has the potential to expand via the increase in fat cell number. To this effect, it is noteworthy to emphasize the recent study by Chapados et al.,[33] who reported that exposure to lipophilic pollutants accentuates the proliferative potential of preadipocytes. At this time, however, it is too preliminary to propose persistent organic pollutants as a new factor contributing to the increase in prevalence of morbid obesity observed in many countries. However, this effect, once again, demonstrates the vulnerability of fat balance to environmental perturbations.

The vulnerability of fat balance also raises the question pertaining to the status of obesity-prone individuals regarding the components of fat balance. A low relative fat oxidation, as reflected by a high RQ (0.86 in postobese vs. 0.81 in control subjects), was observed in postobese individuals following a 27 kg weight loss.[34] This was also found by Lean and James,[35] who compared RQ values between nonobese, postobese, and obese individuals. Furthermore, when fed a high-fat diet postobese women failed to increase their fat to carbohydrate oxidation ratio, which suggests the persistence of a lipid oxidation deficit in these individuals.[36,37]

As indicated earlier in this section, body fat loss promotes a decrease in fat oxidation. According to the RQ-FQ concept, this decrease ultimately becomes sufficiently pronounced to prevent any further lipid deficit. As proposed by Flatt,[1] physical activity is important in a reduced obese state to compensate for the weight loss–induced decrease in fat oxidation and to prevent body weight regain. The experience of members of the Weight Loss Registry reinforces the relevance of regular physical activity participation in the weight-reduced obese state. Indeed, they were able to maintain a 30 kg weight loss over more than 5 years, while maintaining a low-fat diet coupled with regular physical activity including vigorous exercise sessions.[38] This is also concordant with the clinical experience of Nicklas et al.,[39] who showed that the addition of exercise training prevented the decrease in fat oxidation that normally happens during a weight-reducing program, at least in part by maintaining fat cell lipolysis.

26.2.6 Conclusion

Available literature related to the RQ-FQ concept indicates that energy partitioning is not equivalent for each component of macronutrient balance. Although metabolic regulation favors stability for protein and carbohydrate balance as well as preference for alcohol clearance, there is no partitioning for lipid balance that, overall, seems to act as a buffer for imbalances in the regulation of this component. This vulnerability of lipid balance seems to be particularly pronounced in obesity-prone individuals.

26.3 ENERGY PARTITIONING BETWEEN TISSUES

Notwithstanding the apparent lack of available strategies to acutely compensate for a positive lipid balance, there are, nevertheless, substantial individual variations in the amount of fat gain required to reequilibrate fat oxidation and intake over time. As discussed in this section, this at least partly depends on the partitioning of lipids toward oxidative and less oxidative tissues.

26.3.1 Fat–Lean Tissue Partitioning and Obesity

It is generally assumed that adipose tissue contains about 80% lipid.[40] The residual nonfat content of adipose tissue is composed of water, protein, and mineral. These estimates are concordant with the documented body composition changes occurring during weight gain due to overfeeding, although they are subject to large interindividual variations.[41] As described by Bouchard et al.,[42] these variations in fat–lean tissue partitioning seem to be a major determinant of the response to long-term overfeeding. Specifically, a more pronounced energy partitioning toward lean oxidative tissue like skeletal muscle is predictive of reduced weight gain when exposed to a positive energy/fat balance.

Skeletal muscle is frequently considered as being the main morphological indicator of lean tissues. Its functionality has been studied with the intent to better understand its role in the

determinism of obesity. In the first edition of the *Handbook of Obesity*, this issue was reviewed by Simoneau and Kelley,[43] who emphasized that insulin resistance for glucose uptake is one of the main features of skeletal muscle function in obesity. However, the literature that they reviewed could not provide a clear explanation as to why a muscular insulin-resistant state could contribute to excess body fat storage. In this regard, a relevant hypothesis is the possibility that the insulin resistance characterizing some obese individuals might be nontissue specific. Since insulin can stimulate numerous biological functions such as sympathetic nervous system activity,[44] it is plausible that a muscular insulin resistance to glucose uptake also implies a decreased potential of insulin to activate sympathetically mediated thermogenesis and fat oxidation.

Other biological alterations can contribute to suboptimal muscle functioning in obesity. These include reduced capillary density,[45] altered membrane phospholipid composition that might affect membrane fluidity and substrate transport,[46] decreased percentage of type 1 muscle fibers,[47–49] and muscle lipid deposition.[50,51] With respect to the latter characteristic, our experience reveals that it is difficult to reduce fat deposition in muscles.[52] Indeed, a weight loss program based on the regular practice of vigorous physical activity allowed only a partial normalization of this feature in obese individuals. The possibility that fat–lean tissue partitioning could be influenced by heredity has also been investigated. In the Quebec Family Study, the significant familial resemblance for components of body mass provides a first line of evidence supporting a genetic effect on the fat–lean tissue ratio.[53] This is supported by the significant within-twin-pair correlation in fat gain observed in monozygotic twins submitted to long-term overfeeding.[41] Along these lines, Rice et al.[54] reported data suggesting a major gene effect on body proportions of fat and fat-free mass.

Taken together, these observations suggest that fat–lean tissue partitioning is related to large variations in body fat. On the one hand, a high skeletal muscle oxidative capacity, as reflected by high citrate synthase activity, is related to a low muscle fat accumulation.[55] On the other hand, Miljkovic-Gacic et al.[56] described in men of African ancestry a phenotype characterized by an age-related increase in intermuscular fat with a decrease in subcutaneous adipose tissue being predictive of greater prevalence of hyperglycemia. Such variations could be genetically determined, which may explain why exercise training does not necessarily normalize a suboptimal partitioning profile.

26.3.2 Brown Adipose Tissue versus White Adipose Tissue

Brown adipose tissue (BAT) is a potentially important player in the distribution of fat and energy between utilization and storage. As with muscle, BAT can significantly influence energy partitioning due to uncoupling protein 1, which is found only in brown fat cells.[57] BAT thermogenesis is stimulated via adrenoreceptors and has been repeatedly shown in animals to be responsible for variation in adiposity.[58] However, in humans, although adaptive thermogenesis was found to be quantitatively important,[59,60] no study had succeeded, until recently, in attributing a significant part of this thermogenic adaptation to BAT metabolism. With the development of new biomarkers such as ^{18}F-fluorodeoxyglucose (^{18}F-FDG),[61] new radiographic technologies have validated the involvement of BAT in human energy metabolism.[62–64]

In a recent study, Ouellet et al.[65] observed ^{18}F-FDG-stained BAT in 6.8% of people from a large cohort, confirming the prevalence of this phenotype in 5%–10% of adults.[64,66] Interestingly, their results also revealed a highly significant inverse relationship between ^{18}F-FDG-stained BAT and body mass index (BMI) or diabetes status.

Indirect calorimetry has been concomitantly used to quantify differences in energy expenditure between ^{18}F-FDG-BAT-positive and -negative individuals. In the study by Yoneshiro et al.,[67] the response to cold exposure reached 410 and 42 kcal/day for positive and negative individuals, respectively. Concordant results were obtained by Ouellet et al.,[68] who were able to stimulate BAT oxidative metabolism without the activation of adjoining skeletal muscle and subcutaneous adipose tissue. It seems that when ^{18}F-FDG-positive individuals are exposed to a stimulus like cold BAT can play a significant role in body energy partitioning.

26.3.3 Visceral versus Subcutaneous Fat Partitioning

Energy and fat partitioning is not just a matter of distribution between oxidative and less oxidative tissues; it is also clinically relevant when one considers the preferential fat storage in different adipose tissue depots. As early as 1947, Vague[69] described a predisposition to metabolic dysfunction in individuals displaying a preferential abdominal fat deposition. Several decades later, intra-abdominal (visceral) fat accumulation was recognized as the entity specifically contributing to the impairment of glucose and lipid metabolism.[70] In this regard, Després et al.[71] have described numerous clinical dysfunctions related to excess visceral fat deposition. These investigators also demonstrated the relevance and validity of relying on waist circumference as a proxy variable reflecting variations in visceral fat.[72]

The causality of preferential partitioning of fat to the visceral compartment has been explored to investigate the role of both genetic and environmental factors on the visceral fat phenotype. In the Quebec Family Study, Bouchard et al.[53] demonstrated a familial resemblance in fat mass as well as in waist-to-hip ratio, suggesting that beyond a genetic effect on body fat accumulation there might also be a genetic effect on body fat partitioning. Subsequently, the same research group tested the impact of long-term overfeeding in monozygotic twins to evaluate within-pair resemblance as an indicator of a genotype × environment (G × E) interaction effect on both fat mass and fat distribution.[41] Interestingly, after statistical adjustment for variations in body fat gain a highly significant

G × E effect for gain in visceral fat was observed. Specifically, this G × E effect suggested that the response of visceral fat to overfeeding is at least partly genetically determined. Following this, a more precise characterization of genetic contribution to visceral fat was evaluated by targeting specific polymorphisms. In this regard, Buemann et al.[73] reported significant associations between glucocorticoid receptor gene polymorphisms and variations in visceral fat. As recently described by Fox et al.,[74] genome-wide association studies will extend the documentation of the genetic basis of variations in body fat distribution provided that refined phenotypes are available.

Environmental factors have also been shown to significantly contribute to variations in visceral fat deposition. In our opinion, the most significant contribution came from Bjorntorp[75] and colleagues, who demonstrated a link between environmental stress and the predisposition to excess visceral fat deposition. Interestingly, they also found a significant association with the genetic variations at the glucocorticoid receptor gene.[76]

The convergence of genetic and environment-related research toward a role for glucocorticoid receptor polymorphisms is reminiscent of the observations made by Timofeeva and Richard,[77] who emphasized the relative importance of corticotropin-releasing factor receptor types. A dominance of stimulation of type 1 receptors, which activate the hypothalamo-hypophyso-adrenal axis, ultimately results in increased glucocorticoid secretion. Also relevant in this context are the observations of Richelsen et al.,[78] who observed a more pronounced affinity for glucocorticoid binding to omental adipocytes compared to subcutaneous fat cells.

Our understanding of how glucocorticoids affect fat distribution has been broadened by the fairly recent acknowledgment of the importance of local production within adipocytes of bioactive glucocorticoids from adrenal-derived inactive precursors.[79] This reaction is catalyzed by the enzyme 11β-hydroxysteroid dehydrogenase (HSD) type 1, which is expressed in several tissues and is particularly abundant in the brain, liver, and adipose tissue. Inhibition of 11β-HSD1 activity is associated with a large spectrum of beneficial adaptations in models of metabolic dysfunction.[80] In terms of fat partitioning, 11β-HSD1 expression has been reported to be higher in human omentum than in subcutaneous fat,[81,82] although this issue is still being debated. Animal studies involving genetic or pharmacologic manipulation of 11β-HSD1 activity clearly point to depot specificity, with some visceral fat depots being more responsive than subcutaneous fat in terms of adipose mass and metabolism.[83,84] Dampening of local glucocorticoid action through the pharmacological inhibition of 11β-HSD1 is currently considered as a promising therapeutic avenue for the treatment of obesity complications.

Along with sex steroid and glucocorticoid receptors, peroxisome proliferator-activated receptor γ (PPARγ) constitutes another nuclear receptor that impacts fat partitioning among adipose depots. PPARγ agonists such as the thiazolidinediones rosiglitazone and pioglitazone are insulin sensitizers used as adjuvants to treat type 2 diabetes. Although these drugs result in modest fat accretion, clinical studies have reported a redistribution of fat toward the subcutaneous compartment at the expense of visceral fat.[85] Such redistribution, with the appearance of new small, insulin-sensitive adipocytes in the subcutaneous compartment and reduction in visceral fat mass, is thought to contribute to the insulin-sensitizing action of PPARγ agonists. The mechanisms underlying their redistribution among fat depots remain to be fully understood but appear to at least involve modulation of lipid uptake and subsequent storage through depot-specific upregulation of the expression of key relevant genes.[86,87]

In addition to the role of glucocorticoids and their receptors, a number of other hormones, including fat tissue (adipokines) and gastrointestinal tract-derived hormones, may be involved in energy partitioning (storage vs. oxidation) as well as substrate partitioning between various tissues (fat vs. carbohydrate and muscle vs. adipose). For example, leptin, which is secreted at different levels in subcutaneous and visceral fat, increases energy partitioning toward oxidation and also directly alters lipid partitioning in skeletal muscle as well as substrate cycling in adipose tissue.[88–90] Adiponectin, also an adipokine, has the potential to influence energy partitioning, through effects on fatty acid oxidation in muscle, whereas retinol-binding protein 4 (RBP4) increases hepatic gluconeogenesis.[88] Additional recent examples include the observations that nesfatin influences food intake and substrate partitioning,[91] whereas ghrelin, even in the absence of effects on nutrient intake, affects nutrient partitioning and increases adiposity, with direct effects on adipocytes.[92,93] In response to carbohydrate and fat refeeding, the expression of a number of genes involved in nutrient partitioning is altered, contributing to the diet-associated differences in fuel handling and partitioning with a role for fibroblast factor 21 being demonstrated.[94] The now well-accepted cross talk between the immune system and adipose tissue[95] has demonstrated roles for immune system–derived hormones in energy partitioning. Lipopolysaccharide, used to mimic acute infection, induces hypophagia and selective partitioning of fat for energy, an effect that is attenuated by interleukin-10.[96] Another hormone derived from the immune system, acylation-stimulating protein (C3adesArg), alters energy partitioning (storage vs. utilization), with effects on substrate partitioning (carbohydrate and fat) in tissues such as fat and muscle.[97–100]

To summarize, there appears to be a regulated partitioning of fat between subcutaneous and visceral depots, which is an important determinant of some metabolic complications. The propensity to preferentially store lipids in the visceral fat compartment is likely genetically determined, but it is also influenced by environmental factors partly via sex steroid glucocorticoid and other nuclear receptors. Fat partitioning can also be influenced by messengers secreted by fat cells and by factors related to immunity. As further discussed in Section 26.5, current living conditions, in a context of globalization and economic competitiveness, likely exacerbate some of these mechanisms with the consequence being an increased prevalence of abdominal obesity.

26.4 CALCIUM: AN EXCEPTIONAL PLAYER IN ENERGY PARTITIONING

The population data reported by McCarron et al.[101] represent the first observations in humans indicating a relationship between dietary calcium intake and body weight. Subsequently, Zemel et al.[102] confirmed this association in concordant population data by demonstrating the effect of yogurt supplementation on reduction in fat mass, and by documenting the existence of a fat partitioning–related effect in animals. With respect to the latter point, these investigators also showed that a low calcium intake is not only related to bone demineralization but also to an increase in the calcium content of soft tissues.[103] This phenomenon, termed the "calcium paradox,"[104] has a significant impact on fat cell metabolism. Specifically, increased adipocyte calcium content favors a metabolic switch from lipolysis to lipogenesis, which is likely related to reduced fatty acid mobilization.[102] In humans, low-calcium consumers displayed reduced daily fat oxidation.[105] Thus, a low calcium intake might promote fat partitioning toward storage rather than oxidation.

Variations in calcium intake are also associated with fecal fat loss. Calcium, particularly from dairy origin, favors the formation of nonsoluble intestinal soaps, which significantly augment energy loss as fecal lipids, as shown in rats.[106] In humans, Jacobsen et al.[107] and Bendsen et al.[108] found that the energy equivalent of a calcium-augmented fecal fat loss ranged from 50 to 75 kcal/day. The same group attributed the decrease in postprandial lipemia observed after the ingestion of a meal supplemented with calcium to an increased fecal fat loss.[109]

It has been suggested that fluctuations in calcium intake and/or storage could serve as an appetite control trigger. Tordoff[110] reported that calcium restriction promotes an increase in spontaneous food consumption in animals. This agrees with the observations of Paradis and Cabanac,[111] who observed a spontaneous increase in preference of calcium-containing beverages by rats, following a prolonged deprivation of this mineral. In our clinical trials, we also observed that calcium intake might be involved in the weak response of weight loss in obese low calcium consumers.[112,113]

In summary, calcium, a nonenergy dietary component, has the ability to influence energy partitioning. Calcium has the potential to alter oxidative/storage fat ratio, influence intestinal dietary lipid loss, and affect spontaneous energy intake. Moreover, recent data reported by Rosenblum et al.[114] showed that a calcium + vitamin D supplementation could also affect visceral fat loss in response to a weight-reducing program.

26.5 ENERGY PARTITIONING IN A MODERN LIFESTYLE

Industrialization and computerization have considerably changed the daily activity profile of people. Over the past few decades, a switch from physical to mental work in the context of daily labor has significantly changed the type of stimulation to which the body is routinely subjected. From a metabolic standpoint, vigorous physical activity is well-known to increase fat oxidation and energy expenditure not only during exercise but also in the postexercise state,[115] facilitating appetite control[116] and energy intake[117] immediately after exercise and promoting the maintenance of a healthy body weight.[118] Exercise training also favors glycemic stability, attenuating both hyperglycemia and hypoglycemia.[119] Conversely, demanding mental work acutely promotes an increase in energy intake[120] and glycemic instability.[121] A significant increase in plasma cortisol is associated with cognitive effort.[122] Considering the aforementioned links between corticoid receptors and visceral fat, this ties in with the data from Mathieu, ME et al. (unpublished data), who observed an increase in the prevalence of overweight and abdominal fat in children performing more than 30 min/day of school homework perceived as being stressful. Since the pattern of activity in children over the past decades has evolved in a way favoring cognitive work versus physical exercise, it is plausible that changes in the daily activity profile might also underlie a change in energy partitioning.

Another noticeable change in daily activity habits that has been recorded in recent decades is the decrease in sleep duration, which reportedly decreased by at least 1 h/day according to the U.S. National Sleep Foundation.[123] This may also contribute to changes in body energy and fat partitioning as Spiegel et al.[124] demonstrated that an experimental reduction of sleep duration induces an increase in plasma cortisol. Further, a decrease in sleep duration favors a decrease in plasma leptin (a satiety signal) and an increase in plasma ghrelin (a hunger signal) and hunger sensation.[125] This is concordant with data showing that short sleep duration markedly increases ad libitum daily energy intake.[126] Accordingly, short sleep duration has been associated with overweight in children[127] and adults,[128] as well as a more pronounced weight gain over time.[122] Additionally, a greater than predicted waist circumference from BMI was observed in children[129] and adults[130] who were classified as short sleepers. Thus, short sleep duration seems to be a lifestyle factor that exerts a significant impact on energy and fat partitioning as well as body fat distribution.

26.6 CONCLUSION

Body energy partitioning exists, and its differential effects are associated with the predisposition to obesity. In this regard, there is less susceptibility to obesity in individuals with energy partitioning favoring substrate oxidation. In individuals predisposed to obesity the situation is more problematic, especially if partitioning promotes preferential visceral fat storage. The partitioning between fat and lean tissues, as well as between different adipose tissue depots, seems to be partly genetically determined, although environmental factors also play a significant role. Of particular interest is the fact that current lifestyle, in a context of globalization and economic competitiveness, favors a daily activity profile that promotes a less healthy energy partitioning. A common feature of these adaptations is that they seem to be related to hormonal changes, such as glucocorticoids, that may result from a typically more stressful way of living.

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27 Viral Infections and Adiposity

Nikhil V. Dhurandhar, Emily J. Dhurandhar, and Richard L. Atkinson

CONTENTS

27.1 INTRODUCTION

A prevailing theory is that obesogenic behaviors such as overeating and physical inactivity are the major causes of obesity. This implies that the development of obesity and its management are under volitional control. However, many factors affect food intake, physical activity, and metabolic rate that are not under conscious control. Obesity caused by infections is one such example, which challenges the prevailing dogma. Certain infections may cause obesity without the obesogenic behavior of overeating or physical inactivity. The actual cause of obesity, in this case, is the infection, and eliminating such obesity would require treating or preventing the offending adipogenic microbe infection.

Conventional prevention or treatment strategies practiced at the clinical or community level mostly promote a blanket treatment consisting of lifestyle changes and drugs or surgery in rare cases. However, these strategies are ineffective in producing substantial weight loss and maintenance for the majority of participants. Many prominent long-term clinical research trials show a mean weight loss or maintenance of less than 5% of the starting weight at the end of 2 or 3 years [1]. For example, after intensive behavioral counseling, diet and drug treatment for 2 years, about 70% of the subjects failed to lose even 5% of body weight [2]. Although it may be statistically significant, the biological significance of such small weight losses to individuals and its broader contribution to combating the global obesity epidemic is questionable. Obesity has a multifactorial etiology [3]. A better understanding of various factors that contribute to excess weight gain may help design cause-specific and effective weight management approaches that may yield better results. Infectobesity—obesity of infectious origin—is an area that illustrates this point.

Evidence is steadily accumulating to suggest a role of nonspecific and specific infections in obesity. The burden of natural infection in a human population is associated with greater adiposity [4]. While this does not demonstrate causation, in certain situations, an increase in adiposity may be a response to the process of infection. Some evidence suggests that inflammation may precede obesity. For instance, bacterial endotoxin (without bacteria) stimulates an inflammatory response and increases adiposity in experimental animals [5]. In mice, macrophage colony stimulating factor, an inflammatory adipocytokine, induces significant adipose tissue hyperplasia when overexpressed [6]. In humans, markers of inflammation predict weight gain [7].

Adipose tissue plays a critical role in mediating inflammation and response to infection; thus infection may alter adipose tissue metabolism. Several adipokines, especially adiponectin and leptin, mediate immune responses to infection [8]. In addition, the functions of macrophages and preadipocytes are closely related. Preadipocytes can convert to macrophage-like cells [9,10]. Adipose tissue has antimicrobial activity, and the stromal vascular fraction of adipose tissue, which includes preadipocytes and macrophages, displays phagocytic activity [11]. As cells of the immune system expand in response to infection, it is conceivable that the cells of adipose tissue, which show some immune-like function, also proliferate in response to infection.

Another mechanism by which certain infections may produce obesity is damage to the central nervous system (CNS). It has been known for many years that lesions of the CNS, particularly the hypothalamus and amygdala, alter appetite

TABLE 27.1
Infections that Cause Obesity in Animal Models

Infection	Experimental Model	Hypothesized Mechanism	Associated with Human Obesity?
Scrapie agent [14]	Mice (many lines)	Disruption of glucose transport in brain	Unknown
Canine distemper virus [67]	Swiss Albino mice	Downregulation of leptin receptors in hypothalamus Decreased levels of melanin concentrating hormone	Unknown
Rous-associated virus 7 [15]	Leghorn chicken embryos	Decreased thyroid hormone levels	Unknown
SMAM-1 [16]	Leghorn chickens	Unknown	Yes
Borna disease virus [17]	Lewis rats	Hypothalamic damage	Unknown
Ad36 [21]	Chickens, rats, mice, marmosets	Increased adipogenesis	Yes
Chlamydia pneumonia [18]	—	Unknown	Yes
Ad-5 [19]	CD1 mice, golden hamsters	Unknown	Unknown
Ad-37 [24]	Leghorn chickens	Increases adipogenesis	Unknown
Common infection burden: Enteroviruses, herpes simplex viruses 1 and 2, chlamydia pneumonia [4]	—	Inflammatory-related pathways	Yes
Apicomplexa: Eugregarinorida [20]	Dragonflies	Unknown	Unknown

regulation, energy expenditure, and body weight set point [12,13]. Infection may also alter many nutrient-sensing hormones, resulting in overconsumption of food or lack of compensation for overconsumption of food. Finally, adenovirus infection acts directly on adipose tissue to increase both storage of fat within adipocytes and production of new adipocytes. Adenovirus infection in animals causes obesity without changes in energy intake or activity.

The known microbes related to obesity in animal models and in humans are summarized in Table 27.1. In animals, canine distemper virus, Rous-associated virus 7, scrapie agent, borna disease virus, SMAM-1, human adenovirus-36 (Ad36), human adenovirus-37 (Ad-37), human adenovirus-5 (Ad-5), and the parasite Apicomplexa: Eugregarinorida increase adiposity. In humans, SMAM-1, Ad36, chlamydia pneumonia, and a high burden of several common infections are associated with obesity. Among the adipogenic microbes, effects of Ad36 are the best characterized in the scientific literature. This chapter focuses on the experimental models, association with humans, and mechanisms of Ad36-induced obesity.

27.2 ANIMAL MODELS OF AD36-INDUCED OBESITY

Ad36 was the first human virus reported to cause obesity in experimental animal models. Chickens, mice, rats, and marmosets (nonhuman primates) increased adiposity in response to Ad36 infection at various ages and routes of infection [12,21–23]. The adipogenic effect of Ad36 is not a nonspecific result of adenoviral infection but is specific to Ad36, Ad-5, and Ad-37. Experimental infection with adenoviruses chick embryo lethal orphan (CELO), Ad-2, and Ad-31, on the contrary, does not increase adiposity in animals [21,22,24]. Ad36 infection and subsequent adiposity was transmitted from experimentally infected animals to uninfected cage mates, demonstrating a droplet or perhaps a fecal-oral mode of transmission [22]. When blood obtained 36 hours after infecting chickens with Ad36 was injected intravenously into a new set of animals, the recipient animals became infected with Ad36 and developed obesity. These experiments fulfill Koch's postulates and demonstrate multiple methods of transmission of Ad36-induced obesity. Obesity resulting from Ad36 infection is a contagious condition, at least in animals.

Ad36 has a species-specific effect on adiposity [12,21–23]. In chickens, Ad36 significantly increased body fatness and visceral fat depots in just 3 weeks, but not body weight. Rodents and marmosets infected with Ad36 experienced a gradual onset of significant body weight gain over 4–6 months. In mice, Ad36 increased body fat and disproportionately increased visceral fat. Six months after Ad36 infection, marmosets had approximately a fourfold increase in body weight gain and body fat was 66% higher in infected animals compared to uninfected controls. Prevalence of obesity ranged from 60% to 100% in various animal experiments compared to 12%–23% prevalence in uninfected controls (Figure 27.1). In all animal models tested, Ad36 infection did not significantly alter food intake. The effect of Ad36 on increasing adiposity in animals is unequivocal, robust, and consistent.

Ad36 infection has a high transmission rate, and it naturally spreads through experimental cohorts of animals. Natural Ad36 infection as determined by seroconversion (appearance of Ad36-specific antibodies in the blood) was also associated with an increase in adiposity in rhesus monkeys from the

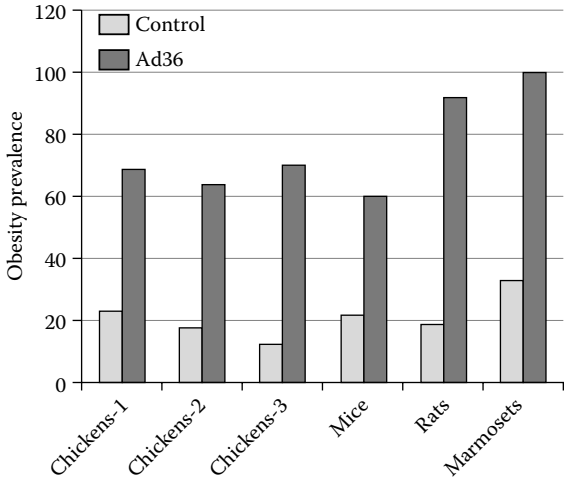

FIGURE 27.1 Obesity prevalence in human adenovirus-36 (Ad36)-infected animals. Obesity in Ad36-infected animals ranges from 60% to 100%, whereas it is present in only 10%–25% in controls. (Recreated from Pasarica M et al., *Obesity*, 14, 1905–13, 2006; Dhurandhar NV et al., *Int. J. Obes. Relat. Metab. Disord*., 24, 989–96, 2000; Dhurandhar NV et al., *Int. J. Obes. Relat. Metab. Disord*., 25, 990–6, 2001; Dhurandhar NV et al., *J. Nutr*., 132, 3155–60, 2002.)

Longitudinal Aging Study at the Wisconsin Regional Primate Research Center [23]. Although body weights of adult rhesus monkeys were stable before the time of infection, after seroconversion, monkeys gained 15% of their baseline body weight (Figure 27.2). Thus, it is conceivable for Ad36 infection to induce weight gain and promote a relative preponderance of adiposity in an otherwise healthy population.

In addition to increasing adiposity, Ad36 influences several metabolic factors associated with obesity. Paradoxically, Ad36 lowered serum cholesterol and triglycerides in marmosets, chickens, and mice despite the increase in body fat [23,24]. In male Wistar rats, Ad36 improved Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR), an indicator of insulin resistance [12].

Despite increased body fatness, infected rats maintained euglycemia with approximately half the fasting serum insulin levels of control mice, which indicated that Ad36 had an insulin-sparing effect. Ad36 also improved glucose metabolism in healthy, chow-fed C57BL/6J mice [25]. Similar to the response of rats, Ad36-infected mice were fatter, but had consistently lower fasting glucose and fasting insulin compared to uninfected controls [25]. In this study, the group of mice infected with Ad2 was not significantly different in adiposity or glucose metabolism compared to uninfected mice.

Ad36 not only protects against hyperglycemia associated with increased body fatness, but also attenuates high-fat-diet-induced hyperglycemia. In C57BL/6J mice made hyperglycemic by feeding a 60% high-fat diet, Ad36 lowered fasting glucose and insulin and improved glucose clearance following a glucose tolerance test. This effect of Ad36 on glycemic control lasted at least up to 20 weeks postinfection, when the experiment was terminated [23]. On a very-high-fat diet, Ad36 is not able to further increase body weight or body fat, over that in the high-fat-fed, uninfected control mice. Such a diet that is highly energy-dense appears to overwhelm the capacity of Ad36 to have further detectable impact on adiposity.

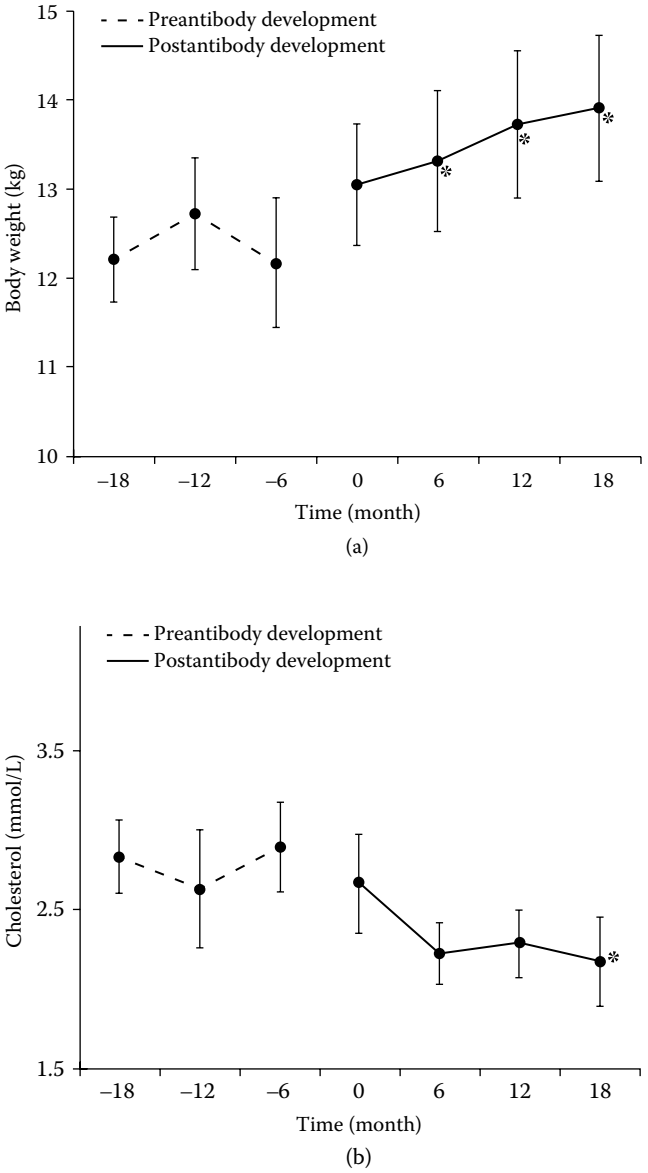

FIGURE 27.2 Adenovirus (Ad)-36 antibody appearance and body weight and cholesterol change in rhesus monkeys. Time 0 denotes when the seroconversion occurred (appearance of human adenovirus-36 [Ad36] antibodies). (a) Body weight values before and after seroconversion. (b) Cholesterol values before and after seroconversion. Values are mean ±SD; $n = 8$. Plasma samples from adult male rhesus monkeys were collected every 6 months for 90 months and tested for antibodies to Ad36 and cholesterol levels. Body weights and cholesterol are plotted for 18 months before the onset of Ad36 antibodies (–18, –12, and –6 months) and after the monkeys became antibody positive (0, 6, 12, and 18 months). *Different from the body weight or cholesterol at –6 months (the last anti-body-free value), $p < .05$. (Reprinted from Dhurandhar, NV et al., *J. Nutr*., 132, 3155–60, 2002.)

27.3 MECHANISMS OF Ad36-INDUCED ADIPOSITY AND IMPROVED METABOLIC PARAMETERS

27.3.1 Physiological Mechanisms Derived from Animal Models

27.3.1.1 Ad36 Promotes Adiposity

Ad36 DNA was detectable in several organs including kidneys, liver, lungs, heart, spleen, skeletal muscle, and adipose tissue only 2 days postinfection [26]. The tropism of Ad36 for adipose tissue is likely relevant to its adipogenic mechanism. The amount of Ad36 DNA in adipose tissue of infected animals significantly correlates with the amount of adipose tissue [22]. Viral mRNA was also detectable in adipose tissue for at least 7 months after experimental infection. Ad36 seems to directly influence adipose tissue and increase adiposity by upregulating adipogenesis. This conclusion is supported by the effect of Ad36 on adipogenic genes in adipose tissue, as described in Section 27.3.2.1, and on adipocyte progenitors and stem cells, as discussed in Section 27.3.2.

In animals, Ad36 infection is accompanied by upregulation of the cascade of adipogenic gene expression in adipose tissue [12]. Compared to uninfected controls, Ad36 robustly upregulates adipose tissue expression of key genes that are involved in promoting adipogenesis. These genes include peroxisome proliferator activator receptor gamma (PPARγ), CCAAT enhancer binding protein β (C/EBPβ), fatty acid synthase (FAS), and glycerol 3-phosphate dehydrogenase (G3PDH). Considering that Ad36 increases adiposity, greater adipogenic gene expression in Ad36-infected animals compared to the leaner uninfected group would be expected. Therefore, to control for the effect of adiposity, adipose tissue gene expression was also compared between pairs of selected animals from an Ad36-infected group and an uninfected group that were matched for adiposity and body weight. Despite similar adiposity levels, the Ad36-infected animals had several-fold increased expression of PPARγ, C/EBPβ, and G3PDH [12]. This suggests a direct effect of Ad36 on promoting an adipogenic cascade and not an indirect result of greater adiposity induced by Ad36.

In addition to upregulating adipogenesis, Ad36 appears to contribute to adiposity in other ways. Ad36 increases proliferation, adipogenic commitment, and differentiation of adipocyte progenitors [25]. Ad36 reduces leptin expression and secretion and upregulates adiponectin, which probably acts in an autocrine/paracrine manner to promote adipogenesis [27–29]. In addition, Ad36 increases lipoprotein lipase expression [27], an enzyme that increases lipid uptake from the bloodstream. Furthermore, Ad36 increases glucose transport into fat cells through Ras-mediated stimulation of glucose transporters [27]. This increased glucose flux into the cell is likely to increase cellular lipid content by promoting FAS expression and de novo lipogenesis [30].

27.3.1.2 Ad36 Improves Glycemic Control

Increased cellular glucose uptake by Ad36 likely increases lipid accumulation in adipocytes and simultaneously improves glycemic control by clearing glucose from circulation. In fact, Ad36 appears to recruit multiple tissues to improve hyperglycemia. In skeletal muscle and adipose tissue, Ad36 circumvents proximal insulin receptor substrate 1 (IRS-1) insulin signaling to increase Glut4 translocation and improve glucose disposal through a Ras-mediated phosphatidyl inositol 3-kinase (PI3K) activation pathway [27]. Ad36 infection also increases adiponectin, an insulin-sensitizing adipokine, expression in adipose tissue [23,28]. Adiponectin is likely a key player in improvement of hyperglycemia by influencing glucose metabolism in skeletal muscle and liver of the Ad36-infected animals.

Ad36 probably improves glucose homeostasis by also improving hepatic lipid and glucose metabolism [23]. Viral DNA and RNA are detectable in the liver following Ad36 infection [23], and the amount of Ad36 DNA in the liver correlates with better glycemic control in mice [23]. A downregulation of hepatic glucose transporter 2 (Glut 2) suggests a reduction in hepatic glucose output in Ad36-infected mice [23]. Ad36 increases hepatic glycogen stores and reduces lipid accumulation by approximately 30%, despite a high-fat diet. Hepatic expression of genes involved in lipid export and fatty acid oxidation, both of which reduce hepatic triglyceride accumulation, is upregulated by Ad36 [23].

Also, the reduced hepatic lipid accumulation is likely mediated through the effect of Ad36 on adipose tissue. Ad36 increases adiponectin abundance in adipose tissue. Adiponectin is a strong activator of 5' adenosine monophosphate-activated protein kinase and fatty acid oxidation in the liver, and its abundance is associated with lower hepatic lipid accumulation [31,32]. In addition, Ad36 infection increases adiponectin receptor levels [23], thus potentiating adiponectin action. Upregulation of adiponectin receptors is mediated by PI3K mediated forkhead box protein O1 (FOXO1) nuclear exclusion [33]. Ad36 significantly upregulates PI3K signaling in the liver [23]. Therefore, PI3K activation by Ad36 may act synergistically by increasing adiponectin production and secretion from adipose tissue and increasing adiponectin receptor expression in liver. Thus, Ad36 has a profound effect on hepatic metabolism, which is probably crucial for its ability to improve hyperglycemia.

Ad36 may also alter systemic lipid and glucose metabolism through adipose tissue-hypothalamic endocrine cross talk. In rodents, Ad36 reduces circulating levels of leptin, which suppress norepinephrine (NE) signaling in the paraventricular nucleus of the hypothalamus that would normally induce corticosterone secretion and inflammation to fight infection [34]. Indeed, Ad36-infected rats have lower NE and corticosterone levels in the hypothalamus, which may be a mechanism to evade an immune system response [12]. Lower levels of corticosterone induced by Ad36 may contribute to reduced inflammation, greater fatty acid deposition, and reduction of lipolysis. Perhaps, this endocrine interaction is the link with improved metabolic health despite increased adiposity in Ad36-infected animals.

27.3.2 Molecular Mechanisms

27.3.2.1 Ad36 Upregulates Adipogenesis

Numerous in vitro studies have demonstrated the ability of Ad36 to induce adipogenesis or the maturation of preadipocytes into adipocytes [35–38]. 3T3-L1 preadipocytes

or human adipose tissue–derived stem cells (hASC), when infected with Ad36, differentiate and accumulate more lipid than uninfected control cells, even in the absence of a medium that induces adipogenic differentiation [35,36]. In the presence of a differentiation medium, Ad36-infected cells accumulate lipid at a faster rate than uninfected control cells. The adipogenic gene cascade is upregulated by Ad36, from increased cyclic adenosine monophosphate activation and Wnt-10b downregulation through increased PI3K activity, aP2 expression, and lipid accumulation [35,36]. Lipid accumulation in hASC occurs in a time- and dose-dependent manner (Figure 27.3). Even hASC exposed to osteogenic media differentiate into adipocytes rather than osteocytes in the presence of Ad36 [36], which indicates a strong influence of Ad36 on promoting commitment of stem cells to adipogenic lineage. In vivo, evidence suggests that Ad-36 depends on monocyte chemoattractant protein-1 (MCP-1) expression for induction of adipogenesis. MCP-1 knockout mice do not

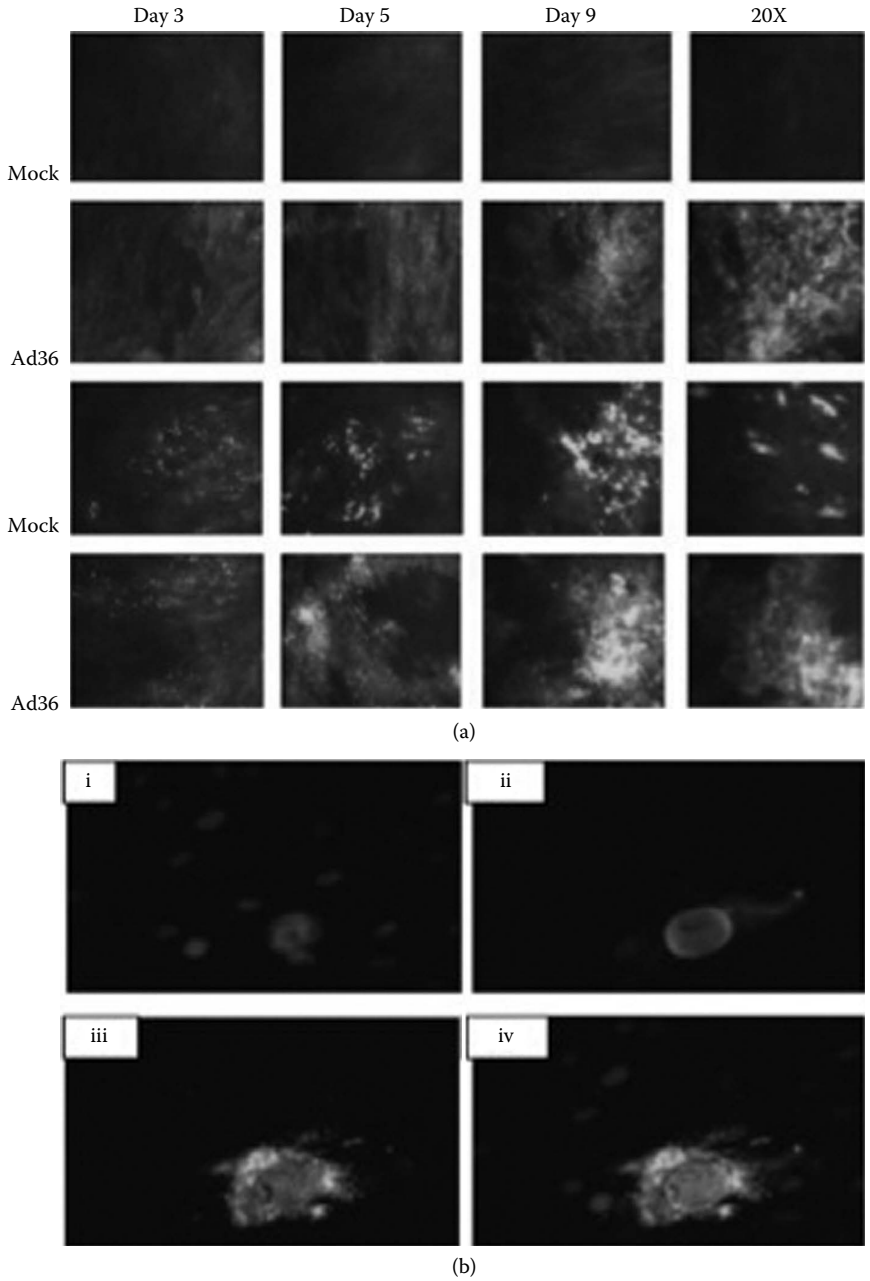

FIGURE 27.3 (**See color insert.**) Lipid accumulation following human adenovirus-36 (Ad36) infection in human adipose–derived stem cells. (a) Lipid accumulation in human adipose tissue–derived stem cells (hASC) after mock or Ad36 infection (3.8 plaque-forming units [PFU]/cell), with (bottom 2 rows) or without (top 2 rows) methyl isobutyl xanthine, dexamethasone, and insulin (MDI). Representative images of lipid-specific boron-dipyrromethene (BODIPY) staining in hASC following Ad36 infection with or without MDI. (b) Several immunochemical stains of the same 40 × field showing that only the Ad36-infected cell accumulates lipid. (i) 4',6-diamidino-2-phenylindole (DAPI) staining of nuclei, (ii) staining of Ad36 hexon protein highlighting one infected cell, (iii) BODIPY staining of lipid in Ad36-infected cell, and (iv) composite image of i, ii, and iii. (Reprinted from Pasarica M et al., *Stem Cells*, 26, 969–78, 2008.).

develop adiposity when infected with Ad-36 compared to wild-type control mice [39].

Ad36 initiates the viral replication process in 3T3-L1 cells, but the process remains incomplete and new viral progenies are not formed. Nonetheless, just Ad36 mRNA expression due to initial viral infection is sufficient to induce an adipogenic effect [37]. Blocking of Ad36 mRNA expression with cidofovir, an anti-adenoviral agent, inhibits the adipogenic effect of the virus on 3T3-L1 cells [37].

The ability of Ad36 to induce adipogenesis is also understood to a large extent at the molecular level. Early gene 4 open reading frame-1 of Ad36 E4 (E4orf1) is necessary and sufficient to induce adipogenesis [38]. Knockdown of E4orf1 with siRNA after Ad36 infection inhibits the effect of the virus on differentiation of 3T3-L1. Transfection with E4orf1 is sufficient to induce adipogenesis in 3T3-L1 and hASC, both with or without a differentiation medium.

E4orf1 DNA sequence is highly homologous to the human ancestral *dUTPase* gene. E4orf1 protein is a small 17 kDa protein and contains a PDZ domain–binding motif (PBM). Through its PBM, E4orf1 binds to several cell cycle regulatory proteins containing PDZ domains and acts as a scaffolding protein. E4orf1 utilizes Ras-mediated activation of PI3K pathway to induce adipogenesis [27]. The mechanism by which E4orf1 activates PI3K is understood through previous work with the E4orf1 protein of adenovirus Ad-9, which has 96% sequence homology to E4orf1 of Ad36. E4orf1 of Ad9 binds to Disks large homolog 1 (Dlg1) through its PBM region [40], and this complex subsequently translocates to the membrane. At the membrane, the complex activates Ras, which in turn activates PI3K [40–42]. This entire mechanism is not fully elucidated with Ad36 E4orf1; however, available information suggests a similar mechanism of action for Ad36 E4orf1. Ad36 E4orf1 is sufficient to activate both PI3K and Ras [38]. Moreover, intact Ad36 E4orf1, but not its PBM mutated form, binds to Dlg1, activates PI3K, and induces adipogenesis [38,43], suggesting the PBM region of Ad36 E4orf1 is crucial for activation of this pathway and adipogenesis.

27.3.2.2 Ad36 Improves Glycemic Control

The molecular mechanisms for Ad36-induced glucose disposal have been investigated. Normally, the mechanism for insulin-induced glucose uptake involves binding of insulin to the insulin receptor (IR), activating insulin receptor substrate 1 and 2 (IRS-1/IRS-2) through tyrosine phosphorylation, which in turn activates PI3K [44]; this is considered proximal insulin signaling. PI3K then phosphorylates and activates AKT (Protein Kinase B [PKB]), which leads to the translocation of glucose transporters (Glut4) to the cell membrane, resulting in cellular glucose uptake [44]; this is considered distal insulin signaling.

Interestingly, the mechanism of Ad36-induced glucose uptake involves inhibition of proximal insulin signaling pathway, but a concomitant activation of distal insulin signaling. Ad36 downregulates proximal IRS-1 and IRS-2 signaling and increases inhibitory IRS-1/IRS-2 serine phosphorylation [25,27]. However, despite the impaired proximal insulin signaling, Ad36 increases the distal glucose disposal components through Ras-mediated PI3K activation of Glut4 translocation, leading to increased glucose uptake in both skeletal muscle and adipose tissue [25,27]. Moreover, Ad36 increases cellular glucose uptake even with IR knockdown [45], which further confirms that Ad36-induced glucose uptake does not require functional proximal insulin signaling and that the Ras-mediated PI3K pathway is sufficient to induce glucose uptake. Ad36 also upregulates several other factors that may aid in glucose disposal. It increases Glut1 abundance [23], the constitutionally active glucose transporter. Ad36 also increases adiponectin expression [12], a key anti-inflammatory adipocytokine that improves whole-body glucose homeostasis.

Interestingly, the viral gene *E4orf1* that is responsible for the adipogenic effect of Ad36 is also necessary and sufficient for the virus to upregulate cellular glucose uptake [43]. When E4orf1 is knocked down after Ad36 infection, the effect of the virus on cellular glucose uptake is reduced. E4orf1 transfection increases glucose uptake in adipocytes and myoblasts and reduces glucose output from hepatocytes. E4orf1 induces the same Ras-PI3K pathway [38,43] activated by Ad36, which leads to upregulation of PPARγ and enhanced adipogenesis and cellular glucose uptake. However, evidence suggests that pathways leading to adipogenesis and glucose uptake diverge downstream of PI3K, so that the two effects could be uncoupled. Ad36 increases glucose uptake in mouse embryonic fibroblasts that lack PPARγ [29]. Considering the key role of PPARγ in adipogenesis, this indicates that E4orf1 induces glucose uptake without its adipogenic effect and that these two phenomena may be separated from each other. This finding has important implications. Because PPARγ activation as a treatment for type 2 diabetes mellitus has many unwanted side effects [46–48], agents that upregulate glucose uptake independent of PPARγ may be the next generation of antidiabetic drugs [49,50]. E4orf1 may be such an agent. Therefore, further investigating the cell signaling that E4orf1 modulates may provide a clue to uncouple PPARγ-induced adipogenesis from glucose disposal.

27.4 Ad36 AND OBESITY IN HUMANS

The precise contribution of Ad36 to human obesity is unclear. Ethical considerations preclude experimental infection of humans. Hence, only indirect evidence for an association of Ad36 with human obesity can be obtained. An alternative approach is required to investigate a relationship between Ad36 and weight gain in humans. Epidemiological associations, followed by prospective epidemiological studies, can first demonstrate the relevance of a particular exposure. The mechanism can then be elucidated through animal and cellular studies, and congruence between human and animal data can serve as confirmation of a true association [51].

Several studies screened humans for the presence of Ad36 antibodies, which was used as an indicator of past naturally acquired infection. Several reported associations between individuals seropositive for Ad36 and body mass index (BMI) are congruent with evidence from animal and in vitro cell

TABLE 27.2
Ad36 Association with Human Obesity

Study	Subject	Ad36 Prevalence	Main Outcomes
Atkinson et al. [53]	360 obese, 142 nonobese adults	Obese 30%, nonobese 11%	Ad36+ had higher BMI, lower triglycerides
Atkinson et al. [53]	26 twin pairs	Obese 22%	Ad36+ twin higher BMI and body fat than Ad36– twin
Pasarica et al. [36]	34 obese, Pima Indian adults	27%	Ad36+ developed eight times more adipocytes
Trovato et al. [54]	68 obese, 135 nonobese	Obese 65%, nonobese 33%	Ad36+ had significantly greater BMI and waist-to-hip ratio
Goossens et al. [59]	136 obese, 281 nonobese, 92 unknown BMI	Obese 6%, nonobese 4%	No association of Ad36 with BMI
Broderick et al. [58]	146 obese, 147 nonobese	Obese 34%, nonobese 39%	No association of Ad36 with BMI, African-Americans and women more likely to be Ad36+
Trovato et al. [55]	65 NAFLD, 114 non-NAFLD adults	NAFLD 32%, non-NAFLD 47%	Ad36+ associated with higher BMI and fat mass
Na et al. [62]	250 obese, 59 nonobese children (6–15 years old)	Obese 29%, nonobese 14%	Ad36+ associated with higher BMI, cholesterol, and triglycerides
Atkinson et al. [61]	83 obese children, 1 nonobese (8–16 years old)	Obese and overweight 30%	Ad36+ associated with BMI z-score and waist circumference
Gabbert et al. [60]	67 obese, 57 nonobese children (8–18 years old)	Obese 22%, nonobese 7%	Ad36+ associated with higher BMI, waist circumference, and waist-to-height ratios
Salehian et al. [52]	One obese adult with abnormal fat depots	Adult with abnormal adiposity, and 5 of 12 obese adults without abnormal fat depots were positive for Ad36 DNA in adipose tissue	Ad36 is present in adipose tissue, Ad36 associated with abnormal fat depots

culture studies (Table 27.2). Seropositivity to Ad36 is associated with obesity in adults in the United States; one study showed that 30% of obese individuals have been infected, whereas only 11% of lean persons have antibodies to Ad36 [53]. Obese Ad36 seropositive subjects in this population were heavier than their uninfected counterparts. Even in the lean group, Ad36 seropositivity was associated with greater BMI, compared to Ad36 seronegative lean individuals. Italian adults also had a positive association of Ad36 seropositivity and BMI, with 65% of obese persons and 33% of nonobese having antibodies to the virus [54]. Infected individuals from this Italian cohort had greater abdominal adiposity as assessed by a larger waist-to-hip ratio. Two additional studies in Italian patients with nonalcoholic fatty liver disease (NAFLD) demonstrated the association of Ad36 with obesity [55,56]. A South Korean study found no association between Ad36 infection and obesity, but it did show an association between Ad36 infection and overweight [57]. Additional evidence about the association of Ad36 infection with obesity came from twin studies. Adult identical twins usually have similar BMI, probably due to the shared genetic background. However, Ad36 antibody positive twins have higher BMI and adiposity than their seronegative identical co-twins [53]. Although this is an association, which does not necessarily establish causation, the twin study provides strong conceptual support for the hypothesized adipogenic role of Ad36 infection in human obesity.

A cohort from the Netherlands and Belgium and another cohort of U.S. military personnel did not show an association of Ad36 with obesity [58,59]. The Netherlands–Belgium study demonstrated a very low prevalence of Ad36 seropositivity in the population tested and may have had insufficient power to detect an association of infection with obesity. Also, the study excluded overweight individuals. In the military cohort, blacks and Hispanics had a higher prevalence than whites. The high BMI in military personnel may have been the result of higher muscle mass since military personnel are required to perform greater levels of physical activity than civilian personnel. Furthermore, military regulations require overweight or obese personnel to be separated from the military, giving a high incentive for individuals to control their weight. This makes interpretation of this study difficult.

Twenty-seven percent of Pima Indians, a population known to have a high prevalence of obesity, had Ad36 DNA in their adipose tissue [27]. This blinded study showed that preadipocytes from adipose tissue of individuals with Ad36 DNA developed eight times more adipocytes when stimulated to differentiate compared to tissue without Ad36 DNA.

This finding highlights the ability of Ad36 to stimulate adipocyte differentiation ex vivo and suggests a highly plausible mechanism for Ad36-induced adiposity in humans.

One could ask whether the association of Ad36 with adiposity is a nonspecific and general effect of infection. However, infections due to other adenoviruses (Ad-31, Ad-2, and Ad-37), which are nonadipogenic in animal models [24], do not show an association with BMI in humans, suggesting the adipogenic effect is not shared by all human adenoviruses or infections in general [50]. Also, it is unlikely that obese individuals may simply be more susceptible to adenoviral infection than nonobese individuals, as the prevalence of nonadipogenic adenovirus infection was similar between obese and nonobese groups.

The correlation of Ad36 with obesity is very consistent in children [60,61]. Adenovirus infection is very common in children. Therefore, children, by definition, are more likely to be recently infected with adenoviruses than adults and are thus more likely to have higher antibody levels and to be actively gaining weight as a result of infection. In addition, other proadipogenic factors to which adults are exposed have had less time to influence body weight in children. In Korean children, Ad36 seropositivity was associated with higher BMI z-score and waist circumference [61,62]. Ad36 antibodies were present in 29%–30% of obese Korean children and in only 14% of lean children. In the United States, the prevalence of Ad36 antibodies in adolescents aged 8–18 years was 15% overall, with 22% of the obese and 7% of the nonobese being seropositive [60]. Of all the seropositive children, 78% were obese and 4% were nonobese. Seropositive obese children in this cohort were 16 kg heavier than seronegative obese children [60]. Thus, Ad36 is associated with obesity across several ethnicities and age groups. This indirect evidence coupled with a direct causative effect in animal studies indicates that Ad36 may promote greater adiposity in humans.

Ad36 infection in humans shows similarities with the phenotypic effects it causes in experimentally infected animal and/or cell models. Mirroring the effect of Ad36 on multiple tissues in animal models [25], in vitro studies show that Ad36 increases glucose disposal in primary skeletal muscle cells and adipose tissue explants from both diabetic and nondiabetic individuals in basal and insulin-stimulated conditions [27,63]. Several, but not all, studies show an association of Ad36 with better measures of glycemic control [25,27,29]. Ad36 seropositive diabetic and nondiabetic adults have lower fasting blood glucose and HbA1C levels than seronegative subjects [27]. Seroprevalence of Ad36 in children and adolescents from several ethnicities is associated with lower fasting glucose, insulin, and HOMA-IR independent of body fatness, gender, and familial relationship [23]. Ad36 is thus associated with better glycemic control in a range of genetic backgrounds. Hispanic children and adolescents are especially prone to developing insulin resistance [64] and may have a stronger predisposition toward metabolic complications. Despite this tendency, Ad36 infection was associated with better glycemic profile in a Hispanic population [23]. Additional studies have shown that Ad36 seropositivity is associated with greater adiponectin in humans [27,29].

Ad36 infection attenuates excessive hepatic lipid accumulation in high-fat-fed mice [25]. This parallels the observation that Ad36 seropositivity was associated with lower intrahepatic lipid content in prepubertal children [25]. Ad36 seropositive subjects had greater adiposity but a significantly lower odds ratio of having NAFLD, as indicated by bright liver on ultrasound [55]. NAFLD is associated with insulin resistance. As expected, among the Ad36 positive subjects, those with NAFLD had greater insulin resistance and lower high-density lipoprotein cholesterol levels compared to those without NAFLD. However, among those with NAFLD, serum lipids or the HOMA index were not significantly different between the seropositive or negative subjects.

Hepatic lipid is associated with insulin resistance independent of body fatness [65,66]; therefore, the effect of Ad36 on hepatic lipid accumulation may improve glycemic control despite its effects on adiposity. Understanding the detailed mechanism of Ad36 action may provide a template to modulate hepatic steatosis and insulin resistance in humans.

The paradoxical effects of Ad36 infection on lipid metabolism are also mirrored in some human studies. Despite increased adiposity in seropositive subjects, Ad36 infection is associated with a decrease in serum cholesterol and triglycerides in American adults. In Korean children, however, Ad36 was associated with increased triglycerides and cholesterol [62]. In addition, Ad36 is associated with increased lipids in Italian adults, and genetically identical twins discordant for antibodies do not show significant differences in triglycerides or cholesterol [53]. Thus, Ad36 may have differential effects on these parameters perhaps depending on age group and ethnicity. Other factors that may modify the association of Ad36 infection with lipid profile in various cohorts of population are unclear.

Antibody prevalence does not indicate the time of infection, so the dynamics of increased adiposity and changes in metabolic profile that follows Ad36 infection are unknown. It is possible that Ad36 infects and induces a change in metabolism, which persists even after the virus is cleared by the immune system, which is referred to as a "hit and run" effect. An example of this phenomenon was described in a study of mice that developed obesity due to canine distemper virus infection [67]. The brains of these animals showed continued lesions even when no virus could be detected. In some other situations, the active virus may be absent, but its DNA may persist. For instance, gammaherpesvirus induces oncogenesis long after infection is cleared, and this is a result of viral DNA remaining in cells [68]. Alternatively, active Ad36 infection may persist at a low level or remain latent and intermittently reappear to induce a change in adiposity and glycemic control over time. Because adenoviral infections are common in childhood and the effect of Ad36 on adiposity is consistent from childhood to adulthood, it is possible that changes in adiposity and glycemic control may last long term following initial infection. Longitudinal studies following Ad36 infection are needed in the future to determine these dynamics. This information would lay the foundation of prevention and treatment strategies aimed at Ad36-induced adiposity. If Ad36 infection

or its DNA remains active and continues to influence adiposity, antiviral treatment may be of use. Agents that block viral action may be important for treatment. However, such treatment will not help if the virus has a hit and run action, as the virus or its DNA will be undetectable by the time a corrective action is sought. In that case, a vaccine that prevents Ad36-induced obesity may be more desirable and preferable. For those already infected, agents that can conceivably reverse the genetic or epigenetic changes might be needed.

27.5 POTENTIAL CLINICAL AND POLICY IMPLICATIONS OF Ad36 INFECTION

Given the aforementioned properties of Ad36 infection, several clinical implications may be pertinent for obesity and diabetes treatment and prevention. Combined animal and human evidence suggests that Ad36 may be one contributor to obesity in humans. Because animal studies show adipose tissue gains without much change in energy intake or activity after experimental infection, reduction in energy intake and/or increased activity from "normal" may be necessary to counter fat gain in newly infected individuals. However, initial studies in humans and animals suggest that with larger reductions in energy intake and increases in activity, infected individuals actually may lose more weight than uninfected individuals [56]. Individuals who have lost weight may remain susceptible to rapid weight regain if they come off their weight reduction program. Uninfected individuals may be protected against Ad36 infection and the consequent obesity if a vaccine against the virus could be developed.

Weight loss as a treatment for obesity could perhaps be modulated depending on Ad36 infection status, since Ad36 affects adipose tissue metabolism. Ad36 may affect both weight gain during positive energy balance and weight loss during negative energy balance. One study suggests that Ad36-infected overweight adults with NAFLD may respond better to lifestyle nutrition interventions for weight loss and improvements in insulin resistance and hepatic lipid content [56]. More studies are needed to confirm this finding, and determine if the phenomenon is valid in children as well.

Lastly, the improvement of glycemic control related to Ad36 infection may impact the development and treatment of insulin resistance; Ad36-infected humans may be protected from developing insulin resistance at a higher BMI. E4orf1 protein and its interaction with host cell signaling offer a potentially beneficial template to improve glycemic control or hepatic steatosis, even in the presence of a high-fat diet. The ability of E4orf1 to stimulate glucose uptake independent of insulin suggests it potentially could have a role for type 1 diabetes treatment. Thus, it may be possible to prevent Ad36-induced obesity on the one hand and, on the other hand, to creatively harness its beneficial properties for improving human health.

27.6 VIRAL INFECTIONS AND OBESITY

In conclusion, several viral infections increase the predisposition to obesity. Some of these have been reported and more may be added to the list in future. If true, this implies that a certain subset of obesity may be prevented by vaccination, which may lessen the burden of population levels of obesity. The treatment of such obesity would require agents targeted at specific offending microbes. More importantly, obesity induced by viral infections effectively illustrates the role of biology and nonbehavioral factors in shaping body weight and highlights the multifactorial etiology of obesity. A deeper understanding of the various contributors to obesity may help in reducing the stigma against obesity and promote the search for effective cause-specific prevention and treatment approaches.

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Dr. Richard L. Atkinson: Dr. Atkinson is Director, Obetech Obesity Research Center and Clinical Professor, Department of Pathology, Virginia Commonwealth University; Richmond, Va. Financial Disclosure: The author is the owner of Obetech, LLC. This company provides assays for adenoviruses that produce obesity and has several patents in the area of virus-induced obesity.

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Part III

Behavioral Determinants of Obesity

28 Obesity
The Influence of the Food Environment on Ingestive Behaviors

Richard D. Mattes and Sze Yen Tan

CONTENTS

28.1 INTRODUCTION

It is widely held that the high incidence and prevalence of overweight/obesity represent recent trends. Discounting epigenetic effects (which may be an error), the trends are attributed to environmental influences, as insufficient time has elapsed for genetic shifts to lead to greater body mass index (BMI). Much of the basis for the recent-onset hypothesis stems from data collected through national surveys in the United States, which reveal that the population BMI was relatively stable during the 1960s and 1970s but has since risen markedly. However, this view may suffer from the proverbial error of searching for answers only where the lights are brightest. Less representative and reliable data from older alternate sources suggest that increases of BMI are of much earlier origin. Data from France indicate a steady rise dating back to at least 1705.[1] In the United States, records show that the BMI of Union Army Veterans increased over successive waves of measurement during the late 1800s and early 1900s.[2] Such a trend has also been noted between 1865 and 1991 among 25- to 64-year-old artisans, professionals, laborers, and farmers in the United States,[3] suggesting the trend is not dependent on sedentary lifestyles or age-specific. Indeed, even the grave concern about rising BMI of children and adolescents may be of long standing. Data from Denmark reveal a continuous rise over the past 80-plus years in this age group.[4]

Until recently, these trends raised little concern, as they were associated with improved nutritional status. In addition, adverse consequences of increased adiposity on quality of life, health status, and longevity were still below consequential levels and/or were offset by various advances in science such as improved sanitation, implementation of vaccinations, and use of antibiotics. Whether new counterweights sufficient to remediate the growing prevalence of overweight/obesity can be identified and implemented is uncertain but of high priority because of the prospect that coming generations will not enjoy as healthy and long a life as the present generation.[5]

The basis of these trends is undoubtedly complex wherein inherent propensities for weight gain are enabled by the changing environment. This review focuses on selected broader features of our food environments suspected of contributing to the rising incidence and prevalence of overweight/obesity globally, which is now estimated at 1.46 billion overweight adults, 502 million obese adults, and 170 million overweight and obese children.[6,7] More detailed analyses would be required to formulate policies and interventions for a particular location or population, as the term "environment" covers a wide range of conditions. The recent surge in the prevalence of obesity in low- and middle-income countries[6] may stem from different factors than those currently facilitating weight gain in affluent nations.

Fundamental to identifying features of the food environment that are most influential on weight trends is knowledge of the controls of feeding. That is, understanding the problem should inform the solution. No consensus exists among scientists, health-care providers, or policymakers. Multiple schools of thought have been articulated, with four dominating current thinking (Figure 28.1). One holds that feeding is not regulated[8] and that the appearance of stability reflects only the influence of independent processes that tend to offset each other reasonably accurately. The failure of compensatory responses to a wide array of perturbations such as acute forced overfeeding,[9] altered variety,[10] manipulation of portion size,[11] and covert changes of energy density[12,13] challenge a view that a regulatory system exists. It is not clear that tight weight stability would be a trait that conferred an adaptive advantage through natural selection. Few other

Models of feeding regulation	Primary target of intervenion
Non-homeostatic	Meal pattern
Homeostatic & functional	Built environment
Homeostatic & dyfunctional	Food choice & lifestyle
Homeostatic & non-functional	Appetite & palatability

FIGURE 28.1 Theoretical models of feeding regulation and their intervention/policy implications.

animals living in natural conditions exhibit stability; rather, body weight fluctuates seasonally. Assuming intake is not regulated, the primary environmental target for intervention may well be feeding patterns such as eating frequency and portion size.

A second view holds that feeding is homeostatically regulated[14] and is functioning in a manner that has proven successful over many millennia. An often-cited argument supporting this position is the observation that annual body weight changes in Americans represent errors of energy balance of less than 0.5%,[15] an improbable outcome based on chance. The question then becomes, what are the elements of the regulatory system? A biological basis is evident from compensatory dietary responses to acute high- or low-energy intakes among children[16] and adults.[17] However, these findings indicate that there is fair precision in the system but not necessarily accuracy. Indeed, the system is likely asymmetrical wherein failure to secure adequate energy prompts strong responses to redress the deficiency, but intake of energy in excess of need elicits weaker biological responses.[18]

This system is adaptive as it would ensure adequate energy reserves to support reproduction[19] and other essential functions when energy resources may be limited. Regulation when intake is high then draws upon a once fairly reliable interaction between biology and the environment. This is exemplified by seasonal fluctuations of body weight by people practicing subsistence agriculture. Food collected during the harvest could be portioned out over the year to match energy needs and to stabilize body weight. However, this is not observed, nor is it the most efficient approach.[20] Compared to storage of the harvest's energy in adipocytes, the portioning approach would require greater production, hence costs, to compensate for food losses due to spoilage, pests, and possible theft from external reserves. Instead, intake is high after the harvest, leading to increased body weight (energy reserves), with a subsequent fall when external energy supplies are diminished. This oscillating pattern of body weight results in no net change over yearly intervals. With advances of agricultural productivity and improved methods of food storage and distribution, seasonal food scarcity no longer occurs in most populations, eliminating a critical check on body weight gain. Thus, successes in the biological and environmental components of an energy regulatory system are implicated in the rise of BMI. These phenomena call for the need to target the built environment (e.g., food accessibility, opportunities for physical activity) for more effective weight management.

A third perspective is that feeding is normally regulated, but some change or changes of biological or behavioral controls have disrupted the system, rendering it ineffective. Many suggestions have been offered, including increased sedentariness,[21] snacking,[22] eating away from home,[23] or greater consumption of energy-yielding beverages.[24] Using the latter as an example, there has been a marked shift toward drinking, as compared to eating, energy that coincides with BMI trends.[25] Approximately, 20% of daily energy intake in the United States is derived from beverages.[26] This shift in energy acquisition practices activates less-effective physiological regulatory processes,[27] resulting in poor dietary compensation.

Considerable emphasis has also been placed on a reduction of physical activity as a driver of weight gain, as it would theoretically lower energy needs and reduce responsiveness to appetitive sensations.[28–31] However, evidence indicates that daily energy expenditure has not changed and is appropriate for our body weight.[32,33] Findings that exercise alone has a limited effect on weight loss[34] raises further questions about this explanation.

No particular recent behavioral/environmental change that could account for the recent rise of BMI has been definitively established. However, if there has been a change in one or more components compromising the sensitivity and/or reactivity to cues involved in energy regulation, it would call for interventions addressing food choice and lifestyle.

Finally, there are those who suggest that while there may be intact and functional regulatory systems for appetite, feeding, or energy balance, they are overridden by the influence of a reward system that is not well regulated.[35] In this instance, positive energy balance occurs because of a stronger motivation to engage in behaviors that are hedonically pleasing than those that are metabolically homeostatic. The oft-cited example is eating in the absence of hunger,[36,37] such as electing to consume a palatable dessert after finishing a meal that provided sufficient energy relative to needs. By this scenario, the logical target for intervention is the palatability and availability of foods and beverages.

These four proposed models of ingestive behavior point toward different environmental targets to remedy the problem of overweight/obesity. Efforts to determine the veracity of these different systems would be worthwhile, but the severity of the overweight/obesity problem calls for a rapid response. Thus, while the root cause of the problem may not be addressed in this chapter, we highlight several high-profile putative environmental contributors to positive energy balance that may warrant prompt attention. Fully acknowledging

that many others are important, we focus on food in terms of its (1) availability, (2) affordability, (3) convenience, (4) marketing, and (5) palatability.

28.2 FOOD (ENERGY) AVAILABILITY

Although there are food shortages in various regions, data from the World Health Organization document an increasing total energy supply per capita in 21 high-income countries including China.[38] This increasing trend is predicted to continue for the next 10 years in these countries. The increasing energy supply in these selected countries explains 41% of the variation in their mean BMI trends.

In the United States, the per capita energy available for civilian consumption has increased from approximately 3200 kcal/day in 1970–1979 to 3900 kcal/day in 2006.[39] This energy supply represents about 1.5 and 2 times the average energy consumed by U.S. adult males and females, respectively. Indeed, food has been so abundant that food waste has increased by 50% since 1974. Waste now represents 1400 kcal/day per capita,[40] an amount sufficient to feed another child aged 2 to 5 or an elderly woman.[41]

The primary sources of increased food energy are carbohydrate and fat, which are estimated to have increased by 20% and 24%, respectively, in the United States since 1970.[39] In absolute amounts, from 1980 to 2009, the per capita consumption of fat increased by 10 kg/year and the caloric sweeteners (sugar and high-fructose corn syrup) by almost 5 kg/year.[39] A majority of the increased fat and sugar intake was in forms added during food processing. The increased sugar intake is largely from the increased consumption of sweetened beverages.[39,42] These trends have prompted some to argue that taxing sugar and fats (like tobacco and alcohol) may be an effective way to curb their availability.[43] However, credible counterarguments hold that imposing a tax to reduce the intake of these foods and produce better public health outcomes may be ineffective.[44]

While the overall food supply has grown in affluent nations, lower-income, minority urban neighborhoods and rural areas (recently referred to as "food deserts") may have limited access to food choice. Food insecurity has been identified as a major determinant of food selection and a contributor to obesity in these areas.[45] Based on U.S. Census data, more than 17 million households in America were food-insecure in 2009, a 3% increase from 2005.[46] The lower density of full-service supermarkets[47] and higher density of fast-food restaurants[48] in food deserts have been associated with poorer diets and a higher prevalence of obesity.

These observations suggest a nonlinear relationship between food availability and BMI. Where food is abundant, available, convenient, palatable, and inexpensive, weight gain is often, though not inevitably, observed. Approximately one-third of the populations of affluent nations with ready access to food maintain healthy body weights. Juxtaposed with this positive association is the evidence implicating food scarcity with higher BMI. These discrepant relationships may stem from different underlying mechanisms that are corollaries of food availability (e.g., cultural views of nonnutritional roles of food, stress responses). Alternatively, they may reflect a common dimension more tightly linked with energy than with food availability. While much of the research in this area focuses on the diversity and nutrient density of the food supply available to different segments of the population, these factors are not strictly linked with energy availability, which is ample to meet and exceed energy needs in areas with both high and low food varieties. If there is a biological basis for eating in excess of need when energy is available, the observed associations may just reflect different strategies for achieving a common purpose. Eating is rewarding at many levels; for some individuals, sensory properties are a primary driver of energy consumption, while others may achieve satisfaction through the rewarding properties of energy intake itself.[49]

28.3 FOOD AFFORDABILITY

A comparison of food costs between selected nations reveals a trend where per capita energy intake increases as the cost per 1000 kcal decreases.[50] The United States has low food energy costs and high per capita energy consumption. The median unadjusted annual income of all families in the United States increased from approximately $35,000 in 1990 to $60,000 in 2009, which is equivalent to an increase of more than 70% over the past two decades.[39] Food prices, as indicated by the consumer price index, have also increased from 132.4 in 1990 to 218.2 in 2009 but at a rate (65%) lower than the unadjusted annual income over the same period of time.[39,51] The percentage of household income spent on food has dropped markedly since 1929[52] (Figure 28.2). The result is increased food affordability.

The low relative cost of food minimizes one barrier to its consumption, and there are dramatic examples of the importance of this factor. A sudden increase of affluence in the Pacific island of Nauru was associated with markedly greater food and energy intake and a rise of obesity that affected almost 85% of the population.[53,54]Alternatively, rates of overweight/obesity in Cuba declined with the dissolution of the Soviet Union and subsequent lack of subsidization of the Cuban economy[55] coupled with more limited access to foods and resources.[56] With improved economic conditions, overweight and obesity are again on the rise.[57]

The high affordability of fats and sugar has been proposed as the primary determinant of increasing energy intake and the high prevalence of obesity in the United States.[58] While intuitively appealing, this view requires critical review. First, given the low cost of food overall, such an argument is largely confined to explaining obesity trends among the less affluent. Second, the basis of the high prevalence of overweight/obesity among those with limited economic resources likely reflects a complex interaction of forces including the strong potential confounder of poor nutrition knowledge as well as a plethora of noneconomic factors influencing food choice. For example, the less affluent and more affluent exhibit divergent food choices with

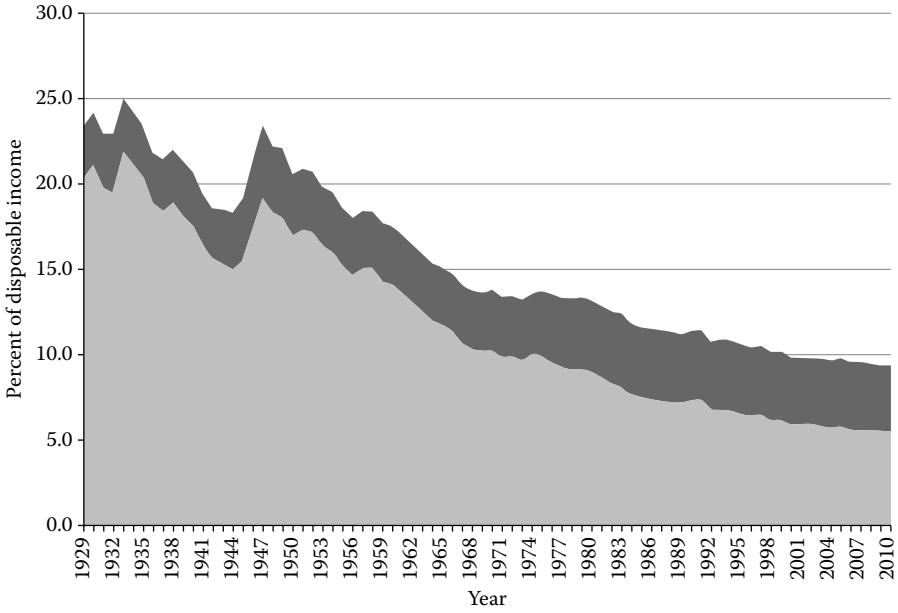

FIGURE 28.2 Food expenditures as a proportion of disposable income. Mean percentage of income expended on food consumed at home (lighter area) and away from home (darker area) in the United States between 1929 and 2010. (Data from U.S. Department of Agriculture, Food CPI and expenditures, Table 7, 2011 (cited February 12, 2012), available from http://www.ers.usda.gov/briefing/cpifoodandexpenditures/data/Expenditures_tables/table7.htm.)

similar properties but dissimilar energy value (e.g., diet vs. regular carbonated beverages, skim vs. regular milk).[59] Third, a corollary of the economic determinism model holds that better access to low-energy-density foods and restricted access to high-energy-density foods would prevent or ameliorate weight gain. Some evidence consistent with this view is available,[60] but there are also data indicating that higher fruit and vegetable intake offers no benefit with respect to BMI or that fruit and vegetable intake can be counterproductive when added to the diet.[61–63]

Overall, the cost of food energy is low, and this enables its acquisition and consumption, often in excess of need, with limited resource expenditure. Importantly, while cost may guide food selection differently in various segments of the population, even when low, cost, in and of itself, does not cause excess energy intake. Food selection still reflects choice, and improved nutrition knowledge may help to guide more healthful decisions. Efforts to reduce the cost of low-energy-density foods have the potential to make them more available to the less affluent, but this may not necessarily result in lower energy intake and body weight.

28.4 FOOD CONVENIENCE

Advances in food processing, storage technologies, and transport have made it more convenient to eat more foods, in more places, over greater periods of time. Foods can be stored longer and prepared more quickly. There is also increased availability of ready-to-eat foods. National survey data indicate that almost everyone in the United States snacks at least once a day,[41] adding a full eating event per day in the population since 1977–78. According to one study, the prevalence of snackers among adults in the United States increased from 71% in 1977 to 97% in 2003–2006,[64] and this likely stems from greater convenience of the food supply. According to the American Time Use Survey, the average time spent on secondary eating and drinking (defined as the eating and drinking events that occur during other primary activities such as watching television and driving) has increased significantly in the past few years.[65] In 2008, about 109 minutes were spent engaged in secondary eating and drinking, a behavior facilitated by foods and beverages made available in convenient forms. About 75% of secondary eating and drinking entailed drinking. This may be especially problematic for weight gain, as beverages elicit weaker physiological responses linked to satiety and compensatory reductions of energy intake.[27,61]

The convenience of accessing food outside the home is widely accepted as a contributor to weight trends. Individuals who are more willing to trade off attributes such as health considerations and taste for convenience are about 8% more likely to eat out every 2 to 3 days.[66] Full-service restaurants and fast-food outlets are the two largest segments of the away-from-home market, accounting for about 77% of the total market in 2010.[67] The National Restaurant Association projected that sales from the restaurant industry will reach nearly $632 billion in 2012, almost 15 times the sales amount in 1970.[68] More than half of consumers are willing to take further advantage of the convenience of food delivery, drive-through, and online food order options offered by full-service or fast-food restaurants. Indeed, the number of meals eaten away from home has increased in the last four decades.[69] In one study, about 75% of consumers reported that at least one meal per week was eaten out.[69] U.S. Department of Agriculture food

intake surveys have shown that approximately 18% of daily energy intake in the 1970s was consumed away from home, which rose to 32% in the 1990s and to 35% in 2007–2008.[41,69]

Though these data are striking, a causal association with weight trends has not been established. The greater reliance on establishments providing food outside the home is potentially problematic because they reportedly serve larger portion sizes[70] than meals prepared at home. Larger portion size leads to higher energy intake in both children[71] and adults[11] within eating events. But while some evidence suggests that overconsumption at one eating event is not later compensated for,[72] other findings challenge this view.[16,17] If the latter is true, occasional large meals are not problematic, and it should be noted that most food consumption still takes place at home.[73]

The more significant contribution of convenient dining options to greater energy intake may lie just in their facilitation of increased eating frequency. However, in this regard, they are not necessarily the primary source. In 2011, sales from vending machines were reported to exceed $12 billion,[74] and cold beverages from vending machines alone yielded $6.2 billion in sales. To address this source of convenient energy, the Patient Protection and Affordable Care Act of 2010 stipulates that nutrition information must be available at the point of purchase.[74] Evidence of the efficacy of this act must be closely monitored to determine whether such information modifies ingestive behavior.

The increased convenience of the food supply has provided greater opportunity to eat more frequently. Given the strong and growing evidence that eating frequency is positively associated with energy intake[22] and weight gain,[75–77] the growing convenience of food poses a challenge for weight management.

28.5 FOOD MARKETING

About 4 cents of every dollar spent on food by consumers supports advertising.[78] In 2010, approximately $1.1 trillion was spent on food in the United States,[52] and this amounted to approximately $43 billion in total food advertising expenditures, up from the $24 billion spent in 1999.[79] This large expenditure alone is evidence for marketing's efficacy at promoting sales and, presumably, consumption. There are many ways food products and services are advertised, from the use of public media such as television, radio, newspapers, and magazines (about two-thirds of the total advertising budgets) to toy giveaways, product promotions at stores, and event sponsorships.

In 2009, $4.2 billion was spent on food advertising by fast-food restaurants in the United States.[80] A big proportion of this expenditure was targeted at children and adolescents.[81] Roughly 1200 fast-food advertisements were viewed by children ages 2 to 11, and over 1700 were seen by youths ages 12 to 17 in 2009.[80]

Some suggest that advertisements of energy-dense, low-nutrient-content foods may lead to a shift in food preference and food choice resulting in higher energy and fat intake,[82] higher frequency of fast-food consumption,[83] and lower fruit and vegetable consumption.[84] While these findings pose a credible concern, they are still only observational, are not documented in representative samples of the population, and may well reflect strong publication bias. They also speak primarily to food choice rather than effects on total energy intake, the more relevant index of an impact on energy balance and weight gain.

Assuming marketing is effective at promoting intake, it should be noted that the principles food advertising draws upon are not bound by the nutrient and energy profile of the promoted item. Consequently, advertisements can also be applied to build positive attitudes of viewers toward many, if not all, types of foods.[85] The issue lies in the motivation and resources available to promote one type of product over another. For example, food advertising expenditures by the food and restaurant industries in 2004 exceeded $11 billion, as compared to $9.5 million spent by the federal and California state governments on the "5 A Day" program that promotes the consumption of 5 servings of fruits and vegetables per day.[86] This does not mean that all foods promoted by industry are unhealthy or that dietary practices advocated by the government will guarantee better weight management by consumers. This example only highlights the importance of monitoring the impact of the media for messaging and guiding food choice and reinforces the importance of making appropriate choices in using media for the public good.

28.6 FOOD PALATABILITY

Some have suggested that documenting palatability effects on intake is problematic because there is so little variability in the association.[87] When food is abundant, unpalatable items are seldom selected and the relationship between food dislikes and rejection is strong.[88] For palatable items, the association between sensory ratings and food choice is less straightforward. When two or more acceptable products differ in perceived health impact; social, religious, or moral implication; cost; convenience; and many other considerations, choices may not follow a strict hierarchy of hedonic impressions. Indeed, the literature is replete with findings indicating that high palatability enhances, depresses, or leaves intake unchanged. The most common interpretation for enhanced intake is that the most palatable foods are more rewarding than less palatable items, and this provides the motivation for their selection and greater consumption. Interestingly, a frequent explanation for an inverse relationship also rests with the reward system, but in this instance, intake is reduced because highly palatable items more efficiently satisfy one's craving or desire for the item.[89]

Further complicating an association, rated acceptability is also an ephemeral characteristic of a food. It changes over the course of its ingestion, reflecting postingestive feedback on ratings. Shifts also occur between eating events based on other recent flavor exposures, changing physiological conditions (e.g., energy and hydration status) and cultural norms (e.g., some foods are deemed appropriate at certain times of day or with other foods, but less appropriate under different circumstances).[90–92]

How is this seemingly conflicting literature to be reconciled? We suggest that the apparent confusion lies primarily in methodological shortcomings of studies addressing the issue. Hedonics is multidimensional. It includes indices of liking that can be defined for absolute concentrations of flavor components; examples include tolerance of repeated exposures to an item and preference of one version of a product over another. Each dimension provides unique information, and different studies solicit different types of responses. Commonly, judges or consumers are not trained to differentiate between these responses, resulting in findings of uncertain interpretation.

With these qualifications aside, the sensory appeal of foods overall is consistently considered the primary driver of food selection and consumption.[93] Cost, convenience, and nutrient content are also highly rated but do not dominate over flavor. While this literature speaks to the issue of food choice, it typically does not quantify effects on energy intake or body weight. More recently, speculation has arisen regarding the potential for certain food ingredients (e.g., sugar, fat) to hold addictive qualities that could promote excessive intake relative to need.[58] Evidence from animal studies has indicated that sugar and fat ingestion stimulate reward centers leading to addictive-like behaviors.[94] This work has been extended to humans with claims that these flavor-active compounds lead to compulsive overeating and weight gain.[95] However, the concept of addiction to palatable ingredients such as sugar and fat is yet to be proven in humans.[96] Indeed, one of the basic criteria for labeling a substance addictive is that tolerance develops with repeated exposure, leading to the need for ever-increasing exposures to achieve a given effect, and this is not observed in humans with sugar and fat.[96,97] Attempts to manipulate sensory properties to control feeding have been largely unsuccessful.[98]

In addition to the contribution of the sensory properties of single foods to their consumption, sensory variety also holds its own appeal.[99,100] To exploit this orexigenic influence, food companies support flavor innovation. This is reflected by sales of $22 billion in the flavor and fragrance industry in 2010, which was $10 billion more than a decade ago.[101] More than 1000 snacks and 800 drinks are now available to consumers, with some snacks offered in up to 13 different flavors.[102] Increasing variety within and between food groups is generally associated with greater food intake.[10] In contrast, monotony typically decreases intake, perhaps most strongly for highly palatable foods.[103] The importance of variety is also apparent from the high and growing popularity of ethnic foods. Total U.S. expenditures for food eaten away from home have increased significantly from $2.6 billion in 1929 to $443.9 billion in 2010,[52] of which $75 billion came from ethnic restaurants in 2010.[104] Though effects of variety are demonstrable in short-term trials, longer-term effects on intake, energy balance, and body weight are not clearly established. The exception is extreme monotony, where weight loss is observed, but the loss is not sustained because of poor dietary compliance.[105]

When consumers or the food industry prepares food, the goal is always to optimize palatability to ensure acceptability and promote consumption. The food industry has been highly successful in this endeavor. Even when the primary goal of product development may be for a purpose other than hedonic impact (e.g., nutrient content, convenience), sensory appeal cannot be compromised, or the item will not be repeatedly ingested. The ready availability of a large array of highly palatable foods and beverages is a likely contributor to intake. There is little motivation from producers or consumers to limit this option. Change here seems most probable for enhancing the palatability of more healthful, lower energy items and educating consumers in their appropriate inclusion in the diet (i.e., as a substitute for higher energy options rather than as an addition to the diet).

28.7 CONCLUSIONS

The food environment is widely characterized as "obesogenic." This is a vague term that is applied to describe the nonbiological conditions that permit or promote weight gain on an individual or population basis. It is invoked equally to account for weight trends of people living in different parts of the world and within the same household, knowing that it actually differs for every individual who is variously influenced by the multitude of forces that can be considered obesogenic. We have reviewed five of the commonly identified elements of the food environment. None can be said to be causally linked to weight gain, and perhaps it is unrealistic to expect that they or any other element will be. All are forces that guide behavior, which is a probabilistic concept. An additional complication is the lack of knowledge of the controls of ingestive behavior (if any controls are actually operational), the factors upon which the environment acts. Nevertheless, the problems of overweight/obesity are substantive and growing, demanding remedial action.

The five factors characterized here are considered individually, but it should not be inferred that they can be addressed in isolation. Doing so would likely be an ineffective approach since each contributes differentially to any given individual, and this contribution varies over time. Plus, environmental influences are interactive. This complexity is illustrated by the common observations that restaurants attempt to provide consumers with the convenience of eating away from home at more locations over longer business hours; strive to set prices for their products that are viewed as affordable or a good value; advertise to make their offerings more visible and enticing; and ceaselessly work to maximize the palatability of their menu. In many instances, a flaw in one element can result in failure, but the high number and diversity of restaurants indicates that there are different niches and that if one element is weak, it may be compensated by another to permit success. When it comes to food, lesser quality may be accepted at the right price, and high cost and inconvenience may be an acceptable trade-off for very high quality. Ultimately, guidance for weight management will require addressing the unique interplay between a given individual's biology and their unique food environment.

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29 Obesity and Related Eating Disorders

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CONTENTS

29.1 INTRODUCTION

With the advent of the "obesity epidemic," health-care providers and researchers alike have attempted to identify patterns of eating that may be modifiable. The two eating disorders most closely linked with obesity are binge eating disorder (BED) and night eating syndrome (NES). While these disorders were identified formally more than a half-century ago by Stunkard, they were not studied more intensively until the 1990s and are currently the subject of increased scrutiny. We present the definition, prevalence, risk factors, comorbidities, and treatments for these disorders.

29.2 BINGE EATING DISORDER

Binge eating was originally described in ancient Greece by Hippocrates as a type of pathological hunger, who referred to this unique presentation of overeating as bulimia (translating to "ox hunger").[1] Stunkard first proposed it as a disorder in 1959 as "binge eating syndrome."[2] The current definition of BED is the consumption of an objectively large amount of food within a 2-hour time period, while feeling a loss of control (i.e., inability to control how much food is consumed and inability to stop eating).[3] BED is distinguished from bulimia nervosa by the lack of inappropriate compensatory behaviors designed to prevent weight gain after a binge (e.g., vomiting, laxative use, and overexercising).[3]

29.2.1 Diagnostic Features

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* included BED as a provisional diagnosis under the category Eating Disorder Not Otherwise Specified, as it necessitated further research at the time of publication. To receive this diagnosis, binge episodes occurred at least twice weekly for 6 months.[3] Individuals also endorsed at least three associated symptoms, including eating rapidly, eating despite a lack of hunger or until feeling uncomfortably full, feeling shame, disgust or guilt, and eating alone due to embarrassment.[3]

These diagnostic criteria were based on two large-scale studies evaluating patients at 12 eating disorder programs.[4,5]

BED has been classified as a formal eating disorder diagnosis (rather than a provisional diagnosis) in the Diagnostic and Statistical Manual V (DSM-V), based on a recent literature review.[6] The frequency criterion was changed in this edition from reporting binges twice per week for at least 6 months to once weekly for at least 3 months.

29.2.2 Prevalence

Reports of prevalence of BED are highly variable, particularly due to methodological variability as well as differing definitions of what constitutes a "binge."[8] Specifically, BED is typically diagnosed more frequently when assessed by self-report measures in comparison to clinician-administered semistructured interviews.[9]

Community studies have reported relatively low prevalence of BED, ranging from 1.8% to 2%.[4,10] Higher prevalence estimates of 8.9% and 18.8% were found in samples of treatment-seeking obese individuals.[11,12] A higher prevalence, 18%, was also observed in a sample of individuals seeking treatment at an inpatient weight loss center.[13] However, prevalence estimates in treatment-seeking diabetic individuals have been found to be as low as 1.4%.[14] In samples of individuals seeking bariatric surgery, prevalence ranges from 4% to 50%.[9,15,16] Prevalence of BED in white men and women is similar; however, the prevalence of BED in black women is higher than in black men.[17–19]

29.2.3 Psychiatric Comorbidity

BED has consistently shown associations with Axis I disorders (e.g., mood, anxiety, schizophrenic, and substance disorders), especially depression[20–24]; Axis II disorders (personality disorders) also co-occur in samples of persons with binge eating.[20,21,23] In individuals seeking bariatric surgery, those diagnosed with BED appear to be more likely to suffer from depressive and anxiety symptoms compared to those without BED.[25] A recent study of treatment-seeking BED patients revealed relatively high lifetime prevalence of psychopathology including mood disorders (54.2%), anxiety disorders (37.1%), and substance abuse disorders (24.8%).[26] Rates of current psychopathology were also relatively high, with mood (26.0%) and anxiety disorders (24.5%) being the most frequently diagnosed comorbidities.[26] The diagnosis of comorbidities was related to lower self esteem, greater depressive symptoms, and more severe eating pathology as assessed by the Eating Disorder Examination.[26,27]

29.2.4 Risk Factors

Research on the role of genetics on the development of BED is mixed, with some research suggesting a link between genetics and BED[28] and others showing no relationship.[29] One environmental risk factor for BED appears to be childhood maltreatment. Compared to overweight and obese control participants, those diagnosed with BED reported greater amounts of emotional abuse and neglect during childhood.[30]

It was once believed that dieting played a direct causal role in the development BED; however, researchers have consistently shown that dieting actually occurs more often following the onset of binge eating.[4,5,31–33] The National Task Force on the Prevention and Treatment of Obesity has released a statement confirming that current research does not support this original hypothesis.[34]

29.2.5 Binge Eating Disorder and Obesity

Although not all persons with BED are obese, individuals with BED are more likely to be obese, especially those who are in treatment.[35] Weight has been shown to increase with greater binge eating severity.[10] Dingemans and van Furth sought to evaluate the differences between normal weight and obese individuals diagnosed with BED.[36] They found that obese patients with BED presented with more weight concerns and greater frequency of binge eating compared to average weight patients; however, these were the only differences between the groups. That is, they displayed comparable restraint, eating and shape concerns, and depressive symptoms.[36]

29.2.6 Quality of Life

Poorer quality of life has been shown in those with BED compared to those without.[37] However, one study revealed that BED status did not independently predict lower weight–related quality of life in a sample of individuals in an inpatient weight loss center.[13] It appears that demographics, body mass index (BMI), and psychological symptoms may contribute to the lower quality of life seen in this population.[13] In fact, Masheb and Grilo found that obesity status and depressive symptomology influenced health-related quality of life scores in individuals with BED.[38] Therefore, it is likely that both the BED *and* its associated factors contribute to declines in quality of life, rather than solely the BED.

29.2.7 Treatment

Treatment options for BED include psychotherapy targeting BED symptoms, standard behavioral weight loss (BWL) treatments, and pharmacotherapy.

29.2.7.1 Psychotherapy

Psychotherapies targeting BED symptomology include cognitive behavioral therapy (CBT) and interpersonal psychotherapy. These interventions are frequently presented in groups and have resulted in decreases in the frequency of binge episodes between 48% and 96%.[39–42] A recent long-term (i.e., weekly sessions for an average of 7 months) CBT intervention resulted in significant reductions in binge eating episodes as well as weight loss. These changes were maintained at long-term follow-up (average of 3.5 years posttreatment).[43] CBT delivered through self-help modalities have also been effective in reducing the frequency of binges.[39,41,44] A mindfulness-based intervention has also been shown to

reduce binge frequency.[45] Despite successes with decreases in binge episodes, these treatments have failed to result in clinically significant weight loss consistently.[8] Across studies, it seems that those patients who reduce binge episodes to the greatest degree are those who lose the most weight.[46]

29.2.7.2 Pharmacotherapy

Several pharmacological agents have been shown to reduce binge frequency and promote modest weight loss in those with BED, such as antidepressants, including Selective Serotonin Reuptake Inhibitors (SSRIs).[47–49] Research on tricyclic antidepressants is mixed regarding their effect on binge eating, while it appears that they do not induce weight loss.[50,51] D-fenfluramine (an appetite suppressant affecting serotonin regulation) was shown to decrease binge eating, but did not result in meaningful weight loss,[52] while weight loss and decreased binge episodes resulted from the use of sibutramine (another appetite suppressant affecting serotonin and norepinephrine).[53] However, both of these appetite suppressants have been removed from the market due to their side effects. The use of topiramate has also resulted in long-term decreases in binge frequency and body weight in a sample of obese individuals with BED, but there is a high frequency of participant discontinuation, usually due to the side effect profile, particularly those that affect cognitive functioning.[54] A recent meta-analysis revealed that pharmacotherapy generally results in clinically significant short-term decreases in binge eating compared to placebo and only modest weight loss.[55]

It should be noted that there is a well-documented placebo response seen in this population in a variety of pharmacotherapy trials including those for imipramine,[51] naltrexone,[51] topiramate,[56] SSRIs,[48,49,56,57] and appetite suppressants,[52,53] with remission of binges in placebo groups ranging from 14% to 33% in these samples. Jacobs-Pilipski et al. investigated these placebo effects in BED and found that 32.6% of their participants were "placebo responders" (i.e., no longer meet criteria for BED or engage in *no more than* 25% of binge episodes compared to pretreatment).[58] At long-term follow-up (1 year), 35% of these responders returned to binge eating at least twice weekly.[58] Interestingly, most participants did not attribute their improvements to the medication, but rather to behavioral factors.[58] With the high frequency of placebo effects and less than optimal weight outcomes, the utility of pharmacological treatments for BED has been subject to debate.[59]

29.2.7.3 Behavioral Weight Loss

Standard BWL treatments with no emphasis on targeting binge eating have also produced decreased binge eating.[60] In addition, these programs tend to result in favorable weight loss outcomes.[40,60,61] Weight loss resulting from a BWL treatment and very low calorie diets do not appear to be related to binge eating severity.[24,61,62] Therefore, it appears that standard BWL treatments can be considered a viable treatment option for those suffering from BED, especially if weight loss is desired.

29.2.7.4 Comparisons of Treatments

In a study comparing the effectiveness of group CBT versus group BWL treatments, significant reductions in binge eating and BMI were seen in both treatment conditions.[63] However, at the end of treatment, CBT resulted in greater improvements in BED symptomology, while BWL resulted in more favorable weight outcomes.[63] It should be noted that at the 1-year follow-up, weight and binge eating outcomes in the two treatment groups were comparable.[63] When a CBT-based self-help program was compared to a BWL-based self-help program, the weight outcomes of the two treatments were comparable, with no meaningful weight loss resulting from either treatment.[64] However, greater remission of BED diagnosis was observed in the CBT self-help group compared to the BWL self-help group.[64] It appears that adding a CBT component to standard BWL may prove beneficial, as Devlin et al. in 2005 reported that this combination showed greater reductions in binge episodes compared to BWL paired with fluoxetine or placebo.[65] The addition of fluoxetine to BWL treatment did not result in any additional benefits.[65]

29.2.8 Binge Eating Disorder and Bariatric Surgery

Disordered eating is common among candidates for bariatric surgery and is a likely contributor to the development of extreme obesity. For example, in the year before seeking treatment, persons with BED, on average, gain 9.5 lbs, and severity of binge eating is related to the magnitude of weight gain.[66] Many patients report that they engage in eating for emotional reasons. Others have formally recognized eating disorders. Bariatric surgery has been shown to result in significant reductions of BED symptoms.[16,67,68] Although binge eating has been found to subside in patients 4 months postsurgery,[67] at long-term follow-up (between 2 and 7 years postsurgery), nearly half of patients reported a recurrence of loss-of-control eating episodes.[68] These patients regained a greater amount of weight than those who did not experience persistent loss-of-control episodes[68] (see Table 29.1).

Although initial research indicated that the presence of presurgical binge eating was a predictor of poorer weight-loss outcomes postbariatric surgery,[69,70] it appears that binge eating behavior before surgery is not associated with less weight loss up to 2 years postsurgery in more recent studies.[71–75] While presurgery binge eating does not appear to affect weight loss significantly, postsurgical binge eating remains problematic. The definition of a binge after surgery is still uncertain, as it seems that the loss of control over eating is more important than the size of the eating episodes in relation to actual eating pathology in this population. Patients after bariatric surgery are not typically physically able to eat objectively large amounts of food, but as they push the limits of portion size each time they experience a loss of control, they could risk stretching the postoperative pouch, resulting in the ability to eat larger portions and weight regain. Postsurgery binge eating as well as experiencing a loss of control when eating (without meeting criteria for clinical binge eating) have been associated with poorer weight loss outcomes.[75–77] Thus, bariatric surgery patients experiencing a recurrence or new

TABLE 29.1
Prevalence and Outcomes for Patients with Binge Eating Disorder Seeking Bariatric Surgery

Study	*n*	Surgery Type	Pre-Op Prevalence	Post-Op Prevalence	Weight Outcomes
Wadden et al.[74]	95	RYGB or adjustable banding	38% diagnosed with BED. Mean number of binge eating days (over the past 28 days): 9.5 ± 1.2 days	At 6 months: Mean number of binge eating days: 0 ± 0.9 At 1 year: Mean number of binge eating days: 1.5 ± 1.3 days	No significant differences in percent loss of initial weight at 1 year between those without BED and those diagnosed with BED presurgery ($p > .309$)
Alger-Mayer et al.[71]	157	RYGB	24% classified as "severe binge eaters" as indicated by binge eating scale (BES) scores of ≥27	Not measured	No significant differences in weight loss between severe binge eaters (BES ≥ 27) and nonsevere binge eaters (BES ≤ 26) up to 6 years follow-up
Colles et al.[76]	129	LAGB	14% diagnosed with BED 31% classified as "uncontrolled eaters"	At 1 year: 3.1% diagnosed with BED 22.5% classified as "uncontrolled eaters"	Presurgery: Those with a presurgery BED diagnosis and presurgery "uncontrolled" eaters experienced similar weight losses compared to those without presurgery BED Postsurgery: Postsurgical "uncontrolled" eaters displayed poorer weight outcomes at 1 year, compared to those without loss of control eating episodes postsurgery ($p = .008$)
Fujioka et al.[72]	121	RYGB	Lifetime prevalence: 32%	Not measured	No significant differences in weight outcomes between those with BED compared to those without, up to 2 years follow-up
Sallet et al.[70]	216	RYGB	Lifetime prevalence: Subthreshold binge eating: 60% BED: 20%	Not measured	At 2 years, nonbinge eaters ($n = 33$) displayed greater percent excess BMI loss compared to those with a lifetime prevalence of subthreshold binge eating ($n = 64$, $p = .003$) and BED ($n = 34$, $p < .001$)
White et al.[73]	139	RYGB	Infrequent binge eating (< once per week): 16% Binge eating at least once per week: 24% Binge eating at least twice weekly: 10.1%	At 1 year: Infrequent binge eating: 8.8% Weekly binge eating: 0.7% Twice weekly binge eating: 0%	No significant difference in weight outcomes among groups according to binge status
Burgmer et al.[75]	149	VBC or AGB	Current prevalence: BED: 2% Recurrent binge eating episodes: 20.1% Prior prevalence: BED: 7.4% Recurrent binge eating episodes: 37.6%	Not measured	No significant difference in weight outcomes between those who reported binge eating episodes compared to those that did not
Kalarchian et al.[68]	99	RYGB	Not measured	At 2–7 years: 44% binge eaters (subjective, loss of control, at least once a week for the past 4 weeks)	Binge eaters regained more weight from lowest weight after surgery (13.9 lb) compared to nonbinge eaters (7.1 lb), based on self-reported weight data
Powers et al.[16]	116	"Gastric restrictive surgery"	52% engaged in binge eating at least once per week 16% met DSM-IV criteria for BED	At mean 5.5 years: 0% reported objective binges, due to inability after surgery to consume a large about of food	No effect of presurgery binge eating on weight outcomes postsurgery (up to mean 5.5 years)
Pekkarinen et al.[69]	27	VBG	Not measured	At mean 5.4 years: 37% binge eaters (based on modified Binge Eating Scale; some questions referred to presurgery status, and others post-op status)	Although initial weight loss was similar, weight regain after 1 year postsurgery was higher in binge eaters (23 kg) compared to nonbinge eaters (5 kg; $p = .01$)

Note: RYGB = Roux en Y Gastric Bypass; LAGB = Laparoscopic Adjustable Gastric Band; VGB = Veritical Banded Gastroplasty; AGB = Adjustable Gastric Band

onset of binge eating and loss of control episodes should seek treatment to avoid suboptimal weight loss or weight regain following surgery.

29.3 NIGHT EATING SYNDROME

In 1955, Stunkard et al. first described the NES as a disorder characterized by morning anorexia, evening hyperphagia, and insomnia.[78] For many years, NES received limited attention by researchers, and until recently, no uniform criteria existed to quantify the disorder. Since that time, increased research attention has enabled researchers to refine diagnostic criteria and identify key features of the syndrome. In 2008, a team of experts convened to come to a consensus on a set of provisional diagnostic criteria for NES.[79] Furthermore, NES now appears for the first time in the DSM-5, under the category of "Otherwise Specified Feeding and Eating Disorders Not Elsewhere Classified."[7]

NES is characterized by an abnormally increased food intake in the evening and nighttime.[80] According to proposed criteria, individuals with NES must ingest at least 25% of their daily food intake after the evening meal and/or experience nocturnal awakenings that are associated with eating (i.e., *nocturnal ingestions*), at least two times per week.[79] Individuals with NES must be aware of their nocturnal ingestions, which distinguish NES from sleep-related eating disorder (SRED), in which individuals are unaware of their night eating.[81] Additionally, individuals must also experience at least three of the following features: morning anorexia, or a lack of desire to eat in the morning; an urge to eat between dinner and bedtime or during the night; delayed sleep onset or insomnia at least four nights per week; a belief that the nocturnal ingestions are necessary to help them to sleep; and a decrease or worsening of mood in the evening. The eating behavior must be associated with distress or impairment in functioning for an individual to meet criteria for NES. Last, for NES to be diagnosed, the disordered pattern of eating must be present for at least 3 months.

29.3.1 Prevalence

The prevalence of NES varies, based on the population, from 1.5% to 42%.[9,16,82-87] Variation in prevalence may also be attributed to a variation in assessment methods and inconsistencies in symptom criteria. In the general population, the prevalence has been noted at 1.5%.[82,83] Among outpatient psychiatric patients, the prevalence is higher at 12.3%, with substance use disorder being the most commonly occurring comorbid psychiatric diagnosis, and obese patients having a fivefold increased risk of NES diagnosis.[84] In obese populations, the prevalence of NES ranges from 10% to 15%,[85,86] and in a population of individuals seeking bariatric surgery, prevalence of NES has ranged from approximately 2% to 55%.[9,16,82,87] Allison et al., using a combination of self-report measures and semistructured clinical interviews, found that approximately 9% of bariatric surgery patients met criteria for NES at the time of the presurgical interview.[9] NES appears to be present in comparable numbers of men and women.[14,85,88,89] Little information is available concerning the effect of preoperative NES on weight loss following surgery. As with BED where loss-of-control over eating may reemerge after surgery without the accompanying objectively large portion sizes, NES may also continue, particularly because the amount of food is not required to be objectively large during nocturnal ingestions.

29.3.2 Diagnostic Features

The core features of NES fall into several categories related to timing of eating episodes and sleep patterns, stress, and heritability. Meal patterns and food intake are often shifted, such that individuals with NES typically consume at least 25% of their food intake after their evening meal and are more likely than normal controls to eat in the middle of the night. The sleep patterns of individuals with NES show that waking for nocturnal ingestions typically occur during non-rapid eye movement sleep. However, sleep onset and offset are not significantly shifted, suggesting that the urge to eat is displaced and disrupting sleep.[80–90]

29.3.3 Onset and Risk Factors

NES typically first appears in the late 20s, and onset may be related to stress.[91] Symptoms may also be exacerbated by stress. Childhood emotional and physical neglect are reported in more than three-quarters of individuals with NES.[30] One study has suggested a strong familial aggregation, such that individuals with NES are 4.9 times more likely to have a first-degree relative with NES than a group of control subjects without NES.[92] A population-based study surveying participants from the Swedish Twin Registry has found that the heritability rates are 0.35 (95% CI: 0.17, 0.52) in females and 0.44 (95% CI: 0.24, 0.61) in men.[93]

Regarding comorbid psychiatric conditions with NES, Axis I disorders such as major depressive disorder and anxiety disorders have been noted.[83,94] The literature is less clear about the prevalence of comorbid eating disorders in individuals with NES or of NES in patients with eating disorders, such as anorexia nervosa and bulimia nervosa, with rates ranging from 5% to 44%.[11,83,95,96]

NES appears to be more prevalent in overweight populations[86,88,92,97,98]; however, there has been some dissent among research findings on this point, with a number of studies showing no differences in BMI when comparing individuals with NES versus controls with no eating disorders.[9,99,100] However, larger, epidemiological studies of night eating symptoms, particularly those among young adults, suggest that those with night eating behaviors are not more likely to be obese.[83] Obesity in individuals with NES may be associated with age of the individual, in that younger individuals with NES do not appear to have higher rates of obesity consistently, but older individuals with NES do appear to have higher rates of obesity than non-NES counterparts.[101] This finding suggests that NES may contribute to weight gain over a number of years. Two prospective studies have provided data to support this possibility.[99,102]

29.3.4 Neuroendocrine Factors

In the first study examining neuroendocrine factors in participants with NES, researchers observed a group of individuals with NES and a group of matched control participants.[103] NES participants had more overall eating episodes and consumed a larger amount of their daily caloric intake at night when compared with non-NES individuals of similar weights. They also woke up more at night (3.6 vs. 0.3) and, about half the time, experienced a nocturnal ingestion during the awakenings. Individuals with NES were noted to have lower plasma melatonin between 10 p.m. and 6 a.m., as well as a shorter duration in the nocturnal rise of leptin, and, lastly, elevated levels of cortisol over the course of the day.[103] The differences in melatonin, leptin, and cortisol align nicely with features of NES in nighttime awakenings, the urge to eat during the night, and the association between NES and stress, as the three hormones are closely linked with sleep, appetite control, and stress. This study is limited, however, in that the subjects were observed over a single 24-hour period and subjects were fed calorie-controlled meals.

In a more recent study of 15 NES and 14 matched non-NES control subjects, NES subjects had higher nocturnal food intake, higher levels of insulin ($p < .001$) and glucose ($p < .07$) and lower levels of ghrelin from 1 a.m. to 9 a.m.[104] NES participants also showed trends of higher thyroid-stimulating hormone than their non-NES counterparts. Authors posit that these neuroendocrine differences are the result of the nighttime eating, as opposed to having a causal relationship with the nocturnal ingestions.

Subsequent analyses of these data revealed phase delays for most of these hormones in NES participants, including an inverted glucose circadian rhythm (delay of 12 hour) and a delay in insulin values by 2.8 hours.[105] There was also a delay of about an hour in melatonin and leptin rhythms, while ghrelin was 5.2 hours phase advanced. Leptin and ghrelin that, like glucose and insulin, are usually synchronized[106] were out of sync by about 6 hours.

The divergent findings in the research described in the preceding discussion may be attributed to differences in methodology, specifically that the study by Birketvedt et al. followed participants for only 24 hours, while Goel et al. observed participants for 3 days (2 days of run-in); feeding paradigms differed in that Birketvedt fed participants three calorie-controlled meals and Goel et al. allowed participants to eat ad libitum meals and nighttime snacks.[103,105]

29.3.5 Eating versus Sleep Disorder

NES shares some overlap with SRED, as both disorders involve nighttime awakenings to eat. However, there are many important differences that make the two disorders distinct from one another. First, while both disorders involve nocturnal ingestions, individuals with SRED report a lower level of consciousness regarding the eating episodes, while one of the criteria for NES is an awareness of the nocturnal eating episodes.[107] Treatments vary between the disorders as well, with sleep medications being ineffective for NES, but efficacious for SRED. Also, psychotherapies have not been shown effective with SRED, as behaviorally based approaches would not be possible when sufferers are sleepwalking or lacking awareness of their actions.[107]

29.3.6 Treatment

Very limited research is available on treatments for NES, with only two randomized controlled trials (RCT) available to date. However, a number of other treatments used to treat the symptoms of NES have shown initial promise, as demonstrated through case studies or open label trials. Each of these will be briefly reviewed and summarized in Table 29.2.

29.3.6.1 Pharmacotherapy

Pharmacologic treatment approaches of NES have been the most heavily investigated. Researchers have most often examined the effectiveness of sertraline,[108–110] but paroxetine and fluvoxamine were also examined in one case series by Miyaoka et al.[111] O'Reardon et al. published the first RCT comparing sertraline versus a placebo in the treatment of 34 participants with NES.[108] After an 8-week regimen of sertraline (dosing ranged from 50 to 200 mg/day) or placebo, participants in the sertraline group noted greater improvements in several NES indices including number of nocturnal ingestions, number of total awakenings, and scores on the Night Eating Symptom Scale (NESS),[110] and lost more weight than those in the placebo group (2.9 vs. 0.3 kg) (all p values $< .05$). Although not significantly different, participants who received sertraline also reduced the total number of calories consumed after their evening meal by 68% versus 29% in the placebo group.[108]

The results from this RCT support previous findings using SSRIs. For example, in a sample of 50 individuals with NES, Stunkard et al. examined the effectiveness of an 8-week regimen of sertraline prescribed "at a distance" by the participants' primary care physicians.[109] Participants completed an initial phone screen, as well as questionnaires every 2 weeks, and a final phone interview. Results showed improvements in NES symptomology, including decreased evening hyperphagia, reduced nighttime awakenings, fewer nocturnal ingestions, and a reduction in participants' scores on the Beck Depression Inventory-II (all $p < .001$). Overweight and obese participants ($n = 41$) lost 3.0 kg on average ($p = .01$).

One RCT was recently reported comparing treatment with another SSRI, escitalopram, as compared to placebo.[112] While night eating symptoms improved significantly in the escitalopram group, these decreases were not significantly different from decreases in the placebo group. Sixty percent of those in the escitalopram group were considered responders as compared to 35% of those on placebo, and 80% of those on escitalopram versus 60% on placebo no longer met full diagnostic criteria for NES at the trial's end (neither comparison was significantly different). This RCT of escitalopram

TABLE 29.2
Treatment Study Outcomes for Night Eating Syndrome

Study	Intervention	*n*	Duration (weeks)	Mean Dose (mg)	Weight Change (kg)	BDI-II	Changes in NES Symptomology
Allison et al.[117]	Cognitive behavior therapy	25	12 (10 sessions)	N/A	−3.1**	−2.5**	Calories consumed after the evening meal decreased by 10%** Nocturnal ingestions decreased by 6.1 per week** Number of nocturnal awakenings decreased by 5 per week* NESS scores decreased by 12.4**
Dalle Grave et al.[89]	Behavioral weight loss	100 (38 NES, 62 non-NES)	27	N/A	−2.7 (NES) versus 3.3 (non-NES) (change in BMI)	−1.5 (NES) versus + 0.7 (non-NES)	8 of 35 participants reported having evening hyperphagia and/or nocturnal awakenings at 6 month follow-up NEQ decreased by 2.8 in the NES group versus 0.6 in the non-NES group 18 of 35 (completers) reported complete remittance of NES in the last 3 months
Friedman et al.[119]	Phototherapy and paroxetine	1	6	40	Not reported	−7	Patient no longer met criteria for NES after 14 daily sessions of phototherapy (One month later, her NES symptoms had returned and phototherapy was reinitiated for 12 more sessions)
Gluck et al.[102]	Behavioral weight loss	76 (11 NES)	4	N/A	−4.4 (NES) versus −7.3 (non-NES)**	Not reported	N/A
Miyaoka et al.[111]	Paroxetine/ fluvoxamine	4	4	See "Changes in NES Symptomology"	Not reported	Not reported	Cases 1–3 treated with paroxetine (20–30 mg/day), decrease in number of awakenings and complete remittance of NES Case 4 treated with fluvoxamine (25 mg/day), decreased number of awakenings, and complete remittance of NES
O'Reardon et al.[110]	Sertraline	17	12	188	−4.8 kg (remitters) versus + 0.6 kg (nonremitters)	Not reported	Nocturnal awakenings reduced by 1.8 per night** Nocturnal ingestions decreased by 1 per night** Self-reported caloric intake after evening meal decreased by 25.7%** CGII - Clinical Global Impression of Improvement Scale ratings reduced by 1.4**

(*Continued*)

TABLE 29.2 (*Continued*)
Treatment Study Outcomes for Night Eating Syndrome

Study	Intervention	*n*	Duration (weeks)	Mean Dose (mg)	Weight Change (kg)	BDI-II	Changes in NES Symptomology
O'Reardon et al.[108]	Sertraline	34	8	127	−2.9 (sertraline) versus −0.3 (placebo)	Not reported	NESS reduced by −18.1 in the sertraline group versus −5 in the placebo group** CGI reduced by 2 in the sertraline group versus 0.8 in the placebo group** Nocturnal ingestions in the sertraline group decreased 6.7 per week versus 0.9 per week in the placebo group** Nocturnal awakenings dropped by 6.5 in the sertraline group vs. 0.9 in the placebo group. Caloric intake after evening meal dropped by 32.5%% of total calories in the sertraline group vs. −13.1% in the placebo group.**
Pawlow et al.[118]	APRT	20 (10 APRT, 10 control)	1	N/A	−0.81 (APRT) versus + 0.27 (control)	−7.7 (APRT) versus +0.5 (control)	APRT had higher morning hunger ratings than control group* APRT group had lower 9:00 PM hunger ratings than control group* ARPT noted nighttime eating 2.8% of the time with the tape versus 50% of the time without the tape Nighttime eating was inversely related to AM hunger ratings and to the number of breakfasts eaten.*
Stunkard et al.[109]	Sertraline	50	8	122	−2.2	−9.6	NESS decreased by 19.7 (based on interview)** Nocturnal awakenings decreased by 11.2 per week (based on interview)** Nocturnal ingestions decreased by 13.4 (based on interview)** Calories consumed after the evening meal decreased by 35.3% of total calories (based on interview)**
Vander Wal[113]	Escitalopram	40 (20 active, 20 placebo)	12	10	−0.4 (escitalopram) versus + 1.1 (placebo)	−2.4 (escitalopram) versus −3.5 (placebo)	NEQ decreased by − 13.0 for escitalopram versus −10.6 for placebo CGI ratings indicated that 12 of 20 escitalopram patients responded to treatment versus 7 of 20 in the placebo group On the NESHI Night Eating Syndrome History and Inventory, 16 active no longer met criteria for NES versus 12 in the placebo group
Winkelman[116]	Topiramate	4 (2 NES, 2 SRED)	Naturalistic (not standardized)	218	−11.1	Not reported	One NES patient had complete remittance of nocturnal eating Two patients (one NES, 1 SRED) had a marked response One patient (SRED) had a moderate response

Between group differences *$p < .05$, **$p < .01$

showed a higher placebo response (35%)[113] than that reported in the RCT of sertraline (18%).[108] Topiramate has been used to reduce symptoms of binge eating successfully[56,75] as described earlier in section 29.2.7.2, and has been associated with weight loss in individuals using the drug for epilepsy and bipolar disorder[114,115] leading researchers to examine the effectiveness of using this agent in individuals with NES. In a small case series, Winkelman treated four patients (two with NES and two with SRED) using topiramate.[116] Following treatment (100–400 mg/day), one patient with NES had a complete remittance in symptoms, two other patients (one with NES and one with SRED) had a 75%–100% reduction in nocturnal ingestions, and the other patient with SRED had a 50%–75% reduction in nocturnal ingestions. The weight losses in the four subjects ranged from 6.8 to 15 kg. The NES patients responded at 75–100 mg, while the SRED patients responded at higher doses. Side effects included sexual dysfunction, mild memory impairment, mild glove and stocking paresthesias, and blepharospasm. While this case series had a small sample size and nocturnal ingestion data were based on the subjects' self-report, the results from this study warrant further research.

29.3.6.2 Psychotherapy

In the first published study using psychotherapy to treat individuals with NES, Allison et al. found that after a 10-session (12-week) CBT protocol, many improvements were observed in the core features of NES.[117] Fourteen of the twenty-five participants who began the treatment completed. Using mixed models analysis examining data from all participants, they reported mean decreases in caloric intake after dinner and decreases in number of nocturnal ingestions, weight, and NESS score (all p values $<.0001$). This uncontrolled pilot study demonstrates the potential utility of CBT for treating NES, but more controlled research is needed.[117]

BWL therapy has also been used as a treatment for NES, with inconsistent results. In the first study, Gluck et al. found that participants with NES lost less weight than non-NES participants in a BWL program.[94] However, in a more recent study, BWL treatment was used to treat 38 obese individuals with NES and 62 non-NES obese individuals with more success.[89] The treatment consisted of a 21-day intensive inpatient protocol, consisting of a low-calorie diet, exercise, and psychoeducation. Participants also received 6 months of outpatient follow-up. There were no differences in weight change in the NES versus non-NES individuals. Notably, only 8 of the 35 NES participants (completers) met criteria for NES upon completion of the study. This study also demonstrated that intensive, inpatient BWL with outpatient follow-up is equally effective for obese individuals with and without NES.

Progressive muscle relaxation has also been examined in a very brief (two-session) RCT.[118] Twenty adults with NES were randomized to receive relaxation training (Abbreviated Progressive Muscle Relaxation Therapy [APRT]) versus a control treatment for two sessions, separated by 1 week.[118] Results showed significant reductions in measures of stress, anxiety, and salivary cortisol after receiving APRT, as well as increased hunger in the morning and decreased hunger in the evening.

Last, due to the circadian disturbances associated with NES, phototherapy (bright light treatment, typically administered at home in the morning with a light box) has been used as a treatment target in two case studies.[119,120] In both case studies, the individuals being treated presented with NES with comorbid depresssion. Both individuals experienced improvements in NES after 2 weeks of phototherapy. However, in one participant, NES symptoms reappeared at the 1-month follow-up, suggesting that for longer-term remission of NES symptoms, regular doses of phototherapy may be required. While these findings are based on case study data, the results are promising. However, larger, controlled studies are necessary before prescribing phototherapy as a treatment for NES to the general population.

29.3.7 Night Eating Syndrome and Bariatric Surgery

As stated earlier (29.3.1), NES is more common in candidates presenting for bariatric surgery than the general population.[121] The few studies that have examined the effects of bariatric surgery on NES have obtained inconsistent results (see Table 29.2). Rand et al. concluded that the prevalence of NES decreased only from 31% to 27% at 32 months postoperatively.[82] Another study reported that the prevalence of NES was unchanged following surgery.[122] Both studies suffered from methodological weaknesses (i.e., retrospective design and small sample) that limited the integrity of the results. More recently, Colles et al. assessed the prevalence of NES prospectively in 129 surgical patients, using both a self-report questionnaire and a semistructured interview (conducted over the phone).[87] The prevalence of NES declined significantly from 17.1% before surgery to 7.8%, 12 months following surgery. Notably, more than half of the participants who met criteria for NES 1 year postsurgery did not have the diagnosis preoperatively. More research is clearly warranted to clarify the effect of bariatric surgery on symptoms of NES.

29.4 CONCLUSION

BED and NES can be chronic, and many studies suggest that they are linked with obesity or weight gain. Effective treatment for these disorders is available, but the impact of treatment of the binge episodes or nocturnal ingestions on weight is mixed. Thus, while the identification and treatment of these distressing disorders has progressed, this advancement in our understanding has not necessarily significantly impacted the problem of obesity. Notably, this field is not alone in lamenting this last statement, but the relief that sufferers of BED and NES experience with successful treatment, independent of weight status, is significant in its own right.

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30 Tobacco Use, Smoking Cessation, and Obesity

Carole Clair, Semira Gonseth, Jacques Cornuz, and Ivan Berlin

CONTENTS

30.1 INTRODUCTION: SMOKING AND OBESITY CROSSROADS

Smoking and obesity are within the top five leading risk factors for global deaths (Figure 30.1).[1] Smoking is the main avoidable cause of death; tobacco-attributable deaths are expected to continue to increase in the future, especially in low- and middle-income countries.[2] In 2030, tobacco-attributable deaths will be as high as 8.3 million according to some sources.[3] Obesity and overweight are major clinical and public health burdens of increasing concerns. It is estimated that up to 58% of the world's adult population could be either overweight or obese by 2030.[4] Smoking and obesity are both risk factors for cardiovascular diseases (CVD), type 2 diabetes,[5] respiratory problems, and certain cancers. They also share common particularities, both having a behavioral component. For a given population, it has been estimated that an increase of two units of body mass index (BMI) or an increase of 10% in smoking prevalence would reduce life expectancy by 1 year.[6,7] Prevention and treatment of smoking and obesity are crucial and increase life expectancy.

The relationship between smoking and obesity is complex. On one hand, smoking is associated with lower body weight, and smoking cessation may lead to weight gain.[8] On the other hand, smoking is associated with increased risk of abdominal obesity and diabetes.[5,9]

In 1995, it was hypothesized that part of the obesity epidemic in the United States was due to smoking cessation.[10] The observation that smoking prevalence was decreasing in the United States in parallel with an increase in overweight and obesity made some experts believe that smoking cessation was responsible, at least partially, for the obesity epidemic. However, more recent analyses have shown that the contribution of smoking cessation to the increase of overweight and obesity is very little.[11] These results have been corroborated by an Australian study that showed no relationship between the increased prevalence of obesity and the concomitant decrease in smoking prevalence.[12]

30.2 ASSOCIATION BETWEEN SMOKING AND BODY COMPOSITION

30.2.1 Weight Concerns and Initiation of Smoking

Weight control has been cited by many smokers, especially young women, as the main reason to begin or maintain their smoking behavior.[13] Cigarette smoking is perceived by women smokers as a way to control their weight and cope with their stress or emotions.[14] Analyzing more than 50 articles, a 2004 review looked at the relationships between body weight, weight concerns, and smoking among adolescents.[15]

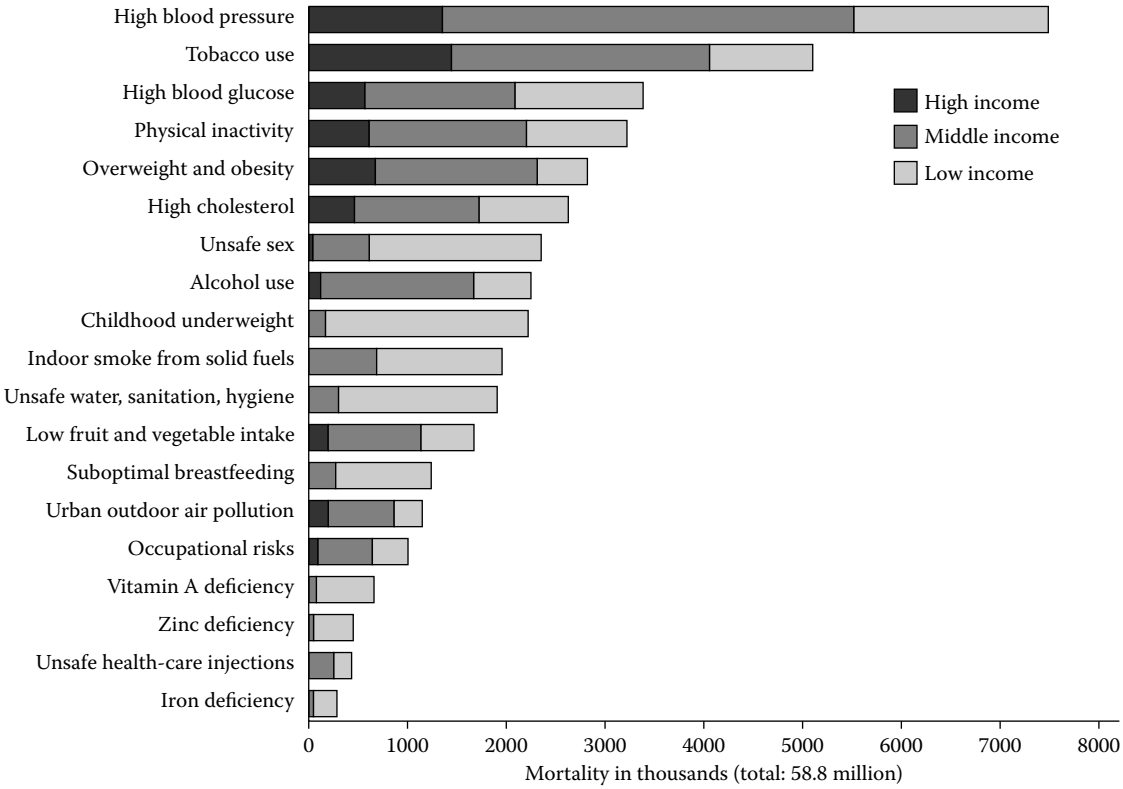

FIGURE 30.1 Deaths attributed to 19 leading risk factors. (From World Health Organization {WHO}, *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks*, 2004.)

Some studies showed a positive association between body weight and smoking. This suggests that adolescents, especially women, with higher BMI are more likely to smoke. However, these findings were inconsistent. Interestingly, several studies showed that there was a positive association between weight concerns and smoking and that the association was stronger among female adolescents compared with male adolescents. This means that, independently of their weight, female adolescents are more likely to initiate smoking because they have weight concerns and probably believe smoking might help them control their weight. Similarly, several studies showed a gender difference as to the associations between dieting behaviors, eating disorders, and smoking. Female adolescents who smoked were more likely to have eating disorders or dieting behaviors compared with male adolescents who smoked. This indicates that female adolescents who smoke might also adopt other dieting behaviors to control weight.

30.2.2 Smoking and Decreased Body Weight

Smokers have on average a lower body weight of 4–5 kg compared to nonsmokers.[16] Age- and gender-adjusted BMI in smokers is on average 1 kg/m^2 less than that of nonsmokers.[17] The mechanisms involved are multiple and not completely understood (Figure 30.2).[18] Smoking acts as a behavioral alternative to eating or snacking. Furthermore, nicotine increases energy expenditure and decreases food intake. Nicotine binds on nicotinic cholinergic receptors in the brain and acts as a sympathomimetic agent.[19] It stimulates the release of catecholamines and of several neurotransmitters in the brain such as serotonin, dopamine, and norepinephrine that modulate appetite and energy expenditure. Norepinephrine leads to an increase in resting metabolic rate. A physiological study has shown that smoking increases 24-hour energy expenditure by 10%, which corresponds approximately to 200 kcal/24 hours for a consumption of one pack of cigarettes per day.[20] This would be equivalent to a loss of about 10 kg over 1 year if caloric intake would remain unchanged. Beside peripheral effects, nicotine also acts centrally in the hypothalamus and influences food intake as well as energy expenditure. The release of monoamines (norepinephrine, dopamine, and serotonin) decreases appetite and food intake.[21] Nicotine also acts on neurotransmitters that regulate food intake and metabolism such as leptin, neuropeptide Y, and orexins.[22] The relationship between nicotine and leptin is complex and shows conflicting findings. The effect of leptin, which is released from adipose tissue and acts centrally to suppress food intake and increase metabolic rate, might be enhanced by smoking.[23]

It is also important to mention that smoking is a risk factor for diseases that induce weight loss such as cancers or chronic obstructive pulmonary disease. Therefore, lower weight among smokers may result in some cases from weight loss due to those concomitant diseases.

30.2.3 Smoking and Body Fat

If smokers have globally a lower body weight compared with nonsmokers, we observe an inverse relationship regarding body fat. Tobacco influences fat distribution through stress

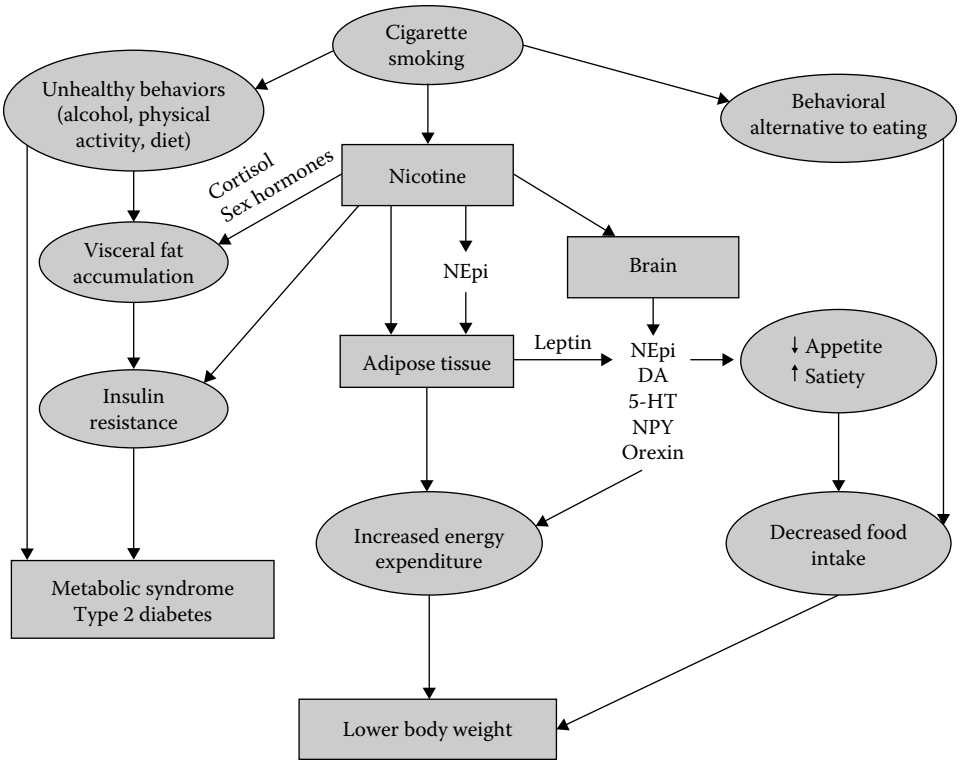

FIGURE 30.2 Metabolic effects of cigarette smoking. DA, dopamine; 5-HT, serotonin; NEpi, norepinephrine; NPY, neuropeptide Y. (Adapted from Audrain-McGovern J. and Benowitz N.L., *Clin. Pharmacol. Ther.*, 90, 164–8, 2011.)

hormones like cortisol that increases abdominal fat deposition.[24] In women, nicotine also has an antiestrogenic effect that favors android fat distribution.[25] Therefore, despite lower BMI, smokers tend to have higher risk of abdominal visceral fat deposition and abdominal obesity compared with nonsmokers.[9,26] Indeed, waist circumference and waist–hip ratio are increased in smokers.[27,28] In parallel, smoking might also influence waist–hip ratio by decreasing hip circumference.[27]

30.2.4 Smoking, Insulin Resistance, and Type 2 Diabetes

Smoking is associated with metabolic syndrome independently of BMI.[29] Indeed, smokers have higher waist circumference, lower high-density lipoprotein cholesterol (HDL-cholesterol), elevated plasma triglycerides, and high C-reactive protein (an inflammatory marker), all of them being part of the metabolic syndrome. Smoking may lead to insulin resistance or inadequate compensatory insulin secretion responses, according to several studies.[30,31] In a meta-analysis of 25 prospective cohort studies, smokers had a 44% increased risk of developing diabetes compared with nonsmokers.[5] In the short term, smoking has a clinically significant effect on both oral and intravenous glucose tolerance tests that could increase the risk of prediabetes and diabetes.[32,33] This could be due to a direct effect of nicotine or other components of cigarette smoke on pancreatic β-cell function. The association between smoking and diabetes might also be mediated through abdominal obesity, which is a risk factor for developing type 2 diabetes.[34]

30.2.5 Smoking and Paradoxical Increase In Body Weight

Studies have shown that the amount of smoking is positively associated with obesity.[26,35] In other words, heavy smokers (those who smoke 20 cigarettes or more per day) have a higher risk of obesity compared with lighter smokers. In the United States, it is estimated that 20% of smokers are obese.[36] Several hypotheses explain this counterintuitive finding. First, smokers tend to be more sedentary, eat less healthy foods, and drink more alcohol compared with nonsmokers.[37] This unhealthy lifestyle could be even more prevalent among heavy smokers in whom the impact of lack of physical activity and unhealthy diet on weight would outweigh the weight-loss effect of cigarettes. Second, smokers often need several attempts to quit smoking successfully. Most smokers, especially if they are very dependent, gain weight after smoking cessation. If they relapse, they will lose weight but incompletely, that is, former smokers who resume smoking will not totally lose the weight they had gained when they quit smoking. Therefore, each quit attempt will be associated with weight gain that will accumulate over time.[9]

30.2.6 Environmental Tobacco Smoke Exposure and Body Weight

Few studies have assessed the effect of secondhand smoke exposure on obesity. One study, performed among 2000 children in Germany, showed that exposure to tobacco smoke during the first years of life was a strong risk factor for

development of childhood overweight measured at age 6 years.[38] Studies in adults have also shown that environmental tobacco smoke exposure is associated with an increased risk of metabolic syndrome[39] and type 2 diabetes.[40]

30.2.7 Smokeless Tobacco and Body Weight

Several studies have assessed the influence of smokeless tobacco such as snus, a moist tobacco product used orally, with body weight. A study found that among snus users followed prospectively for 5 years in Sweden, stable current use was not associated with lower body weight; on the contrary, it was associated with weight gain and incident obesity compared to never having used any kind of tobacco.[41] Another study found that people gained weight when they stopped using smokeless tobacco, but smokers who switched from cigarettes to snus gained less weight.[42] Few studies have assessed the association between smokeless tobacco and the risk of type 2 diabetes. One study reported that smokeless tobacco was not associated with a significant increased risk of type 2 diabetes.[43] A more recent study showed that high consumption of smokeless tobacco predicted the risk of developing type 2 diabetes.[44]

30.3 SMOKING CESSATION AND BODY WEIGHT CHANGE

30.3.1 Weight Concerns and Quitting

Weight gain and fear of weight gain after smoking cessation are the most common causes of not attempting to quit or relapsing. In a study performed among more than 1500 young adult smokers in the United States, weight gain was reported as a barrier to quitting among 58% of women and 26% of men.[45] This suggests that women are more worried about weight gain following smoking cessation than men. This might either dissuade them from quitting or make them more likely to relapse if they try to quit.[46] However, studies showing risk of relapse because of weight gain are contradictory. In one prospective intervention study, women were more likely than men to relapse during the treatment period, but weight gain after cessation increased the risk of relapse only among men and not among women.[47] This is the opposite of what we would have expected based on the findings that women are more afraid of gaining weight. Thus, in women, the idea of post-cessation weight gain might be greater than the actual effects of real post-cessation weight gain. A study performed among 87 U.S. women smokers showed that they would accept a maximum weight gain of 2.3 kg if they quit smoking compared to 3.5 kg in men.[48] Post-cessation weight gain is a serious concern, and it is important to understand and address it to find ways to limit weight gain after quitting and to increase attempts at quitting and chances of success among both men and women.

30.3.2 Amount of Weight Gain

Smoking cessation is associated with weight gain in 80% of the cases.[49] A recent meta-analysis, including 62 trials of pharmacologic and nonpharmacologic interventions for smoking cessation, showed that on average, smokers gained 4–5 kg after 12 months of abstinence, and most of this occurred within the first 3 months after quitting.[8] A small proportion of people lost weight after cessation (16%) whereas 13% gained more than 10 kg. The 4–5 kg that smokers gain when they quit smoking corresponds to the known difference in weight between smokers and nonsmokers. In other words, smokers who quit will likely recover the weight they would have had if they had remained nonsmokers.

Other studies have described a more worrying picture. The Lung Health Study prospectively followed more than 5000 middle-aged smokers in the United States and Canada and measured annually body weight and smoking status (with biochemical validation).[50] People who had quit smoking and managed to remain abstinent (the sustained quitters) had an average weight gain at 5 years of 7.6 kg for men and 8.7 kg for women, whereas 5-year weight gain was 1.3 kg for men and 2.0 kg for women who continued to smoke (Figure 30.3). Intermittent smokers, those who had tried to quit and relapsed at least once during follow-up, also gained weight, 5.2 kg for men and 5.8 kg for women, on average. In this cohort, over a third of sustained quitters gained 10 kg or more. These data reflect increased weight gain and are probably closer to what happens in the real world than observations made in interventional trials in which only treatment-seeking smokers are included. Predictors of weight gain are younger

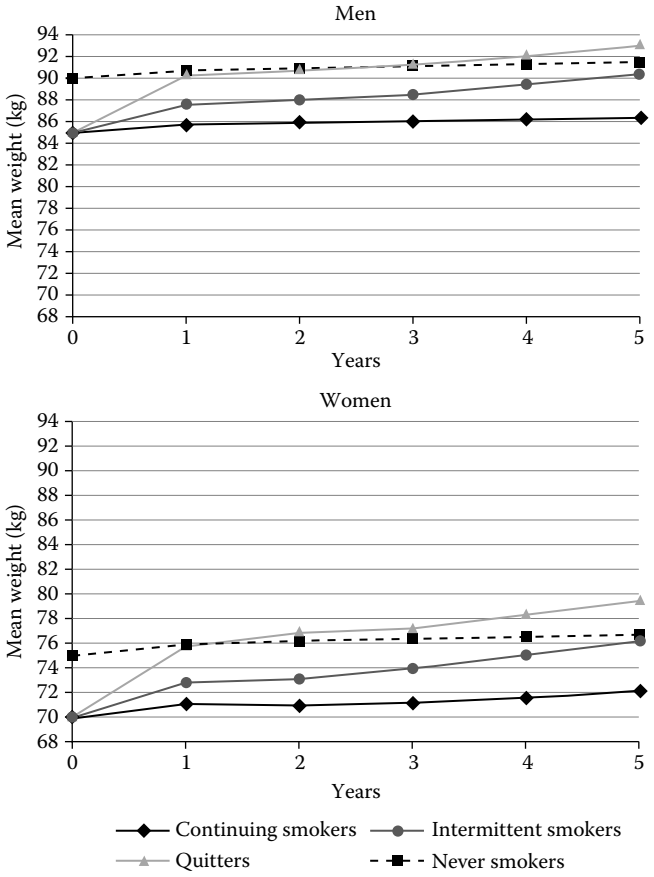

FIGURE 30.3 Average changes in body weight (in kg) over 5 years by smoking status. (Based on data from O'Hara P et al., *Am. J. Epidemiol.*, 148, 821–30, 1998.)

age, higher baseline BMI, low socioeconomic level, amount of smoking (more than 25 cigarettes per day), African-American race, pregnancy, and a genetic predisposition.[16,51] According to some studies, weight gain following smoking cessation might be more pronounced among women.[16,51,52] For example, in a study,[16] the difference in weight gain between sustained quitters and continuing smokers was 3.8 kg among women and 2.8 kg among men. The proportion of women who gained more than 13 kg was also higher (13.4%) compared with men (9.8%).

Weight gain after smoking cessation consists mainly of fat mass, and mechanisms are multiple, involving clinical, biological, and behavioral factors. First, the resting metabolic rate decreases after smoking cessation by about 200 kcal/25 cigarettes.[20] If former smokers do not compensate this by increasing their physical activity or decreasing their caloric intake, the decreased metabolic rate will lead progressively to weight gain. Second, increase in appetite is part of smoking withdrawal symptoms. After smoking cessation, the appetite-suppressant effect of nicotine on the brain is reversed, resulting in increased hunger. People who attempt to quit tend to compensate for smoking by increasing their caloric intake and tend to favor food high in fat and sugar, which activates the same rewarding pathways as nicotine in the brain.[9,53] Some studies have also reported that there is a decrease in physical activity after smoking cessation.[54,55] Finally, there are also changes in adipose tissue metabolism that occur after smoking cessation. It has been reported in a small sample of 10 premenopausal women that adipose tissue lipoprotein lipase activity increased twofold to threefold after 4 weeks of smoking abstinence.[54] A high adipose tissue lipoprotein lipase activity increases the efficiency of energy storage and might contribute to weight gain. Nicotine also acts on neurotransmitters that regulate food intake and metabolism. Leptin is considered a potential mediator of weight gain following smoking cessation[56,57] or a marker for the difference in body weight observed between smokers and nonsmokers.[23] Similarly, neuropetide Y and orexin, which are both stimulators of food intake, might also be influenced by nicotine exposure and thus play a role in weight gain after smoking cessation.

30.3.3 Smoking Cessation and Risk of Diabetes

Studies have shown that former smokers have a risk of diabetes that is intermediate between nonsmokers and smokers. In the meta-analysis assessing the relationship between smoking and diabetes that we cited previously (in Section 30.2.4), former smokers had a 23% increased risk of developing type 2 diabetes compared with nonsmokers.[5] Indeed, smoking cessation has been shown to improve insulin sensitivity[58] and decrease systemic inflammation, which might also play a role in reducing insulin resistance.[59] However, a recent study assessed prospectively the effect of quitting smoking on the short- and long-term incidence of diabetes among more than 15,000 middle-aged adults.[60] Smokers had an initial increased risk of diabetes in the first 3 years after quitting smoking, but it decreased thereafter until no significant difference could be detected between former smokers and nonsmokers. Weight gain after smoking cessation was a mediator of the initial increase in risk of diabetes. This means that smoking cessation might be associated with an initial increase in diabetes probably attributable to weight gain, but in the longer term, weight stabilizes and the improvement of insulin sensitivity and systemic inflammation decreases the risk of diabetes compared to continuing smoking, as shown in Figure 30.4.

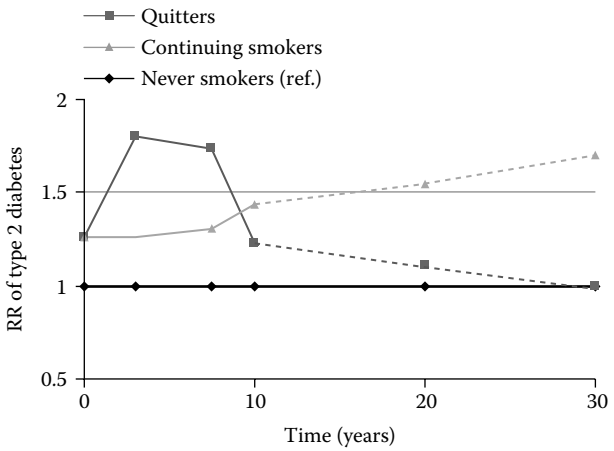

FIGURE 30.4 Estimated relative risks (RR) of type 2 diabetes mellitus for continuing smokers and quitters compared with never smokers (reference). (Based on data from Willi C. et al., *JAMA*, 298, 2654–64, 2007; Yeh H.C. et al., *Ann. Intern. Med.*, 152, 10–7, 2011; and hypothetical future projection.)

30.4 IMPACT OF WEIGHT GAIN ON THE HEALTH BENEFITS OF QUITTING SMOKING

Smoking cessation is associated with a transitory elevation of blood lipid levels.[61,62] However, smoking is associated with low levels of HDL-cholesterol in a dose-dependent manner.[63] HDL-cholesterol increases after smoking cessation independently of weight gain.[64] Similarly, insulin sensitivity improves after smoking cessation independently of weight gain.[58] Studies have uniformly shown that smoking cessation is associated with a decrease in morbidity and mortality.[65] Smoking cessation decreases risk of cardiovascular events by 50% after 1 year of abstinence.[64] The mechanisms of the decrease in risk of CVD associated with smoking cessation are multiple.[66] Cigarette smoking has both short- and long-term cardiovascular effects that are reversible shortly after cessation.[67,68] Furthermore, cardiovascular risk factors such as low HDL-cholesterol and insulin resistance improve after smoking cessation and act as mediators of the decreased CVD risk. Finally, people who manage to quit smoking are probably more health-conscious than those continuing to smoke and might adopt a healthier lifestyle, for example, by being physically active and eating less fat.[37]

However, weight gain might attenuate the cardiovascular benefits of smoking cessation. Smokers, who are already at risk of CVD, might be frightened by the consequences of weight gain on their health. One study indirectly assessed the effect of weight gain following smoking cessation on CVD in a population of Japanese men without diabetes.[61] Smokers who had successfully quit smoking for at least 6 months gained weight

and had a significant worsening of their blood pressure, total cholesterol, triglycerides, and fasting blood glucose. In contrast, their HDL-cholesterol levels improved. It was estimated that successful quitters had a 24% decreased risk of coronary heart disease compared with smokers despite weight gain. Recently, a study performed among more than 3000 participants of the Framingham Heart Offspring Study directly assessed the impact of weight gain following smoking cessation on CVD events.[101] This study confirmed that quitters had a decreased risk of CVD compared to continuing smokers with a hazard ratio (HR) of 0.47 (95% CI, 0.23-0.94) for those who had recently quit (≤4 years) and a HR of 0.46 (95% CI, 0.34-0.63) for longer-term quitters (>4 years). Even though short-term quitters had a greater weight gain after smoking cessation, the CVD benefits of quitting smoking were not attenuated by weight gain. Among participants with diabetes there were similar findings but the results did not reach statistical significance due to a smaller sample size. This study shows that there is a net cardiovascular benefit of smoking cessation despite subsequent weight gain. Many other studies have proven the benefits of quitting on CVD, without taking into account weight gain.[65] In the Nurses' Health Study, a cohort of more than 100,000 female nurses followed long term, one-third of the excess risk of coronary heart disease was eliminated within 2 years after smoking cessation.[69] Among people with diabetes, studies have demonstrated the CVD benefits of quitting smoking.[70–72]

The effect of weight gain after smoking cessation on lung function has also been studied.[73] Overall, smoking cessation was associated with an improvement in lung function, but weight gain substantially diminished the benefits of quitting on lung function, especially in men.

FIGURE 30.5 A 1930 American Tobacco Company advertisement targeting women and weight gain. (From American Tobacco Company, marketing campaign: Future shadow faces, Stanford School of Medicine, 1930, available at: http://tobacco.stanford.edu/tobacco_main/search_results.php?-skip=0&-max=25.)

30.5 ROLE OF TOBACCO INDUSTRY IN THE CONTROL OF BODY WEIGHT

Since 1929, the tobacco industry has targeted women with a simple advertising campaign: "smoking is slimming." The tobacco industry created women-targeted brands, like the "Slim Cigarette" or "Virginia Slim,"[74,75] and created ads that suggested that smoking could protect against weight gain (see Figure 30.5). Some tobacco companies also financially supported scientists' reports on smoking and weight loss; for instance, one of these reports was titled "Doctor says cigarettes help you lose weight."[76]

The tobacco industry has been very aware that smoking and smoking cessation are associated with variations of weight and appetite, and it has developed strategies to enhance these effects. Since the 1940s, the tobacco industry has expressed an interest in investigating "the anti-appetite characteristic of cigarettes"[77] and produced numerous studies about the metabolic effects of smoking. The tobacco industry documents have been made public and can be found online at the University of California, San Francisco Legacy Tobacco Document Library (http://legacy.library.ucsf.edu). These documents reveal that the tobacco industry conducted, commissioned, commanded, or financed laboratory studies to understand the differences in body weight between smokers and nonsmokers, to understand variations of body weight following smoking cessation, and to assess body weight concerns among smokers. It also performed studies to understand and promote body weight control as a "positive aspect" of smoking.[78,79]

Moreover, since the 1960s, tobacco companies have added appetite suppressants such as tartaric acid and 2-acetylpyridine to cigarettes to attract new smokers concerned about their body weight.[80] Other substances like ephedrine, amphetamine, menthol, mariolide, laughing gas, and propylene glycol were studied by the industry as potential appetite-suppressor agents.[81]

30.6 PREVENTIVE MEASURES AND INTERVENTIONS TO REDUCE WEIGHT GAIN AFTER SMOKING CESSATION

The most effective strategy to avoid weight fluctuations associated with smoking is to never start smoking. In 2003, the World Health Organization (WHO) adopted the world's first public health treaty, the WHO Framework Convention on Tobacco Control.[82] As of 2012, there were 176 parties to the

treaty. Its aim is to "protect billions of people from the devastating impact of tobacco consumption and exposure to tobacco smoke." This international treaty includes price tax measures to reduce the demand for tobacco as well as nonprice measures such as protection from passive smoke exposure, monitoring tobacco use and prevention, offering help to quit tobacco use, warning about dangers of smoking, banning tobacco advertising and promotion, and not selling tobacco to minors. This represents a global effort with structural and societal measures that have been shown effective in decreasing tobacco use.

Interventions for preventing weight gain after smoking cessation can be behavioral, pharmacological, or both. Behavioral interventions to promote smoking cessation and prevent weight gain have shown some efficacy but only in the short term.[83] After 6 months, there is no longer a significant benefit in terms of smoking abstinence and weight control. This supports the idea that following a hypocaloric diet or modifying another behavior concomitant with smoking cessation are not the best options. A recent Cochrane review showed that regular physical activity performed over at least 1 year after smoking cessation may reduce the risk of weight gain.[84] A pragmatic approach among smokers concerned about weight gain after cessation could be to adopt a healthier lifestyle (increasing physical activity and adopting a healthier diet) before planning a quit date. If smokers have already adopted a healthier lifestyle before quitting, it might be easier to maintain it after smoking cessation and thus limit weight gain. This approach has not been tested, and its efficacy is not proven. Addressing weight concerns might also be an interesting approach. A study tested an intervention to reduce concerns about gaining weight among women.[85] Women who received this intervention, which discouraged dieting, had higher rates of smoking abstinence and gained less weight at 1 year compared with women who received an intervention focused on preventing weight gain.

Some pharmacological treatments used for smoking cessation might also have an effect on weight gain. Nicotine replacement therapy, bupropion, and varenicline can limit weight gain but during therapy only.[8,84] Nicotine replacement therapy is available in different forms: skin patches, gums, nasal sprays, or inhalers. Nicotine replacement therapies, especially gums, have been shown effective in reducing weight gain by 0.5 kg on average in a dose-response manner.[86] However, when the nicotine replacement therapy is discontinued, after 2–3 months of smoking abstinence, people gain weight, usually the same amount as their counterparts who have not used nicotine replacement therapy. Bupropion is a non-nicotine-based treatment used for smoking cessation that inhibits the reuptake of dopamine and norepinephrine. Bupropion decreases weight gain by 1.1 kg.[87,88] Varenicline, the latest treatment for tobacco dependence, is a partial agonist of the nicotinic cholinergic $\alpha 4\beta 2$ receptor. It reduces weight gain by about 0.4 kg, but again, this effect disappears at the end of treatment.[84] Preventing weight gain, even if temporarily, could be beneficial for some people by preventing discouragement during the first few months after cessation when the risk of relapse is higher. When considering quitting, they would not have to worry about their weight, and this could increase motivation. It is probably easier to address weight issues later when people are abstinent for a couple of months and less susceptible to relapse.

30.7 SMOKING DURING PREGNANCY AND RISK OF CHILD OVERWEIGHT AND OBESITY

In the United States, it is estimated that about 14% of women smoke during their pregnancy, according to data from 2005.[89] In European countries, the prevalence of smoking among pregnant women is variable, ranging from 8% in women with a high educational level[90] to 28% (in a sample of women where smoking status was validated with cotinine).[91] Maternal smoking during pregnancy is associated with a huge number of perinatal disorders, in particular with fetal growth restriction and low birth weight, independent of prematurity.[92–95] It is estimated that 20%–30% of all low-birth-weight deliveries in the United States are a consequence of in utero exposure to tobacco.[93]

Paradoxically, maternal smoking during pregnancy is also associated with an increased long-term risk for overweight and obesity in childhood and adult life.[89] A recent meta-analysis of 14 observational studies showed that children whose mother smoked during pregnancy had a 50% increased risk for overweight compared with children whose mothers did not smoke during pregnancy.[96] The significant increased risk, even after adjustment, suggested that the relationship was not explained by sociodemographic or behavioral differences between smoking and nonsmoking mothers, though residual confounding might persist. The association was independent of birth weight and postnatal weight gain, suggesting that low birth weight and weight gain after birth did not (or not entirely) mediate the association. Timing of exposure during pregnancy is also important, as suggested by some studies. In general, smoking throughout pregnancy is associated with a greater risk for child overweight than smoking only in early pregnancy.[97,98] Low birth weight is correlated with an increased propensity to being overweight or obese later in childhood and to develop metabolic disturbances such as type 2 diabetes.[99,100] Therefore, prevention of maternal smoking during pregnancy is an important element of prevention of obesity and metabolic diseases.

30.8 CONCLUSIONS

Cigarette smoking is associated with lower body weight and is used by some smokers to control their weight. The tobacco industry has taken advantage of the so-called slimming properties of cigarettes in advertisements to promote its products and target women in particular. However, there is increasing evidence that smoking is associated with abdominal obesity, insulin resistance, and type 2 diabetes. These metabolic effects are often not known by smokers and have important consequences in terms of morbidity and mortality.

Smoking cessation is associated with weight gain in most cases. No data have shown that the benefits of smoking cessation are diminished by weight gain, but further studies are needed to measure more specifically the influence of

post-cessation weight gain on certain diseases such as cardiovascular events and on pulmonary functions.

Few interventions have been shown effective at preventing or decreasing weight gain long term after smoking cessation. Sustained physical activity should be counseled, and smoking cessation treatments might be offered to limit weight gain and increase chances of lifelong smoking abstinence.

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31 Breastfeeding and Later Obesity

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CONTENTS

31.1 INTRODUCTION

Obesity is a complex disease arising from interactions between genes and the environment. Early infant nutrition is one of the most powerful environmental factors that influence early growth and development. Breastfeeding may be protective against the development of obesity, but the evidence is inconclusive [1–5]. This chapter reviews the role of breastfeeding on later development of obesity, considering (1) the evidence from observational and randomized controlled trials, (2) meta-analyses, (3) plausible underlying biological mechanisms, and (4) limitations of existing evidence, reflective of the difficulty of demonstrating causality between early infant nutrition and long-term outcomes.

31.2 EVIDENCE FROM OBSERVATIONAL STUDIES

One of the earliest studies to evaluate the role of breastfeeding on later obesity was by Charney et al. [6] (Table 31.1). In a series of 366 infants born in 1945, the risk of becoming overweight or obese at 20–30 years was not influenced by breastfeeding history; however, breastfeeding was not the norm in the United States at this time; only 18% of the infants were breast-fed in this cohort. Shortly, thereafter, Kramer et al. [7] reported the relative risk for obesity at age 12–18 years was 2.35 if not breast-fed based on a clinical study of 427 Canadian adolescents. Of the potential confounders (age, sex, race, ethnicity, birth order, socioeconomic status [SES], and family history of obesity), only family history of obesity was significant. Controlling for family history, the protective effect of breastfeeding against later obesity persisted. In a subsequent Canadian study, duration of breastfeeding, birth weight, sex, and ideal infant body habitus were significant determinants of body mass index (BMI) at 12 months, accounting for only 13% of the variance in a cohort of 382 infants [8,9]. Duration of breastfeeding and birth weight explained even less of the variance in BMI at 24 months (7%).

In prospective studies conducted in New Zealand and Australia, the protective effect of breastfeeding on later obesity was no longer significant after controlling for confounding factors. In 562 New Zealand children followed from birth to 7 years of age, there was no difference in body fatness between infants who had been exclusively breast-fed or formula-fed for the first 3 months of life [10]. In ~1000 New Zealand children followed from 3 to 26 years of age, breastfeeding for more than 6 months was associated with a lower risk of obesity at 9–18 years of age, but not at the earlier (3–7 years) or later (>21 years) ages [14]. After controlling for maternal BMI and other confounders, the adjusted odds ratio (AOR) was not significant. In a prospective study of 4062 5-year-olds in Australia [15], O'Callaghan et al. [15] also did not find a significant association between duration of breastfeeding and obesity after controlling for birth weight, sex, gestational age, infant feeding and sleeping problems, parental BMI, education, and income. There was no consistent dose–response relationship between duration of breastfeeding and obesity.

In 9357 German children, ages 5–6 years, the prevalence of obesity in children who had been breast-fed (2.8%) was lower than those who had not been breast-fed (4.5%) [16]. A dose–response relationship was seen between obesity prevalence and the duration of breastfeeding: 3.8% for 2 months of exclusive breastfeeding, 2.3% for 3–5 months, 1.7% for 6–12 months, and 0.8% for greater than 12 months. After adjusting for potential confounding factors (number of older siblings, parental age and education, child's health, early feeding, actual frequency of eating selected foods, own bedroom, time playing outside in winter and summer, and mother smoked during pregnancy), breastfeeding remained a significant protective factor against obesity. In another study of 2108 German children, breastfeeding was associated with a reduced risk of obesity, after controlling for nationality, SES, parental education, parental age, environmental tobacco smoke, dietary habits, birth order, birth weight, and preterm birth [17]. A dose–response relationship with duration of exclusive breastfeeding was also detected in

TABLE 31.1
Studies on the Effect of Breastfeeding on Later Obesity

Reference	Study Design	Number of Participants	Age Measured	Definition of Feeding Modes	Outcome Variables	Results
Charney [6], USA	Retrospective, 1945–1955	BF = 65 FF = 301	20–30 years	BF > 2 weeks	Overweight: >10% median WT for HT Obese: >20% median WT for HT	Overweight or obese at 20–30 years: NS
Kramer [7], Canada	Case control, 1980	I. BF = 95 FF = 332 II. BF = 55 FF = 242	12–18 years	BF = if ≤1 bottle feeding/ days	Obese: >120% WT for HT, skinfold > 95th or both > 90th percentile	RR = 2.25–2.35, if not BF
Kramer [8, 9], Canada	Prospective, 1981–1982	BF = 382 FF = 347	1–3 days, 2, 4, 6 weeks, 2, 3, 4 months, 1, 2 years	Exclusively BF = no regular bottle feeding	BMI, skinfolds	BMI at 1 year, 2 years, and skinfolds at 2 years: negative correlation with duration of BF
Birkbeck [10], New Zealand	Prospective, 1972–1973	BF = 280 FF = 382	0, 3, 7 years	Exclusively BF or FF for at least first 12 weeks	BMI, skinfolds	BMI and skinfolds at 7 years: NS
Strbak [11], CSFR	Prospective,	BF = 741 FF = 165	0–7 years	BF < 1 to > 6 months; FF: BF < 2 weeks	Percent obesity	%Obese: higher if BF < 3 months vs. > 3 months
O'Callaghan [15], Australia	Prospective, 1981–1984	BF = 3119 FF = 790	0, 5 years	BF ≥ 6 months FF not BF at all	BMI > 94th percentile	AOR = 0.71 (0.43–1.25) duration BF – NS
Tulldahl [12], Sweden	Prospective, 1979	BF = 390 FF = 391	15–16 years	FF or BF < 3 months versus BF > 3 months	WT, BMI, %FM DXA, skinfolds	WT, BMI, %FM DXA, skinfolds: NS
von Kries [16], Germany	Retrospective, 1997	BF = 5184 FF = 4022	5–6 years	Exclusively BF < 2, 3–5, 6–12, > 12 months	BMI > 97th percentile	AOR = 0.75 (0.57–0.98)
Wadsworth [20], UK	Retrospective, 1946	BF = 2873 FF = 858	6 years	BF ≤ 2, 3–4, 5–10, > 10 months	BMI > 97th percentile	AOR = 0.83 (0.65–1.04)
Liese [17], Germany	Cross-sectional, 1987	BF = 1754 FF = 354	9–10 years	BF ≤ 2 to > 6 months	BMI > 90th percentile	AOR = 0.66 (0.52–0.87)
Poulton [14], New Zealand	Prospective, 1973	912	26 years	BF ≤ 6 to > 6 months	BMI > 25	AOR = 1.11 (0.83–1.47)
Hediger [24], USA	Cross-sectional, 1987	BF = 1158 FF = 1498	3–5 years	BF ≤ 2 to ≤ 9 months	BMI > 95th percentile	AOR = 0.84 (0.62–1.13)
Gillman [26], USA	Cross-sectional	BF = 9633 FF = 4744	9–14 years	Exclusively or mostly BF, or FF	BMI > 95th percentile	AOR = 0.78 (0.66–0.91)
Armstrong [22], Scotland	Retrospective, 1996	BF = 8751 FF = 23,449	3–4 years	Exclusively BF 6–8 weeks	BMI > 95th percentile	AOR = 0.72 (0.65–0.79)
Toschke [23], Czech Republic	Cross-sectional, 1992	BF = 30,641 FF = 3127	6–14 years	BF ≤ 2, 3–4, 5–10, > 10 months	BMI > 97th percentile	AOR = 0.80 (0.66–0.96)
Li [13], UK	Cross-sectional, 1983	BF = 1655 FF = 976	4–18 years	Not stated, FF: BF < 1 week	BMI > 95th percentile	AOR = 0.98 (0.78–1.23)
Bergman [18], Germany	Prospective, 1990	BF = 329 FF = 151	6 years	Exclusively BF FF never BF or < 2 months	BMI > 97th percentile	AOR = 0.46 (0.23–0.92)
Parsons [21]	Prospective, 1958	BF = 4164 FF = 2767	33 years	Exclusively or partial BF.1 months	BMI ≥ 30	AOR = 0.88 (0.75–1.04)
Grummer-Strawn [25], USA	Retrospective, 1988–92	BF = 5503 FF = 7084	4 years	FF: never BF	BMI > 95th percentile	AOR = 1.01 (0.93–1.09)

Notes: AOR, adjusted odds ratio; BF, breast-fed; BMI, body mass index; CSFR, Czech and Slovak Federal Republic; DXA, dual-energy x-ray absorptiometry; FF, formula-fed; %FM, percent fat mass; HT, height; NS, not significant; RR, relative risk; WT, weight.

this study. Unfortunately, analyses did not control for parental history of obesity. However, a later study in 480 German children did control for maternal BMI, maternal smoking during pregnancy, and SES and demonstrated a protective effect of breastfeeding for 3 months and more on obesity at age 6 years [18]. Quantile regression was used to examine the effect of breastfeeding on different subgroups of BMI in preschool German children [19]. In 14,412 children, the protective effect of breastfeeding was confined to the upper quantiles (0.9 and 0.97) of the BMI distribution suggesting a lower proportion of obesity among breast-fed children.

In contrast, prospective studies conducted in the United Kingdom did not confirm the effect of breastfeeding. In a national longitudinal data of British children born in 1946, there was no significant relationship between breastfeeding and obesity among 3731 6-year-olds, after controlling for social class, birth weight, household crowding, and fat intake at age 6 years [20]. In a 1958 British birth cohort ($n = 12{,}857$), breastfeeding and BMI at age 7 years were not associated [21]. A protective effect on BMI was seen at ages 16 and 33 years in females and at 33 years in males, but this effect was no longer significant after adjustment for confounding factors.

Protective effects of breastfeeding have been reported from large retrospective studies from Scotland and the Czech Republic. Among 32,200 Scottish preschool children, the AOR for obesity was significant with a lower risk of obesity in the breast-fed group at ages 3–4 years, after controlling for SES, birth weight, and sex [22]. In 33,768 children 6–14 years of age from the Czech Republic, breastfeeding was also associated with a reduced risk of obesity after controlling for parental BMI, educational level, maternal smoking, child birth weight, television watching, number of siblings, physical activity, and dietary factors [23]. A significant dose–response relationship was seen with duration of breastfeeding for BMI > 90th but not for BMI > 97th percentile.

Mixed results have also been published on the U.S. population. Based on the National Health and Nutrition Examination Survey (NHANES) III survey of 2685 children, the risk of obesity at 3–5 years of age was not associated with breastfeeding [24]. The analysis was adjusted for birth weight, race/ethnicity, gender, age group, maternal BMI, and timing of solids. Based on the Pediatric Nutrition Surveillance System, breastfeeding was not associated with a decrease in mean BMI at age 4 years [25]. However, a dose–response of breastfeeding duration greater than 6 months was seen among non-Hispanic white, but not black or Hispanic children. In the Growing Up Today Study, a nationwide cohort study of diet, activity, and growth of ~15,000 children, breastfeeding for the first 6 months of life was significantly associated with a reduced risk of obesity at ages 9–14 years, after adjusting for several potential confounders, including age, sex, stage of sexual maturation, energy intake, time watching television, physical activity, maternal BMI, SES, and other lifestyle factors [26]. Also, the AOR for obesity declined with the duration of breastfeeding, with the lowest AOR (about 0.75) associated with greater than 9 months of breastfeeding.

31.3 EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials are designed to demonstrate causal relationships between the intervention and outcomes and are commonly used to test safety and efficacy [27]. Strict adherence in infant nutrition studies that require randomization of healthy term infants to breastfeeding or formula feeding is not ethical or feasible, since human milk is considered optimal for feeding term infants. In the case of preterm infants, optimal feeding is controversial, particularly in the 1980s when the British Multicenter Trial on Feeding of Low Birthweight Infants was conducted [28]. In this study, unsupplemented banked donor human milk and infant formula were randomly assigned to 926 preterm low–birth weight infants. There was no significant effect of human milk feeding on body weight or composition at ages 10, 13–15, or 20 years.

In the only randomized controlled trial involving term infants, 17,046 mother–infant dyads in 31 maternity hospitals and clinics in Belarus were randomized either to the Promotion of Breastfeeding Intervention Trial or to usual care [29,30]. The intervention successfully increased the exclusivity and duration of breastfeeding in the intervention group. The rates of exclusive breastfeeding were 43.3% versus 6.4% and 7.9% versus 0.6% at 3 and 6 months in the intervention and usual care groups, respectively. No significant differences were seen in BMI, waist, hip circumference, or skinfold thicknesses at age 6 years. Risks for overweight and obesity were similar between groups.

31.4 META-ANALYSIS

Several meta-analyses have been published on the relationship between breastfeeding and later development of obesity [1–5]. Observational studies have shown a modest protective effect of breastfeeding on obesity, whereas the limited randomized controlled trials failed to demonstrate an effect. In these meta-analyses, the association between breastfeeding and later obesity was attenuated with adjustment of the available confounding factors. Inconsistency across studies is attributable to potential heterogeneity with respect to study design, population, sample size, and age at follow-up, definition of obesity, misclassification of infant feeding mode, and residual confounding.

A meta-analysis of 28 studies (298,900 subjects) by Owen et al. [2] addressed the effect of breastfeeding on later obesity at ages 0.5–33 years. Breastfeeding was associated with a reduced risk of obesity compared with formula feeding. The odds ratio (OR) for later obesity was 0.87 (95% CI: 0.85, 0.89). In six studies, adjustment for parental obesity, maternal smoking, and social class reduced the OR from 0.86 (95% CI: 0.81, 0.91) to 0.93 (95% CI: 0.88, 0.99).

Another meta-analysis in 36 studies (355,301 subjects) by Owen et al. [1] explored the effect of breastfeeding on adiposity later in life, ages ranging from 1 to 70 years. Breastfeeding was associated with slightly lower BMI than formula feeding (−0.04; 95% CI: −0.05, −0.02). Adjustment for SES, age,

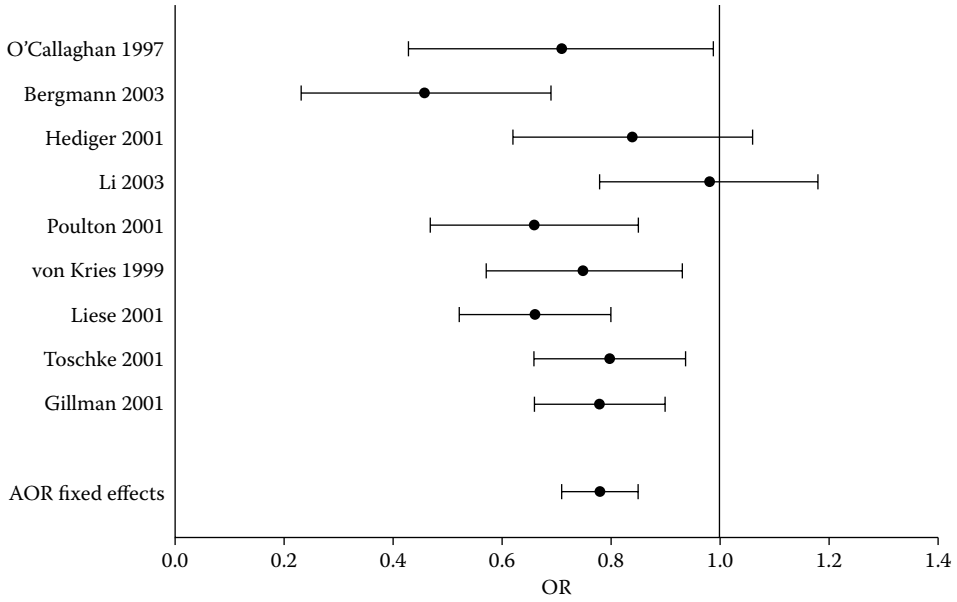

FIGURE 31.1 Effect of breastfeeding versus formula feeding on childhood obesity: covariate-adjusted odds ratios (AOR) of nine studies and pooled odds ratio (OR). OR is the ratio of the odds of an event or condition occurring in one group to the odds of it occurring in another group, in our application breast-fed versus formula-fed infants. (From Arenz S et al., *Int. J. Obes. Relat. Metab. Disord.*, 28, 1247–56, 2004. Reproduced with permission from the *International Journal of Obesity*.)

maternal BMI, and maternal smoking in 11 of the studies eliminated the effect of breastfeeding on mean BMI (−0.10, 95% CI: −0.14, −0.06 to −0.01, 95% CI: −0.05, 0.03). In three of the studies, prolonged breastfeeding had a slightly greater protective effect on BMI, but it was not significant with adjustment for SES, maternal BMI, and maternal smoking in two studies. Breastfeeding may be associated with a lower prevalence of obesity, but the effect may not be evident from the mean BMI.

A meta-analysis of 17 studies by Harder et al. [3] investigated the effect of breastfeeding duration on the later risk of obesity. Breastfeeding duration was negatively associated with the risk of obesity; the crude OR was 0.94 (95% CI: 0.89, 0.98). OR decreased with increasing duration of breastfeeding from 0.81 for 1–3 months, 0.76 for 4–6 months, 0.67 for 7–9 months, and 0.68 for greater than 9 months. Meta-analysis demonstrated a dose–response relationship between the duration of breastfeeding and obesity, but only eight studies controlled for confounding factors.

Quigley [4] repeated the meta-analysis by Harder et al. [3], adjusting for confounding factors where possible. In five studies that used the definition of childhood obesity as ≥95th or 97th BMI percentile, the crude OR was 0.95 (95% CI: 0.92, 0.98). Adjustment for confounders weakened the AOR to 0.97 (95% CI: 0.94, 0.99). In four studies that used the definition of childhood obesity as ≥90th BMI percentile, the crude OR was 0.94 (95% CI: 0.89, 1.01). Adjustment for confounders decreased the AOR to 0.97 (95% CI: 0.93, 1.02). While breastfeeding duration seems to be associated with a reduction in childhood obesity, it is unclear if this is due to residual confounding. Several studies did not collect data on potentially confounding factors. While it might be argued that it is unlikely that the exposure–confounder associations would exaggerate the dose–response gradient, confounding factors such as the extent of maternal obesity or family diet and physical activity practices may covary in a graded response with breastfeeding duration [31].

In a systematic review, Arenz et al. [5] used a priori selection criteria of eligible studies and identified nine studies including 69,000 participants to investigate the effect of breastfeeding on childhood obesity (Figure 31.1). A priori selection criteria were obesity defined as BMI ≥ 90, 95, or 97 kg/m^2, age at follow-up assessment between 5–18 years, risk estimate provided, and adjustment of at least three of the following confounding factors: birth weight, parental overweight, parental smoking, and SES. AOR for breastfeeding on later obesity was 0.78 (95% CI: 0.71, 0.85). A dose-dependent effect of breastfeeding duration on the prevalence of obesity was reported in four of the studies. No heterogeneity was noted among studies but residual confounding and publication bias could not be ruled out. These authors concluded that breastfeeding appears to have a small but consistent protective effect against obesity. Further adjustment for other confounders might reduce the effect, but it unlikely would be reduced to zero.

31.5 PLAUSIBLE BIOLOGICAL MECHANISMS FOR THE EFFECT OF BREASTFEEDING ON LATER DEVELOPMENT OF OBESITY

Plausible biological mechanisms underlying the protective role of breastfeeding on later obesity are based on the unique composition of human milk, metabolic and physiological responses to human milk, distinct growth patterns and related body composition, and the breastfeeding experience.

The nutrient composition of human milk is qualitatively and quantitatively different from infant formula. Higher energy, protein and mineral intakes affecting accretion rates have been well described in formula-fed infants compared with breast-fed infants [32–34]. Human milk also contains bioactive factors including hormones [35], specific proteins [36], cytokines [37], and growth factors [38] that might have an effect on lean tissue and adipose cell differentiation and proliferation, but their regulatory role has not been established [39].

The effect of breastfeeding on later development of obesity might be attributed to differences in growth patterns and not the unique features of breastfeeding or human milk per se. Faster weight gain in infancy is associated with increased risk of later obesity. A systematic review of 18 studies examined the relationship between infant weight or BMI and rapid infancy weight gain on later obesity [40]. The ORs for infant weight or BMI and obesity at ages 3–35 years ranged from 1.50 to 9.38. The OR for rapid growth and later obesity ranged from 1.17 to 5.70. There was no convincing evidence that exposure at a particular time during infancy was more critical than others. Infants defined as obese, at the upper end of distribution for weight or BMI, or who grew rapidly during infancy were more likely to develop obesity. No significant interaction between birth weight and rapid infancy weight gain on the risk for later obesity was detected [41]. Full-term infants who experience catch-up growth after intrauterine growth retardation are not protected against an increased risk of later obesity.

Growth patterns of breast-fed and formula-fed infants differ during the period of exclusive milk feeding [42]. In studies with clearly defined feeding groups and sufficient sample sizes, rates of weight gain have been shown to be lower in breast-fed than formula-fed infants. Breast-fed infants consume not only less energy than formula-fed infants but also disproportionately less protein and fewer micronutrients [32–34,43,44]. In a prospective study of 884 children, weight-for-age z-score between birth and 6 months mediated the association between breastfeeding and BMI at age 3 years, implying that the weight of the infant accounted for the BMI later in childhood [45].

A limited number of studies compared breast-fed and formula-fed infants using in vivo measurements of body composition. Bellù [46] reported lower weight and body fat mass (FM) using total body electrical conductivity (TOBEC) among the breast-fed infants at 12 months of age; however, these infants were significantly smaller at birth. de Bruin et al. [44] also using TOBEC reported significantly higher fat-free mass (FFM) and FM, but not %FM, in formula-fed girls at 1–4 months of age. Butte et al. [47] applied a multicomponent model of total body water, total body potassium, and bone mineral content to monitor 40 breast-fed and 36 formula-fed infants from birth to 24 months of age. Higher FM and %FM in breast-fed than formula-fed infants were observed at 3–9 months of age, but no differences at 12–24 months of age. A meta-analysis on 11 studies, including the preceding studies, examined differences in body composition in relation to early infant feeding [39]. Breast-fed infants had significantly higher FM and %FM than formula-fed infants at 3–4 and 6 months of age, but significantly lower FFM at 3–4, 8–9, and 12 months of age.

Maternal and infant behaviors during breastfeeding may influence the infant's ability to regulate intake. Breastfeeding "on-demand" may instill in the infant some ability to modulate their intake in response to dietary challenges, but this may be overridden by caregivers' behavior and an environment with readily available food and sedentary lifestyles. Among 18 breastfeeding mother–infant pairs, evidence was found for infant self-regulation of intake [48]. Infant demand was the primary determinant of the amount of milk consumed. Infants with higher weight for length were less precise in self-regulating intake. Lower levels of "maternal control" over child feeding at 18 months were observed in mothers who breast-fed for at least 12 months compared with less than 12 months [49].

31.6 LIMITATIONS OF EXISTING EVIDENCE

Observational studies have shown associations between breastfeeding and a modest reduction in obesity, mainly in populations of white European descent. The implications of these studies have been questioned because of (1) potential heterogeneity among studies with respect to study design, population, and sample size; (2) residual confounding, that is, the failure to control for confounding factors that can result in spurious associations; (3) publication bias favoring significant results; (4) reverse causality; (5) generalizability; and (6) misclassification of feeding modes [27,50–52].

Confounding factors including maternal BMI, education, SES, and age partially or fully explain the association between breastfeeding and later obesity [50]. Significant dose–response relationships between breastfeeding duration and later obesity may be explained by the fact that breastfeeding and obesity are socially patterned in the same direction in many societies. In industrialized countries, mothers who breast-fed tend to be more educated, higher SES, have more social support for breastfeeding, and these factors in turn are associated with healthier lifestyles. Overweight/obese women are more likely to have overweight children and less likely to initiate and continue breastfeeding [53].

A cross-cohort comparison of populations with different confounding structures did not support a causal effect of breastfeeding on BMI. Brion et al. [54] compared cohorts from a high-income country, the United Kingdom, and a moderate income country, Brazil. Higher SES was associated with breastfeeding prevalence in the United Kingdom but not in Brazil. In the United Kingdom, longer duration of breastfeeding was associated with lower BMI at age 9 years, even after adjustment for SES (child sex, family income, parental education, and family occupational social class). However, in Brazil, there was a nonsignificant trend between longer breastfeeding duration and higher BMI with or without adjustment for SES.

In more recent epidemiological studies, confounding factors were more often included in the risk analysis and inevitability attenuated the protective effect of breastfeeding on later obesity. Because child obesity is strongly linked to parental obesity

for both genetic and environmental reasons, it is important to control for the latter when examining the association between breastfeeding and child obesity. Complete adjustment for lifestyle differences between feeding groups over the child's lifetime is difficult. Two factors that are particularly difficult to measure are long-term diet and physical activity patterns. Because parents who choose to breast-feed may have a healthier lifestyle in general, it is possible that physical activity levels are higher in such families and this may be the causal link between breastfeeding and later child obesity.

In conclusion, a modest but consistent protective effect of breastfeeding against later obesity has been demonstrated by epidemiological studies but not confirmed by two experimental trials. Epidemiological studies are inconclusive due to potential publication bias, reverse causality, poor generalization, misclassification of feeding mode, and most importantly, residual confounding. Two available experimental trials also have limitations due to study population (preterm vs. term infants) and comparison group. Human milk is exquisitely designed for optimal infant growth and development, and therefore, breastfeeding should be promoted regardless of its modest influence on later obesity.

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32 Beverages and Obesity
Biology, History, Trends

Barry M. Popkin and Frank B. Hu

CONTENTS

We have learned that we are what we drink more than what we eat. In the past half-century, the world has undergone a profound transformation in a shift from drinking minimal calories from beverages to consuming hundreds of calories a day from them. More recently, really in just the past two decades, we have learned that we compensate very little in our food intake when we consume additional calories as a beverage. A large literature that encompasses short-term to long-term feeding studies, longitudinal epidemiological studies, intervention studies, and random controlled trials has emerged. We know that the form of the beverage does not matter, as there appears to be little variance in compensation when the beverage is fat-, carbohydrate-, or protein-based.[1] We also realize that we have consumed water for hundreds of thousands of years but only recently have shifted to consuming any amount of caloric beverages. In this chapter, we review current knowledge about the relationship between beverage form and energy intake and the subsequent relationship with an array of cardiometabolic problems. We also discuss additional health problems linked with excessive refined carbohydrate intake and excessive fructose intake. We then present some historical evidence on beverage consumption and discovery and review recent patterns and trends of beverage consumption.

One of the most important aspects of the entire literature of beverages and health is the dearth of research on water and health. Clearly, we drank water for hundreds of thousands of years, and our physiological systems are finely attuned to protecting us against dehydration. Although the bulk of our body is composed of water, we focus far more attention on removing other beverages than on understanding the strengths and importance of water.[2]

32.1 BEVERAGE INTAKE: EFFECTS ON HEALTH

32.1.1 Ingestive Behavior

The biological basis for an obesity-prevention policy to decrease sugar-sweetened beverages (SSBs) is the relationship between beverage intake and food intake. There appears to be little reduction in food intake when caloric beverages are substituted for water and other low-nutritive sweetened or "diet" beverages.[1,3,4] (Rolls is one of the scholars who has a small number of studies that somewhat contradict this lack of compensation.[5,6]) This relationship between beverage intake and food intake occurs despite studies showing that individuals who consume caloric beverages feel they are sated.[7,8] While they may feel more sated, they do not reduce their food intake. Consequently, individuals who fed water or noncaloric sweetened low-calorie beverages consume reduced total energy intake when compared to those consuming caloric beverages. This relationship appears to hold as food and beverage form changes. That is, whether it is a carbohydrate-, fat-, or protein-based beverage (e.g., SSB, coconut milk, or cow's milk), the relationship holds.[1] A more detailed examination shows that intake of calorically sweetened beverages does not reduce the intake of solid food a corresponding amount.[3–6,9–16]

The effects of consuming water with meals compared to various types of caloric and diet beverages have been less studied.[17] A systematic review of English language studies evaluating the impact on energy intake and/or weight status of not drinking water or drinking other beverages compared with water was underaken.[17] Relevant clinical trials and epidemiological and intervention studies were collected, and findings across the literature were summarized. Using clinical trials, average differences in total energy intake at test meals (ΔTEI) were calculated across studies for several beverage categories compared to water. The literature for these comparisons is sparse and somewhat inconclusive. One of the most consistent sets of studies compared drinking SSBs with water among adults at a single meal. Total energy intakes were increased 7.8% (ΔTEI range: –7.5–18.9) when SSBs were consumed. Studies comparing noncaloric sweetened beverages with water were also relatively consistent and found no impact on energy intake among adults (ΔTEI = –1.3, range: –9–13.8). Much less conclusive evidence showed that replacing water with milk and juice increased TEI by an estimated 14.9% (range: 10.9–23.9).

In a yearlong intervention study, Muckelbauer et al.[18] instituted both educational and environmental interventions to increase water intake in 17 German schools (15 control schools had no intervention). Teachers presented four empirically developed lessons about the body's water needs and the water cycle. Special filtered drinking fountains were installed, water bottles were distributed, and teachers were encouraged to organize the filling of water bottles each morning. After 1 year, children completed 24-hour beverage intake recalls in class. Interventions schools had higher water intakes (1.1 glasses/day, $p < .001$), and lower adjusted risk of overweight (OR = 0.69, 95% CI: 0.48–0.98).

32.1.2 Weight

Hu and colleagues[19] conducted a meta-analysis evaluating change in body mass index (BMI) per one-serving increase of SSBs per day and found a significant positive association between SSB intake and weight gain (0.08, 95% CI: 0.03–0.13 kg) among studies that did not adjust for total energy intake.[20–24] Given the mediating role of SSB on caloric intake, many studies that control for SSB energy intake are likely to provide misleading results. In adult studies, the effect was strongest in larger studies with longer durations of follow-up that used robust dietary assessment methods such as food frequency questionnaires rather than a single 24-hour diet recall, which is not able to capture patterns in dietary intake.[20,21] A variety of reviews support these results.[25–27]

Among adults, more epidemiological work has been undertaken. Cross-sectional studies are not optimal because of the high potential for intractable confounding and reverse causation. Prospective cohort studies tend to provide the most robust evidence despite a large degree of diversity between studies in terms of outcome measurements, size, and duration of follow-up. Therefore, greater emphasis should be placed on larger studies of longer duration, which are better powered to detect an effect. In this literature, the longest and largest studies[28,29] show stronger and more consistent associations compared to smaller and shorter studies.[30,31] For example, in the study by Schulze et al.[28] with more than 50,000 nurses followed for two 4-year periods (1991–1995 and 1995–1999), a higher consumption of SSBs was associated with a greater magnitude of weight gain. After adjustment for potential confounders, women who increased their SSB consumption from 1991 to 1995 and maintained a high level of intake gained on average 8.0 kg over the two periods while women who decreased SSB intake between 1991 and 1995 and maintained a low level of intake gained on average 2.8 kg over the two periods.

32.1.3 Cardiometabolic Effects

Hu and colleagues searched the MEDLINE database up to May 2010 for prospective cohort studies of SSB intake and risk of metabolic syndrome (MetSyn) and type 2 diabetes (T2DM).[32] Eleven studies (three for MetSyn and eight for T2DM) were included in a random effects meta-analysis comparing SSB intake in the highest to lowest quantiles in relation to risk of MetSyn and T2DM. Based on data from these studies, including 310,819 participants and 14,957 cases of T2DM, individuals in the highest quantile of SSB intake (most often—one to two servings/day) had a 26% greater risk of developing T2DM than those in the lowest quantile (none or < one serving/month) (RR = 1.26, 95% CI: 1.12–1.41). Among studies evaluating MetSyn, including 19,431 participants and 5803 cases, the pooled RR was 1.20 (95% CI: 1.02–1.42).

While SSBs increase the risk of MetSyn and T2DM partly because of their contribution to weight gain, an independent effect may also stem from the high levels of rapidly absorbable carbohydrates in the form of added sugars in these beverages. The findings by Schulze et al.[28] suggested that approximately half of SSBs' effect on T2DM was mediated through obesity. In a 2009 study among over 88,000 women followed for 24 years, those who consumed more than two SSBs per day had a 35% greater risk of coronary heart disease compared to infrequent consumers, after adjusting for other unhealthy lifestyle factors (RR = 1.35, 95% CI: 1.1–1.7, $p_{trend} < .01$).[33] Additional adjustment for potential mediating factors including BMI, total energy, and incident T2DM attenuated the associations, but they remained statistically significant, suggesting that the effect of SSBs is not entirely mediated by these factors.

Because SSBs have been shown to raise blood glucose and insulin concentrations rapidly and dramatically[34] and are often consumed in large amounts, they contribute to a high dietary glycemic load (GL). High-GL diets are known to induce glucose intolerance and insulin resistance, particularly among overweight individuals,[35–38] and can increase levels of inflammatory biomarkers such as C-reactive protein, linked to risk of T2DM.[39–43] High dietary GL has also been linked to development of coronary heart disease in a relatively short time frame,[44] since inflammation impacts the development of atherosclerosis, as well as plaque stability and thrombosis.[33] Findings from the Nurses' Health Study and the Health Professionals Follow-up Study indicate that a high dietary GL also increases the risk of developing cholesterol gallstone disease, which is

associated with insulin resistance, MetSyn, and T2DM.[45,46] Endogenous compounds in SSBs such as advanced glycation end products, produced during the process of caramelization in cola-type beverages, may also affect pathophysiological pathways related to T2DM and MetSyn by increasing insulin resistance, inflammation, and endothelial dysfunction.[47,48] SSBs may also increase risk indirectly by inducing alterations in taste preferences and diet quality resulting from habitual consumption of highly sweetened beverages; this effect also been noted for artificially sweetened beverages.[49,50]

32.1.4 Random Controlled Trials

To date, one well-executed random controlled trial has been completed. The CHOICE (Choosing Healthy Options Consciously Everyday) clinical trial focused on the impact of shifting from normal caloric beverages to either water or diet beverages among adults involved in active weight loss.[51] The hypothesis was that participants assigned to the beverage substitution groups would achieve greater weight loss at 6 months compared with control participants who made dietary changes of their choosing (diet beverages [DB] > active choices [AC]; and water [WA] > AC). The AC group was given equal attention control and was on an active weight loss program but was not provided with any beverages or advice regarding beverage pattern selection. Secondary outcomes were to compare the noncaloric beverage groups to the control group on criterion measures of weight loss, waist circumference, blood pressure, glucose, and osmolality as a marker of hydration from 0 to 3 months and 0 to 6 months.

Despite similar or somewhat smaller weight losses, WA showed statistically significant reductions in fasting glucose and improvement in hydration compared with AC. DB also showed improvements on many of these parameters by 6 months but was not significantly different from AC. In the completers analysis, the improvements in systolic and diastolic blood pressure in WA compared with AC reached statistical significance.[51] This study showed that an approximately two-serving reduction in caloric beverages resulted in a 2-kg weight loss at 6 months across DB and WA.

In the intent-to-treat analysis, all groups significantly reduced weight and waist circumference and improved systolic blood pressure from 0 to 6 months. Average percentage weight losses (±SE) at 6 months were DB −2.54% (0.45), WA −2.03% (0.40), and AC −1.76% (0.35); there were no significant differences between groups. DB had greater odds of achieving a 5% weight loss at 6 months compared with AC (OR = 2.29, 95% CI: 1.05–5.01, $p = .04$). WA showed a significant reduction in fasting glucose at 6 months ($p = .19$) and improved hydration at 3 ($p = .0017$) and 6 months ($p = .049$) compared with AC. In a combined analysis, participants assigned to replace beverages were two times more likely to have achieved a 5% weight loss (OR = 2.07, 95% CI: 1.02–4.22, $p = .04$) compared to AC.[51]

The strengths of this study are that it is the first randomized trial in adults examining a simple strategy for calorie reduction and weight control, with participants masked to the study purpose, including over 50% racial and ethnic minorities, strong retention rates, 24-hour dietary recalls, provision of beverages, an attention control group, and objective weight and physiological outcome measures.[51] Importantly, the attention control group was not a "no treatment control group"; participants were taught general weight-control strategies, reported weight and general behavior (not kilocalories) weekly, and attended 60-minute monthly treatment meetings equating for contact time and other variables known to affect weight loss among motivated individuals. Limitations of the study include the potential for being underpowered, self-report measures of diet and physical activity, underrepresentation of men, the relatively short study duration of 6 months to allow benefit of a small caloric change like beverage substitution to accrue, and lack of long-term follow-up.

On a population level, the replacement of caloric beverages with noncaloric alternatives could be an important public health message. This strategy also has implications for health-care settings, as assessing SSB intake is feasible and the prescriptive recommendation to replace caloric beverages with noncaloric alternatives is simple and straightforward. Replacing SSB with either diet beverages or water, based on the consumers' preference and ability to adhere, appears warranted at this stage of research based on these findings. Future research should examine the long-term effects on health of consuming either beverage as a replacement for caloric beverages before specific recommendations can be made.

32.1.5 Does the Type of Caloric Sweetener Matter? Is High-Fructose Corn Syrup the Culprit?

At one point, there was extensive concern that high-fructose corn syrup (HFCS) might pose a major impact on health. Bray et al. hypothesized that the large shift toward use of HFCS,[52] coupled with the unique metabolic properties of fructose, posed a major problem.

Subsequent research has provided clear evidence that all sugars are equal in their impact on cardiometabolic health; nevertheless, the fructose component of sugars such as sucrose and HFCS might lead to additional cardiometabolic risks.[53–57] These range from gout, linked with the high concentration of uric acid,[58] to many other cardiometabolic complications, particularly related to renal function.[59–62]

32.1.6 What About Noncaloric Sweeteners?

An increasing component of the beverage market, particularly in high- and middle-income countries, consists of beverages with either noncaloric sweeteners (NCS) or a combination of caloric sweeteners and NCS. There is minimal evidence that NCS pose any toxicological effect on health.[63] However, there is a large set of epidemiological studies suggesting that consumption of beverages with NCS is linked with increased cardiometabolic risks ranging from diabetes to incident MetSyn to doubling the risk of obesity.[64–66]

Two recent studies question this relationship. A recent study by de Koning and colleagues found that an observed association between intake of beverages with NCS and increased risk of T2DM is attenuated and no longer statistically significant following multivariate adjustment for detailed measures

of family history, previous weight change, dieting, Healthy Eating Index score, and total energy intake (top vs. bottom quartile of intake: HR = 1.09, 95% CI: 0.98–1.21, p for trend = .13).[67] Although de Koning et al. addressed possible confounding by diet more completely than other studies have, their results still could have missed important interactions between dietary pattern and diet beverage consumption.

A second publication went a step further. Using CARDIA (Coronary Artery Risk Development in Young Adults) longitudinal data, Duffey et al. found that persons with a Western dietary pattern who were diet beverage consumers had a higher risk of cardiometabolic outcomes, except elevated blood pressure, compared to the other three groups (diet beverage consumers with a prudent dietary pattern and diet beverage nonconsumers with a prudent or Western dietary pattern).[68] Nonconsumers of diet beverages with a prudent dietary pattern had a lower risk for MetSyn, high waist circumference, and high triglycerides (compared to consumers with a Western dietary pattern), but consumers with a prudent dietary pattern had a lower risk of high fasting glucose and low high-density lipoprotein cholesterol. Although both the prudent dietary pattern and the nonconsumption of diet beverages were associated with lower risk of incident MetSyn, the results suggest that dietary pattern and diet beverage consumption interact in the prediction of cardiometabolic risks and should be examined jointly. In other words, there are healthy and unhealthy eaters who consume beverages with NCS. The Big Mac/Diet Coke crowd increases its risk of cardiometabolic problems, while the healthy eaters who consume beverages with NCS do the opposite.

An unpublished study illustrates the complex issues we face related to the use of NCS in beverages and foods. Piernas et al. compared dietary patterns of those in the above-mentioned CHOICE trial. Those adults randomized to replace caloric beverages with diet beverages, when compared to those who replaced caloric beverages with water, showed a short-term increase in nonsugar carbohydrates and carbohydrate-rich foods that is suggestive of a potential dietary effect. This is a small study not powered to examine this topic, but it is suggestive of a potentially important issue.

32.2 MECHANISMS AND HISTORY: WHEN DID CALORIC BEVERAGES ENTER THE HUMAN FOOD SYSTEM?

It is well known that humans will die within 3–7 days if they do not consume water. Water comprises 75% of the body weight in infants to 55% in the elderly and is essential for cellular homeostasis and life.[2] From the time that primeval species ventured from the oceans to live on land, a major key to survival has been the prevention of dehydration. The critical adaptations cross an array of species, including *Homo sapiens*.[2] To prevent dehydration, reptiles, birds, vertebrates, and all land animals have evolved an exquisitely sensitive network of physiological controls to maintain body water and fluid intake by thirst. Humans may drink for various reasons, particularly for hedonic ones, but most drinking is due to water deficiency, which triggers the so-called regulatory or physiological thirst. We understand from extensive research on the topic that the hydration system of a human is finely tuned to protect us.[2] What is not clear is how this thirst mechanism is different from the hunger or feeding mechanism. We know that humans will die if they do not eat over a 1- to 12-month period, depending on their initial weight, so there appear to be some evolutionary reasons behind the lack of compensation in food intake when they drink water or caloric beverages.[69]

A consideration of our evolutionary history may help to explain our poor compensatory response to calories from fluids. Elsewhere, the history of eight important beverages (milk, beer, wine, tea, coffee, distilled alcoholic beverages, juice, and soft drinks) was reviewed, and two hypotheses were formulated.[70] First, humans may lack a physiological basis for processing carbohydrate or alcoholic calories in beverages because only breast milk and water were available for the vast majority of our evolutionary history. Alternatives to those two beverages appeared in the human diet no more than 11,000 years ago, but *H. sapiens* evolved over a 100,000- to 200,000-year period. Second, carbohydrate- and alcohol-containing beverages may produce an incomplete satiation sequence that prevents becoming satiated on these beverages.

32.3 CURRENT PATTERNS AND TRENDS OF BEVERAGE INTAKE

32.3.1 Global Aggregate Trends

Across the globe, there is evidence of a shift toward increased consumption of SSBs and, more recently, beverages with NCS. A recent study examined patterns of carbonated soft drink availability using the two largest and most influential producers of sweetened beverages, The Coca-Cola Company and PepsiCo, who together control 34% of the global soft drink market, examining their product portfolios globally and in three critical markets (the United States, Brazil, and China) from 2000 to 2010.[71] This study used Euromonitor International's definition of "soft drink," which includes the aggregation of (1) carbonates/carbonated soft drinks, (2) fruit/vegetable juice, (3) bottled water, (4) functional drinks, (5) concentrates, (6) ready-to-drink tea, (7) ready-to-drink coffee, and (8) Asian specialty drinks. Thus, although the term "soft drink" may refer specifically to carbonated soft drinks in everyday use, the 34% market share takes into account other beverage categories, with carbonated soft drinks considered a subset of soft drinks overall.

On a global basis, total revenues and energy per capita sold increased from 2000 to 2010, yet the average energy density (kJ/100 mL) sold declined slightly, suggesting a shift to lower calorie products. Per capita volume sales showed similar worldwide trends during the past decade, with modest increases in sales of carbonated soft drinks alongside marked increases in bottled water, fruit/vegetable juice, and sports and energy drinks.[71]

What is most interesting is the differential trends in the United States versus the developing markets of Brazil and China. Despite the global increase in energy and volume sold per capita by Coca-Cola and PepsiCo from 2000 to 2010, there

is a clear decrease in energy and volume sold per capita in the United States over the same time period because of a shift toward reduced kilocalories per milliliter of sales. In contrast, the opposite was true in Brazil and China, with total per capita energy increasing greatly in China and to a lesser extent in Brazil. Daily energy per capita sold by Coca-Cola increased 41% in Brazil between 2000 and 2010, while daily energy per capita sold by PepsiCo rose 168%, largely because of increases in energy from carbonated soft drinks. Likewise, in China, daily energy per capita sold by Coca-Cola increased 215% between 2000 and 2010, while daily energy per capita sold by PepsiCo rose 147%, also driven by carbonated soft drinks. Energy from carbonated soft drinks alone sold by both Coca-Cola and PepsiCo experienced an even stronger upward growth trend in China between 2000 and 2010.[71] Figure 32.1 shows the global increases in this one component of soft drink sales from these two companies. The remarkable increases in Brazilian and Chinese sales per capita are presented in Figure 32.2.

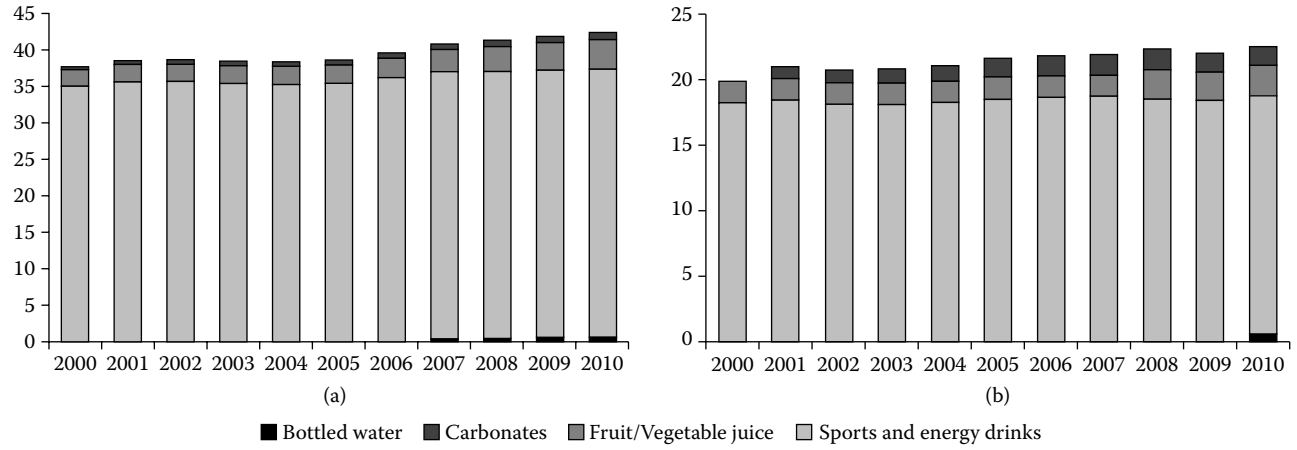

FIGURE 32.1 Global trends 2000–2010 in daily calories sold. (a). Per capita daily energy sold (kJ). The Coca-Cola Company—World. (b) Per capita daily energy sold (kJ). PepsiCo—World. (Data from Kleiman S et al., *Obes. Rev.*, 13, 258–74, 2012.)

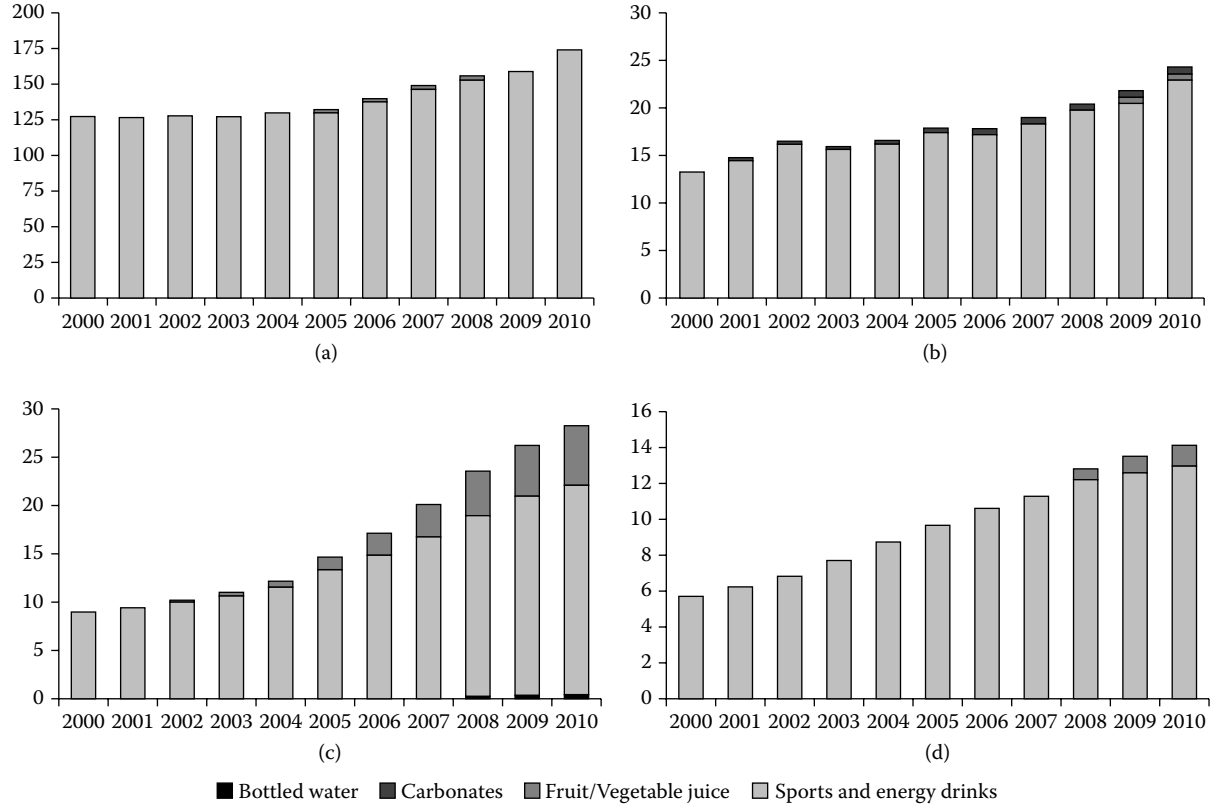

FIGURE 32.2 Brazilian and Chinese trends 2000–2010 in daily calories sold. (a). Per capita daily energy sold (kJ). The Coca-Cola Company—Brazil. (b) Per capita daily energy sold (kJ). PepsiCo—Brazil. (c) Per capita daily energy sold (kJ). The Coca-Cola Company—China. (d) Per capita daily energy sold (kJ). PepsiCo—China. (Data from Kleiman S et al., *Obes. Rev.*, 13, 258–74, 2012.)

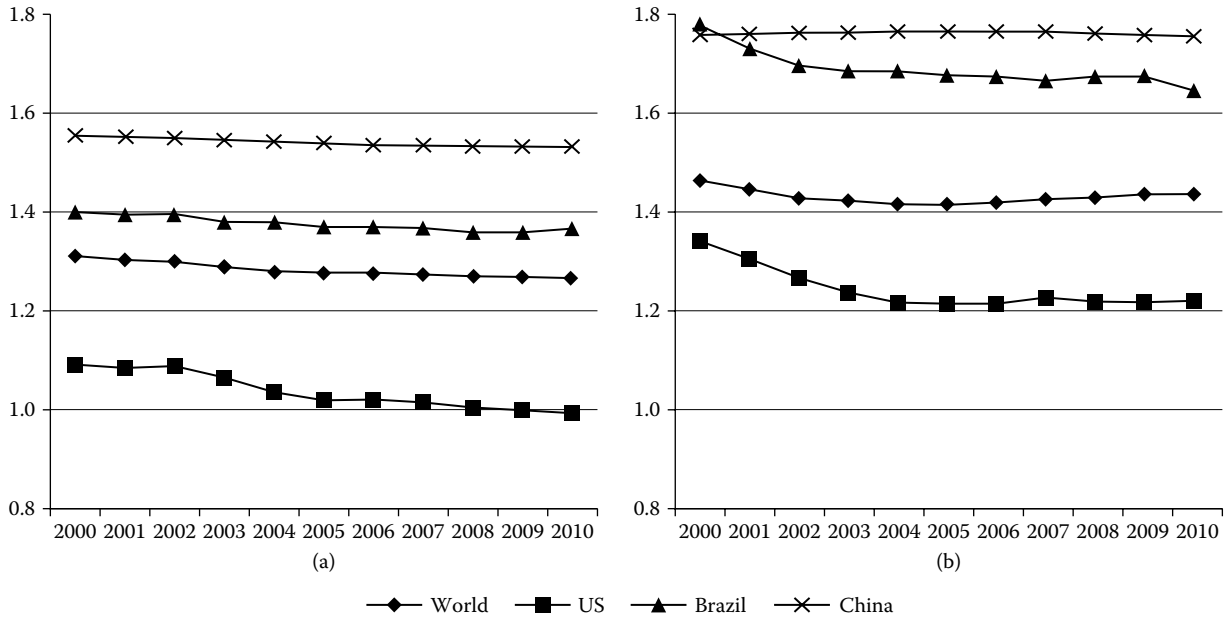

FIGURE 32.3 Trends 2000–2010 in calories per milliliter sold: Global, the United States, Brazil, and China. (a) Kilojoules per 100 milliliters sold. The Coca-Cola Company—carbonates. (b) Kilojoules per 100 milliliters sold. PepsiCo—carbonates. (Data from Kleiman S et al., *Obes. Rev.*, 13, 258–74, 2012.)

A major objective of the global beverage companies has been to increase sales of water and beverages with NCS and to reduce their total sale of calories. Figure 32.3 highlights the much lower average energy density of carbonated soft drinks sold by Coca-Cola and PepsiCo in the United States versus globally and in Brazil and China as well as the reduction in average energy density of carbonated soft drinks for both companies. In contrast, the energy density of carbonated soft drinks has not changed in China while there is a slight reduction by PepsiCo in Brazil. Caution is warranted in interpreting Figure 32.3. First, Coca-Cola and PepsiCo represent only the two largest companies, but in each local market, there are many other companies, few of which have the capacity to promote sales of nonnutritively sweetened beverages like these two companies do. Second, Figures 32.1 and 32.2 show that overall caloric beverage sales increases represent potentially important current risks to energy imbalance and weight gain.

32.3.2 Individual Dietary Intake Patterns

In examining patterns of beverage intake in Mexico, the United States, the United Kingdom, and Europe over the past decade or more, including intake by children and adolescents, it is clear there are some strong and in some cases disturbing trends:

- Regular unsweetened milk is being replaced by sugar-sweetened whole milk among children and adolescents in the United States, the United Kingdom, and Europe.[72–74] Contrary to public pronouncements, there is no clear increase in milk intake associated with sweetened whole milk. In fact, as Lasater et al.[72] show, in the United States, the declining trend in milk intake was not reduced or diminished by a marked shift toward nutritively sweetened whole-milk products. Figures 32.4 and 32.5 highlight the sweetened milk consumption patterns.
- The variety of caloric sweetened beverages is increasing rapidly. Energy drinks, sports drinks, and many other categories of beverages are combining with the traditional colas as diversity of caloric beverages expands.
- Fruit juice is the new focal point for some countries. As found in an unpublished study, fruit juice concentrate is not subject to the same trade barriers and quotas as other sugars and carries a natural, healthy aura. Thus a large number of SSBs are now sweetened with fruit juice concentrate, and fruit juices themselves are being pushed very hard as a natural health drink. In fact, in this same study, an exploration of detailed ingredients in the 400,000-plus products sold by consumer packaged goods companies in the United States found that 31% of SSBs contained fruit juice concentrate and even 29% of so-called diet-sweetened beverages contained fruit juice concentrate. Of course, current research suggests that, biologically, fruit juices have the same cardiometabolic problems as SSBs and provide virtually no health benefits except in unique, rare circumstances.[75,76]
- Country by country, we have seen remarkable shifts in marketing and sales of nutritively sweetened beverages over the past 25 years. The consumption increases that occurred in the United States in the 1980s and 1990s have been followed by a doubling of intake of caloric beverages in Mexico in

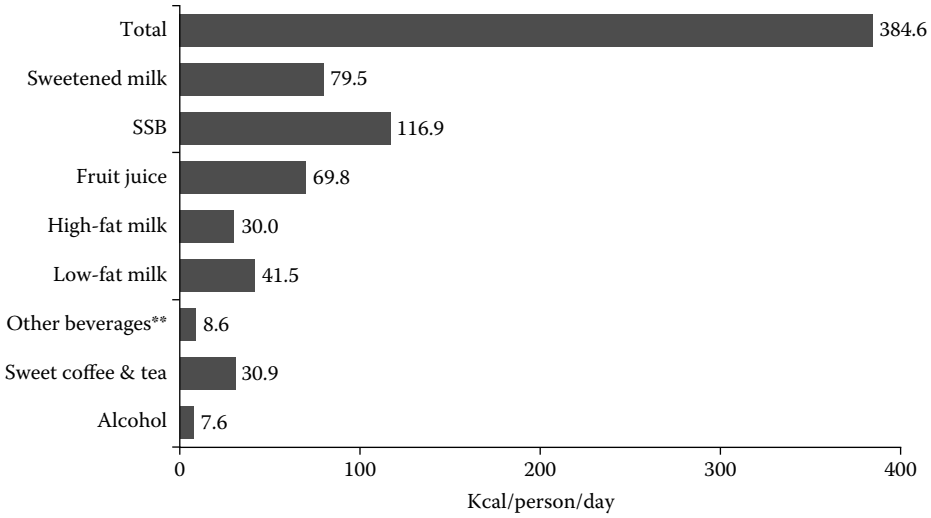

FIGURE 32.4 Total beverage consumption patterns of European adolescents 12–17.5 years (kcal/person/day). **Other beverages include vegetable juice, vitamin waters, energy drinks. (Data from Duffey KJ et al., *Eur. J. Clin. Nutr.*, 66, 244–52, 2012.)

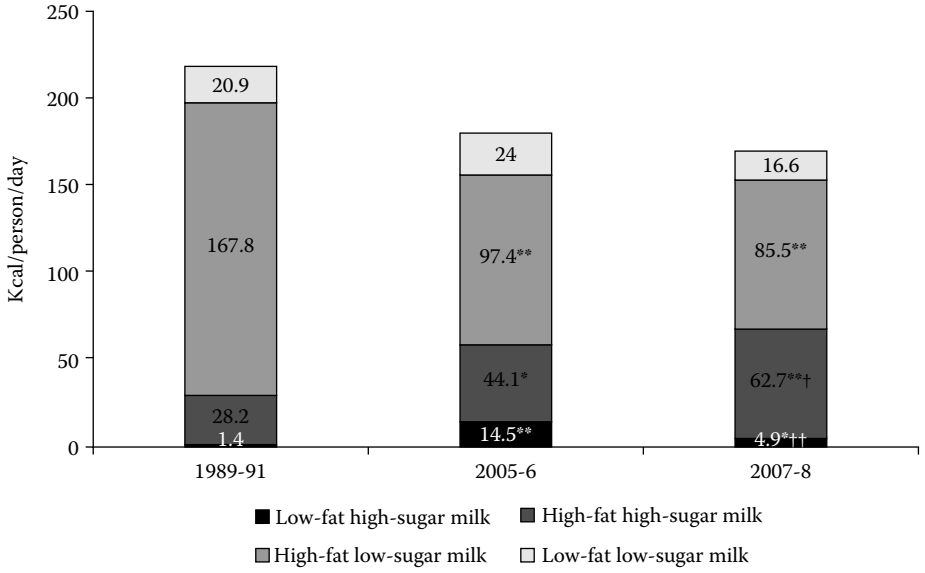

FIGURE 32.5 Trends in total kcal per capita from milk groups by U.S. children 6–11 years. Comparing with 1989: *$p < .05$, **$p < .001$. Comparing with 2005: †$p < .05$, ††$p < .001$. (Data from Lasater G et al., *Nutr. J.*, 10, 103, 2011.)

the 1999–2006 period and similar rapid shifts in Brazil, China, and other low-income countries. In 2006, Mexican adolescents and adults consumed 20.1% and 22.3%, respectively, of their energy from energy-containing beverages.[77] In addition, Mexican preschool children consumed 27.8% of their energy and schoolchildren consumed 20.7% of their energy from caloric beverages in 2006.[78] The three major categories of beverages consumed were whole milk, fruit juice with various sugar and water combinations, and carbonated and noncarbonated beverages.

- In Europe, it has been much more difficult to document the large shifts in caloric beverages. In the United Kingdom, trends data from the 1997–2009 period show reductions in dairy consumption followed by modest increases in caloric beverages.[74] SSB intake in the United Kingdom is high among all age groups but does not match the very high levels found in other countries (50–131 kcal/day) across various age-gender groups; however, fruit juice intake is often higher in the United Kingdom.
- In a study among European adolescents aged 12–17.5 years, the average adolescent consumed very high levels of SSBs (117 kcal/day), sweetened milk (80 kcal/day), and fruit juice (70 kcal/day), with quite heterogeneous patterns across the eight countries studied.[73] Overall levels of kilocalories from beverages varied from highs in Germany (507 kcal/day) and Austria, Belgium, and Sweden (all 400 kcal/day) to a low in Italy of 248 kcal/day. If we look separately

at each subpopulation of consumers of different beverages, we find very high levels of intake. For example, among the 52.8% of adolescents who consumed SSBs, 32.5% who consumed sweetened milk, and 46.8% who consumed fruit juice, they reached very high levels of intake of 221, 245, and 149 kcal/day, respectively.

- U.S. levels remain very high, with 400 kcal/day from beverages consumed across children and adults and SSB intake remaining the highest component despite some declines during the recent recession.[79]

32.4 DISCUSSION AND THE FUTURE

An expanding literature suggests that caloric beverage intake is linked with obesity and excessive weight gain. One of the clearest causal linkages between our food supply and excessive weight gain and an array of cardiometabolic problems is the excessive intake of the array of SSBs. Our concern is echoed by experts in the heart, cancer, diabetes, and many other fields, as well as in much public debate.[80,81] Nevertheless, the sugar and beverage sectors represent two of the more powerful interests in our society, dwarfing the tobacco sector.[82] Country after country is attempting to limit consumption of SSBs and other caloric beverages, and in many cases, they are succeeding.

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33 Sedentary Time and Obesity

Neville Owen and Marc Hamilton

CONTENTS

33.1 INTRODUCTION

The body of evidence suggesting that too much sitting—as distinct from too little exercise—can have unique consequences for metabolic health has been growing over the past decade.[1–5] Typically, adults spend the majority of the time sedentary during their waking hours, as a consequence of those required or voluntary engagements for which sitting is the sole or primary option. Prolonged sitting time can be largely unavoidable (e.g., commuting by car at the beginning and the end of each working day and sitting in front of a computer at work) or can be the most convenient and attractive behavioral choice (sitting watching favorite TV shows in the evening or sport on the weekend). Sedentary behaviors, from the Latin *sedere*, which means "to sit," can be most simply defined in terms of the posture involved (sitting or reclining).

At the physiological level, sedentary posture can be linked to low energy expenditure demand or, more directly, to the contractile activity in skeletal muscles important for common activities involving being upright—standing and light ambulation.[1,6,7] Importantly, this type of muscular contractile activity that is essential for good health is of much lower intensity and different in many ways from what is associated with exercise programs,[1] and it includes most notably the intermittent pattern of light-intensity contractions spread throughout the entire day; these contractions account for the 4–8 h/day of nonexercise physical activity responsible for the abundant yet widely variable (e.g., 300–1500 kcal/day) nonexercise activity thermogenesis when people are not sitting.[8–10] This is in contrast to traditional aerobic exercise programs that have focused on adding blocks (≥10 minutes) of moderate to vigorous exercise, such as brisk walking or bicycling, often with the minimal goal of accumulating a relatively modest duration of approximately 150 min/week.

Central to research on sedentary behavior and obesity, there is the challenge of disentangling the behavioral consequences of obesity (particularly predispositions to be less active and to sit more) from obesity as a consequence of sedentary behavior. Nevertheless, prolonged periods of time spent sedentary and the ensuing physiological effects are likely to be important for health, regardless of the cause of obesity in any given individual. We highlight recent evidence suggesting that there may be distinct metabolic health benefits from reducing sedentary time, independent of obesity. Developing strategies for reducing sedentary time is thus important for those who are already obese, regardless of weight loss.

33.2 SEDENTARY BEHAVIOR AND METABOLIC HEALTH: OBSERVATIONAL STUDY EVIDENCE

It is not our purpose here to present a comprehensive review of studies on sedentary behavior, obesity, and related health outcomes. These have been reviewed elsewhere in the literature.[1,3,5,11–13] A recent review by Thorp and colleagues[12] (Figure 33.1) examined the findings from prospective studies on sedentary behavior–obesity relationships and relationships with other health outcomes. With the exception of three studies that showed no relationship, a relationship in men only, or a relationship in women of normal weight at baseline only, higher levels of sedentary time were consistently associated

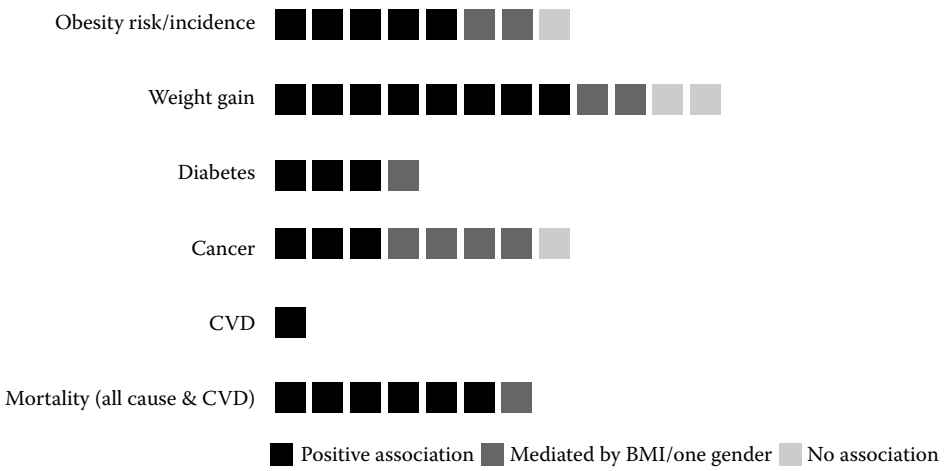

FIGURE 33.1 Associations of sedentary behavior with obesity and related adverse health outcomes: findings are from prospective studies, 1996–2011. (Data from Thorp AA, Owen N, Neuhaus M et al., *Am. J. Prev. Med.*, 41, 207–15, 2011.) Each square represents one study. CVD refers to cardiovascular disease.

with weight gain in men and women, after adjustment for the type of leisure-time physical activity most people associate with aerobic exercise (brisk walking, bicycling, etc.).

33.2.1 TV-Viewing and Sitting Time Studies Using Self-Report Exposure Measures

Some key findings on relationships of sedentary behavior with adverse markers of metabolic health are illustrated by the body of work from AusDiab (the Australian Diabetes, Obesity, and Lifestyle Study), a national study of obesity, diabetes, and related risk factors. The AusDiab findings include demonstrations that one of the most common sedentary behaviors—prolonged TV viewing time—can be associated with abnormal glucose metabolism,[14] the metabolic syndrome,[15] continuous measures of metabolic syndrome components,[16] elevated insulin and glucose levels,[17] and adverse microvascular health markers.[18,19] Other notable TV-viewing time findings from AusDiab include prospective relationships of TV-viewing time with premature mortality attributable to cardiovascular disease[20] and estimates that for every hour of TV viewing after 25 years of age Australian adults can expect a 22-minute reduction in their life expectancy.[21] These relationships are impressive, considering that the modest precision of the self-report measures used can lead to misclassification errors in terms of which people are identified as more or less sedentary.

The health risks associated with high TV-viewing time are also highlighted by prospective observational study findings from the National Institutes of Health–American Association of Retired Persons Diet and Health Study with some 240,000 adults initially aged 50–71 years.[22] Those who reported more than 7 h/week of moderate to vigorous physical activity during leisure time and also watched TV for 7 h/day or more had a 50% greater risk of death from all causes and twice the risk of death from cardiovascular disease when compared to those who reported the same amount of moderate to vigorous leisure-time physical activity but watched TV for less than 1 h/day.

Another large prospective study from Australia using self-report to characterize total sitting time[23] reported about a doubling in the risk associated with sitting time in the most active people (reporting >5 h/week of leisure-time physical activity). This reinforces the implications of AusDiab studies and other findings that leisure-time moderate to vigorous physical activity appears to be not sufficient to protect against spending large amounts of time in sedentary behaviors.

There are challenges in moving toward public health recommendations regarding the commonly asked yet problematic question as to how much sitting is safe or unsafe. In summarizing the relative risks, Katzmarzyk and Lee[24] provided the theoretical estimate that the population life expectancy in the United States would be 2 years higher if adults reduced their time spent sitting to less than 3 h/day and 1.38 years higher if they reduced TV-viewing time to less than 2 h/day. However, such estimates are qualified by the fact that sitting time can be poorly estimated by self-report, depending on the measurement instrument that is used, and thus should not be taken to be literal recommended targets.

Other observational studies (as summarized in Figure 33.1) have shown TV-viewing time to be associated prospectively with weight gain. For example, among 1867 colorectal cancer survivors recruited from a population-based registry who were assessed at 24 months and 36 months post diagnosis,[25] there was a significant increase over baseline in mean body mass index (BMI) for those reporting 5 h/day or more of TV viewing compared to those watching less than 3 h/ day at baseline. In a follow-up study[26] with 3846 AusDiab study participants, increases in TV-viewing time over 5 years were associated with increases in waist circumference; these associations were independent of baseline TV-viewing time, baseline physical activity and change in physical activity, and other potential confounders.

The challenges in quantifying overall sedentary time, or in estimating it from surrogate measures such as TV-viewing time that have been used in many studies, are critical to the strength of the conclusions and likely to continue to evolve.

Errors in accurately ascribing the amount of exposure to sedentary time in epidemiological studies may lead to serious "underestimates" of the absolute magnitude of sedentary time. This may have an influence on the strength of relationships that can be identified between exposure (sitting time) and health outcomes, compared to other risk factors that are more easily quantified (such as BMI) or that are more easily ascertained. As a general principle, imprecise and inaccurate categorization of the amount of exposure leads to dilution of the true effect of the relationships with risk factors. In other words, the strength of the relationships between sedentary time and a health outcome such as weight gain may be rendered smaller than they are in reality because self-reported total sitting time is likely to include elements of misclassification.

33.2.2 Accelerometer-Measurement Studies of Sedentary Time

The findings from TV-viewing time studies that have relied on self-reports of the exposure measure generally have been confirmed by studies using device-based (accelerometer) measurements of sedentary time. Accelerometers are small devices typically worn on the hip, sensitive to movement in one to three axes, and are most sensitive to deceleration during the strike of the foot during walking or vibrations in the vertical orientation. Most typically, a cut point of 100 counts per minute has been set as the threshold for defining what is sedentary and what is active. One such study[27] used accelerometer measures in the 2004–2005 AusDiab follow-up. Sedentary time was found to be deleteriously associated with a number of cardiometabolic risk markers, including waist circumference, blood glucose, and triglycerides. Furthermore, even when accounting for total sedentary time and time spent in moderate- to vigorous-intensity physical activity, those whose sedentary time was mostly uninterrupted (those who sat for prolonged, unbroken periods of time) had a poorer cardiometabolic health profile compared to those who had more frequent breaks in their sedentary time.[28]

The initial findings on breaks in sedentary time from 168 adults in the AusDiab study were examined further by accelerometer data from 2118 fasting and 4757 total participants aged 20 years and older from the 2003–2004 and 2005–2006 population-representative U.S. National Health and Nutrition Examination Survey (NHANES).[29] Total sedentary time was deleteriously associated with more adverse patterns of cardiometabolic biomarkers (high-density lipoprotein–cholesterol, triglycerides, insulin, insulin sensitivity, and C-reactive protein).[29] When examining the association of these cardiometabolic biomarkers with breaks in sedentary time (transitions from minutes with movement to periods with movement <100 counts per minute independent of total sedentary time), the inflammatory marker of C-reactive protein, which is known from many studies to be strongly correlated with body fat and waist circumference, was the only biomarker with statistical significance. Importantly, the analysis was adjusted for not only age, sex, race/ethnicity, medical history, plus significant sociodemographic covariates but also objectively determined exercise time.

A notable feature of these findings (Figure 33.2) is that those who were in the lowest quartile of breaking up sedentary time (i.e., those who sat for the most prolonged periods) had a 4.1 cm greater waist circumference compared to those who more frequently broke up their sitting time, the highest breaks quartile. However, total accelerometry-determined sedentary time showed a relatively weaker relationship. Thus, it appears that total sedentary time and breaks from sedentary behavior have distinct associations. Total sedentary time may be important for the biochemistry of lipids and insulin sensitivity, whereas breaks may be more important for body weight, keeping in mind that these are cross-sectional associations.

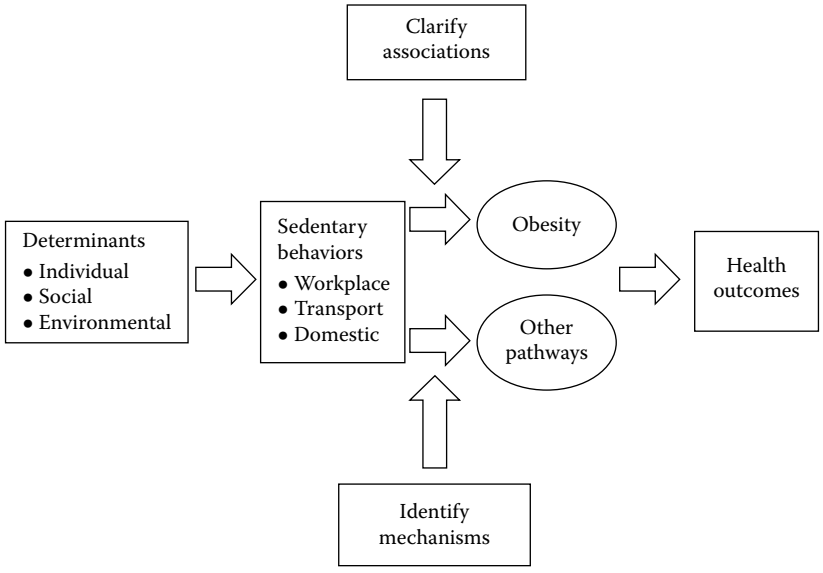

FIGURE 33.2 Schematic showing the main elements of a sedentary behavior–obesity research agenda.

33.2.3 Need for Experimental Evidence on the Metabolic Consequences of Sedentary Behavior

Although there are now many consistent findings from observational studies indicating health concerns from sedentary behavior, they do not establish a "causal relationship" of sedentary time and the breaking up of sedentary time with important aspects of metabolic health. Put simply, one cannot exclude the possibility that those who are overweight and less healthy may be more likely to sit for long periods. This is in contrast to the initial laboratory studies using animal models of "inactivity physiology" that showed effects on lipoprotein metabolism and the biochemistry of lipid regulation; these studies had strong elements of experimental control of the relevant exposures and also controlled for the roles of potential biological and behavioral confounding factors.[1–3]

Now, human experimental evidence is needed, particularly from studies in which sedentary time and breaks in sedentary time are manipulated in a controlled fashion. Hypothesis-driven experimental studies from animal models have focused mostly on the rapid time course of effects of inactivity, which has led to the current thinking about acute effects.[1–3,6,7,30] Following from this understanding, the recent emergence of human trials has thus far focused on extending the hypothesis that significant physiological effects of inactivity become evident within a single day, whether it be for rapid insulin resistance,[31] inappropriately sustained appetite during reduced energy expenditure,[32] or exaggerated postprandial hyperglycemia.[33]

33.2.3.1 Intensity Defined Little Exercise Breaks Study

To test a key hypothesis from observational study findings and animal experimental evidence, a recent human experimental study, intensity defined little exercise (IDLE) breaks,[33] examined the acute effects of uninterrupted sitting on postprandial plasma glucose and serum insulin, compared with experimental conditions in which sitting was interrupted regularly. The interruptions to sedentary time were short bouts of treadmill walking. Participants were overweight middle-aged adults. The study used a crossover design, with each participant completing each of the experimental conditions over a 7-hour period: (1) uninterrupted sitting, (2) sitting interrupted by light-intensity (3.2 km/h) treadmill walking, and (3) sitting interrupted by moderate-intensity (5.8–6.4 km/h) treadmill walking. Participants were given a standardized test drink (200 mL, 75 g carbohydrate, 50 g fat) after an initial 2-hour period, and the positive incremental areas under curves (iAUCs) for glucose and insulin were calculated for the respective treatments.

To put these treadmill walking intensities into perspective, the higher of the two intensities was clearly within the intensity range that is advised in physical activity guidelines for adults. However, some of the study participants were unable to walk for even 2 minutes at the initially designed pace of 6.4 km/h. Thus, this intensity was typically thought of as brisk walking and sufficient to produce the energy demands and effort as advised in the guidelines for moderate to vigorous exercise. The lower of the two intensities was chosen because it could be easily completed by all participants and was estimated to increase energy expenditure closer to the light- to moderate-intensity threshold of 3 metabolic equivalents (METs) (with 1.0 MET equal to ~1 kcal/kg/h, which is by convention the typical metabolism at rest of an "average" individual).

Relative to uninterrupted sitting, the glucose iAUC was reduced after both activity-break conditions (light: 24%; moderate: 30%). Similarly, the iAUC for insulin was reduced by 23% after the activity-break conditions compared to uninterrupted sitting.[33] There were no differences in the glucose and insulin responses between the moderate-activity and the light-activity conditions.

It would thus appear that quite brief activity interruptions to sitting time can reduce postprandial glucose and insulin, and this may occur irrespective of activity intensity. It is, however, not possible to infer from these findings the case over longer term exposures to a prolonged and more frequently interrupted sitting time. Nevertheless, these glucose and insulin responses to the activity-break conditions provide experimental support for the aforementioned observational study findings.

33.2.3.2 Assessing Longer Term Exposures to Changes in Sedentary Time

The IDLE breaks experimental study specifically addressed the cardiometabolic consequences of prolonged sitting. Although these initial findings are promising, there is a need for further studies to identify potential implications for obesity and its health consequences. For example, it will be important to identify the impact of longer term exposures, the metabolic changes that occur with differences in the frequency and duration of interruptions to prolonged sitting, whether there are differences in these responses for men and women, and whether there are important differences related to variations in adiposity status. To date, evidence from such long-term randomized controlled trials is lacking.

In exercise training trials, there is the benefit that the baseline exercise time in sedentary subjects is close to zero; thus, the total exercise exposure is about the same for every subject. In contrast, everyone sits at baseline by a widely variable amount from day to day. Thus, the standardization of interventions aimed at reducing sedentary time (or increasing it) poses difficulties, especially in free-living studies. Long-term randomized controlled trials have not yet been performed, in part because of those limitations but more importantly because the experimental studies to date have provided remarkably compelling evidence that the mechanisms regulating the effects of inactivity operate in large part almost immediately and do not necessarily require more slowly evolving processes as in other lifestyle interventions. Thus, one outstanding hypothesis is that most of the high-impact effects related to reducing sedentary time may not produce slow and gradual changes in health, as would be required by treatments that impact health primarily by a reduction in body fat.

33.3 SEDENTARY BEHAVIOR DISPLACES SUBSTANTIAL AMOUNTS OF ENERGY EXPENDITURE ASSOCIATED WITH VOLUMES OF LIGHT-INTENSITY PHYSICAL ACTIVITY

Sitting is the most common behavior of adults' waking hours. Accelerometer-derived estimates from total body movement time (which underestimate sitting per se) are some 7.5–9h/ day or more; this can be up to 65 h/week for most age groups.[34,35] The level of muscular contractile activity and the associated energy demand are obviously much lower during the periods of the day that are spent sitting compared to the time spent on the feet and moving around. However, from a measurement perspective it can be challenging to characterize the time that is spent neither sitting nor meeting the criteria for moderate to vigorous physical activity. In part, this is because of the minute-by-minute increases and variability in behavior and contractile activity when up on the feet and moving around. However, the time when not sitting that is spent doing various forms of nonexercise physical activity can reasonably be categorized as light-intensity physical activity (LIPA), with beneficial energy expenditure and metabolic characteristics.[3]

Typical sedentary behaviors require an energy expenditure close to about 1.0 MET or approximately 1 kcal/kg/h, and values much higher than this are likely atypical for sustained periods of sitting. By comparison, moderate to vigorous physical activities such as brisk walking, bicycling, or running are characterized by energy expenditures in the range of 3 to >12 METs. Because these more intense activities will usually account for no more than some 30–40 minutes of adults' waking hours, time spent in sedentary behaviors will primarily displace time spent in LIPA. Such light activities (e.g., household tasks involving standing such as self-care and typical ambulation of modest physical effort such as walking inside houses, stores, and offices) typically require an expenditure <3 METs. The well-defined lower thresholds historically used to define moderate- and vigorous-intensity physical activity have been set at 3 and 6 METs, respectively.

The variability in time that adults spend in sedentary behavior will mostly be offset by the time spend in LIPA. Thus, there is the potential to impact upon obesity and its health consequences through a better understanding of the role of LIPA. This is not only in relation to its contribution to energy expenditure but also through the action of lipoprotein lipase mechanisms in skeletal muscle. It now seems highly plausible that health can be improved by reducing sedentary time and increasing the amount of LIPA.[6,7,30] This is not to discount the importance of moderate to vigorous physical activity that forms a cornerstone of current public health recommendations. Rather, it is to put into perspective the potential significance of sedentary behavior in understanding the complex multiple causes and consequences of obesity.

33.4 ADULTS' SEDENTARY TIME AND LIGHT-INTENSITY AND MODERATE- TO VIGOROUS-INTENSITY PHYSICAL ACTIVITIES: A POPULATION-BASED PERSPECTIVE

The large volume of time spent sedentary as defined by accelerometer measurements that characterize the U.S. adult population is illustrated by Figure 33.3, showing the variation in sedentary time and different intensities of physical activity based on seven days of data from accelerometer measurement.[34] The data are from a nationally representative sample of 1714 white adults aged 20–59 years who took part in NHANES. From these methods, the most sedentary 25% have an average of 10.2 hours (or some 612 minutes) of sedentary time per day. When every minute of accelerometer data exceeding the threshold for moderate to vigorous physical activity (MVPA) is taken into account, the average active time is around 0.3 h/day (18 min/day); in this most sedentary group, there is an average of 4.1 hours (246 minutes) of light-intensity physical activity (LIPA). It appears that sedentary time may displace significant amounts of LIPA. The least sedentary 25% of this population sample averages a little over 40 minutes of MVPA and 456 minutes of LIPA. This is a

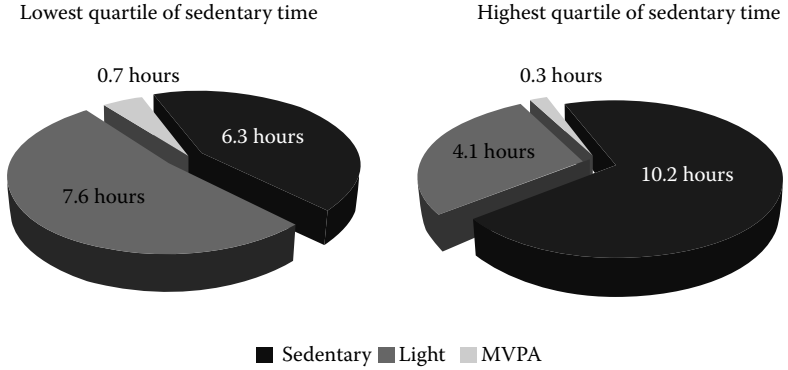

FIGURE 33.3 Bottom and top quartiles of U.S. adults' daily time spent sedentary, in light-intensity activity, and in moderate- to vigorous-intensity activity (MVPA), derived from previously reported findings on accelerometer measurements in a large population-based sample of adults from the U.S. National Health and Nutrition Examination Survey. (From Owen N et al., *Mayo Clin. Proc.*, 85, 1138–41, 2010.)

210 min/day difference in minutes of LIPA between the most sedentary and the least sedentary quartiles of U.S. adults.

When considering all sources of physical activity that impact on human energy expenditure, it is important to appreciate the contribution of the balance between sedentary time and LIPA relative to the time spent exercising. For example, moving from a warehouse work to a desk job could exchange some 2 h/day of LIPA (at about 2.0 METs) for sitting (at about 1.0 MET). This would be associated with a decrease in activity-related energy expenditure of some 10 MET-hours over a 5-day working week—some 647 kcal in a 70 kg person. Such a decrease in energy expenditure would equate to a 20% increase in the approximately 10 h/day that makes up an adult's sedentary time (Figure 33.3). Such an exchange would be entirely within the wide range of intra- and interindividual variability in sedentary time. Notably, this exchange of LIPA for sedentary time would exceed the increase in energy expenditure associated with meeting minimum recommendations for participation in moderate-intensity physical activity.[36] Walking for 150 min/week, involving an increase in energy expenditure from 1.0 to 3.5 METs (a 2.5 MET increase for 2.5 hours, or 6.75 MET-hours), would expend some 437 kcal—substantially less than the 647 kcal of energy expenditure increase from LIPA through a 20% reduction in workday sedentary time.

Thus, the point is that although walking induces a greater increase in energy expenditure per minute, the total time involved is quite small for the vast majority of the adult population. This needs to be contrasted with the entire day in which much more energy expenditure can be accumulated through reductions in sedentary time and increases in LIPA (Figure 33.3).

A theme of inactivity physiology has been to test the hypothesis from the original description of the concept (see the studies by Hamilton and colleagues[1–3]) that inactivity physiology and exercise physiology represent two different sets of physiological stimuli impacting bodily processes. The optimal dose–response parameters (duration, frequency, intensity, and modality) to overcome the physiological processes caused by sitting most of the waking day will be different from the major focus of physical activity and health guidelines.[1] Specific and potent solutions to combat the obesity problems caused by being sedentary for most of the waking day may not be found in traditional exercise programs.[3] Instead, it is necessary to identify specific and effective lifestyle changes capable of reducing sedentary time as much as possible, whether or not the affected people exercise sufficiently.

33.5 SEDENTARY BEHAVIOR AND OBESITY: PRACTICAL CHALLENGES AND RESEARCH OPPORTUNITIES

There is an imperative to conduct further studies of sedentary behavior to inform the obesity prevention agenda. A particular concern for sedentary behavior and obesity research remains the relative dearth of evidence supporting the assumption that changing sedentary behavior in the longer term will significantly impact the likelihood of obesity. The influence of sedentary behavior on key metabolic, inflammatory, and other outcomes is likely to be an important element in the complex causation of obesity and also likely to be a factor that leads to further weight gain and poorer metabolic health in those who are already overweight or obese.

Practical initiatives have already been put forward: observational study evidence on sedentary behavior is such that there are now broad recommendations from the American College of Sports Medicine[36] and from Australia by the National Heart Foundation of Australia[37] on the likely importance of reducing sedentary behavior to improve health outcomes. What is needed most particularly is a body of human experimental evidence—allowing stronger causal inferences about the health effects of too much sitting—without which recommendations on sedentary behavior, obesity, and health will remain general and tentative. The 2010 "Global Recommendations on Physical Activity for Health" document from the World Health Organization[38] notes the potential importance of health outcomes of too much sitting but stops short of making explicit recommendations. Stronger and more comprehensive evidence (Figure 33.4) on sedentary behavior, obesity, and health is thus needed to inform future guidelines and recommendations.[39]

Promising research opportunities in the field of sedentary behavior and obesity include the following:

- Identifying the dose–response relationships and mechanisms linking sedentary behavior with obesity.[39]
- Improving self-report and device-based measures that will be suitable for epidemiological and health behavior studies on sedentary time and obesity.[40,41]
- Identifying the potential moderating role of different types of physical activity in sedentary behavior–obesity relationships, for example, does physically active transport moderate cross-sectional and prospective relationships of sedentary behavior with weight maintenance and weight gain?[42,43]
- Examining the determinants of sedentary behavior and obesity within studies of environment/physical activity relationships[44,45]; by using device-based measures in such studies,[46] it will be feasible to identify sedentary time and breaks in sedentary time and whether these behaviors mediate environment–obesity relationships.[5]
- Conducting intervention trials[47,48] to determine the feasibility of interventions to change sedentary behaviors and whether the maintenance of such changes will prevent weight gain and adverse health consequences.
- Gathering evidence on changes in sedentary behaviors, adiposity, and biomarker changes from "natural experiments," for example, the introduction of height-adjustable workstations or changes in community infrastructure that may act to reduce the time spent sitting in cars.[5]

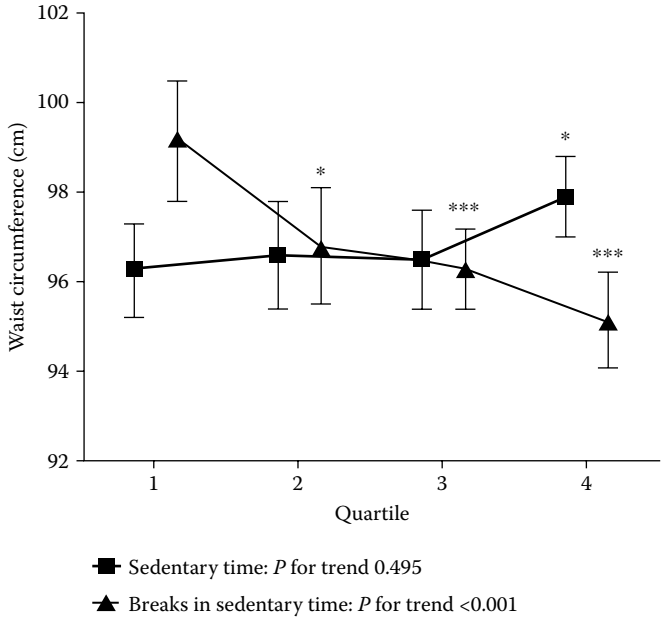

FIGURE 33.4 Associations of sedentary time and breaks in sedentary time with quartiles of waist circumference, adjusted for age, sex, race/ethnicity, moderate- to vigorous-intensity activity, and other potential confounders: breaks in sedentary time are adjusted additionally for total sedentary time. Figure is based on previously reported findings. *$P < 0.05$; ***$P < 0.001$ from quartile 1—reference category. (From Healy GN et al., *Eur. Heart. J.*, 32, 590–7, 2011.)

33.6 CONCLUSIONS

Studies provide evidence that many of the health risks that typically are associated with too little time spent exercising and with excess adiposity may be independently impacted by sedentary behavior, regardless of weight status and how much someone exercises. Thus, sedentary behavior may be seen as a key concern not only because it is related to reductions in energy expenditure that can lead to weight gain but also because there are rapid effects of reduced LIPA due to reduced contractile activity of postural skeletal muscles. For such light-intensity activity, device-based measurement will soon deliver more precise perspectives through advances in the analysis and interpretation of postural and movement-count data based on pattern recognition, machine learning, and neural networks.[49,50] Studies of sedentary behavior are now also able to use biomarker assessments more routinely, significantly reducing the time frames within which inferences can be made about likely impacts on obesity and health.[3,5] Such evidence should point to better targeted obesity prevention and obesity management approaches. It will be crucial to obtain further human experimental evidence, particularly from acute and longer term intervention trials examining dose–response issues and mechanisms.[33,39] Capacities to characterize contextual influences on sedentary behavior should also make important advances. Geographic information systems now allow the routine objective assessment of environmental attributes in neighborhoods and the broader environment, allowing future studies of sedentary behavior and obesity to better account for the roles of such contextual factors.[45,51–53]

Research on sedentary behavior and obesity is at an exciting early stage in its development. Scientific advances are occurring in research addressing underlying biological mechanisms; population-based studies employing biomarkers known to reflect important underlying metabolic, inflammatory, and autonomic processes; behavioral studies supported by more accurate device-derived measures; and studies of the environmental, social, and personal determinants of sedentary behavior and obesity. Further intervention trial findings will soon provide a better understanding of the longer term impacts on obesity of changing sedentary behavior.

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34 Occupational Work and Obesity

Nicholas D. Gilson and Catrine Tudor-Locke

CONTENTS

34.1 INTRODUCTION

Weight changes leading to obesity are fundamentally due to a continuing imbalance in energy intake relative to energy expenditure over time. Any number of factors, reviewed in detail in many chapters in this *Handbook of Obesity*, may act or interact to produce this imbalance. This chapter considers the contribution of occupational work to obesity.

Work is a significant part of many people's lives. Most adults spend a third to almost half their waking day at work,[1,2] and global labor statistics indicate that the number of people employed has increased by half a billion over the past decade, with close to half or 3.1 billion of the world's population being employed in 2010.[3] Women now represent 40% of the global workforce and between 60% and 90% of the world's part-time workers.[4] Many people hold multiple jobs and work longer hours,[5] and overtime, shift work, and unusual work hours are commonplace,[6] as is delaying retirement to an older age.[7] Modern occupational work is highly dynamic, pressurized, continually evolving, often subject to rapid change, and progressively more dependent on technological innovation and international markets.

Given these facts, it is little wonder that occupational work is an important focus area for obesity research, practice, and policy. Moreover, employers are particularly interested in obesity because it impacts revenue. A cross-sectional study of more than 10,000 workers from 49 companies in the Netherlands reported that obesity accounted for more than 10% of sick leaves and losses in productivity.[8] The economic implications for obese employees are also significant. In the United States, for example, the overall estimated impact of obesity on the lifetime earnings of men and women born between 1982 and 1993 was close to $1 trillion.[9]

In this chapter, we focus on how occupational work, physical activity (PA), and sedentary behavior shape energy expenditure and, in turn, how occupational work plays a role in obesity. We then consider recent attempts to increase the energy expenditure of typically low energy expenditure occupations and working conditions. We close with a chronological presentation of review articles of interventions that have addressed obesity-related behaviors through occupational energy balance, first with an explicit focus on PA as a sole contributor to the energy balance equation and then, over time, with the recognition of the contributory roles of diet and sedentary behavior.

34.2 OCCUPATIONAL WORK, PHYSICAL ACTIVITY, AND SEDENTARY BEHAVIOR

PA is classically defined as any bodily movement produced by skeletal muscles that results in energy expenditure.[10] Sedentary behavior specifically refers to activities at the very low end of the energy expenditure continuum[11] (usually defined as 1.0–1.5 metabolic equivalents [METs]; rest = 1 MET = 3.5 mL oxygen/kg/min or approximately 1 kcal/kg/h) and in recent years has become synonymous with sitting time.[12] Occupational work has a role to play in both PA and sedentary behavior, and both behaviors will ultimately impact the energy expenditure side of the energy balance equation. For example, Proper and Hildebrandt[13] surveyed 2417 Dutch workers in 2000–2002 and concluded that work contributed 30% to total daily PA. The relative proportion of daily PA attributed to work varied according to occupational category, with higher proportions reported by those working in agricultural occupations (51%) and lower proportions by those working in policy and higher executive occupations (19.5%). In a follow-up survey,[14] an expanded sample of Dutch workers ($n = 7720$) reported that 30% of daily sitting time was at work and again this varied by occupation, with clerical workers and legislators reporting sitting for proportionally longer periods

(relative to the total day) than agricultural and service sector workers. Furthermore, workers who spent a substantial part of their workday seated did not appear to compensate by adopting a pattern of less sitting outside of work.

Studies that used body-worn, objective devices to measure PA have also illuminated the contributions that occupational work makes to daily accumulated amounts of PA (Figure 34.1). Pedometer studies of Amish farmers[15,16] have indicated that a relatively high number of steps per day (15,000–18,000) are accumulated in the course of low-technology, traditional farming occupations. Steele and Mummery[17] showed that Australian university blue-collar workers (e.g., tradespersons and grounds staff) (8757 steps per day; $n = 30$) took around 5000–6000 more daily steps than university white-collar (e.g., clerical staff) (3616 steps per day; $n = 30$) and professional (e.g., administrators) (2835 steps per day; $n = 30$) workers. In a New Zealand study, Schofield et al.[18] reported similar steps per day for blue-collar workers (10,334; $n = 9$) and lower values for general office (5380; $n = 63$) and university academic (4422; $n = 40$) workers.

In addition to differences in the number of daily steps, it appears that accumulation patterns during the day differ, with stepping rates (i.e., steps accumulated per unit of time) suggesting varying activity intensity. Balogh et al.[19] have provided the only study to date to assess daily stepping rates in different occupational groups. This study reported that cleaners ($n = 48$) accumulated 720 more steps per hour than office workers ($n = 41$) during the working day. Several studies have used accelerometers to describe occupational PA patterns. van Domelen et al.[20] showed that weekday PA levels (measured using mean total activity counts) among full-time U.S. adult workers ($n = 1826$) were 22%–30% higher for those with active occupations (e.g., farmworkers and construction laborers) compared to those employed in low-activity occupations (e.g., secretaries and transport drivers).

As a final example, a study of 21 U.S. workers by McCrady and Levine[21] reported that occupational work, in general, was associated with more sitting time and less walking and standing time. Again, sample size was small, but the data were highly detailed. Using accelerometer and inclinometer data comprising approximately 350 million discrete movements collected over 10 days, the authors found that workers sat more (110 minutes) and stood or walked less (76 minutes) on workdays compared to nonworking days.

In summary, cross-sectional studies using surveys, self-reported behaviors, and objective measures highlight how occupational work shapes both PA and sedentary behavior and therefore, logically, energy expenditure. Workers in agricultural and physical labor–based occupations tend to be the most active, probably because of the high physical demands required for specific work tasks. Conversely, clerical or office workers tend to be the least active at work, with these types of occupations characterized by low physical demands and high levels of sedentary time.

34.3 OCCUPATIONAL WORK AND ENERGY EXPENDITURE

Occupational PA and sedentary behavior combine with resting metabolic rate, the thermic effect of food, and activities outside of work (e.g., travel, domestic chores, and leisure-time PA) to determine total daily energy expenditure. In a review of activities performed in 24 hours by a representative sample of U.S. adults ($n = 7515$), Dong et al.[22] estimated that, excluding sleeping, occupational work contributed to around a quarter of daily energy expenditure. Of the 31 activities identified and ranked by the authors, 10 were occupational (e.g., working in a factory or at a construction site). Office work was the highest occupational contributor (9.2%) to daily energy expenditure and the second highest overall contributor next to driving a car (10.9%).

In 1955, Passmore and Durnin[23] were the first to quantify energy expenditure due to occupations such as office work, light industries, laboring activities, postal delivery, building, mining and quarrying, iron and steel work, agriculture, lumber work, fishing, divers and frogmen, and armed services.

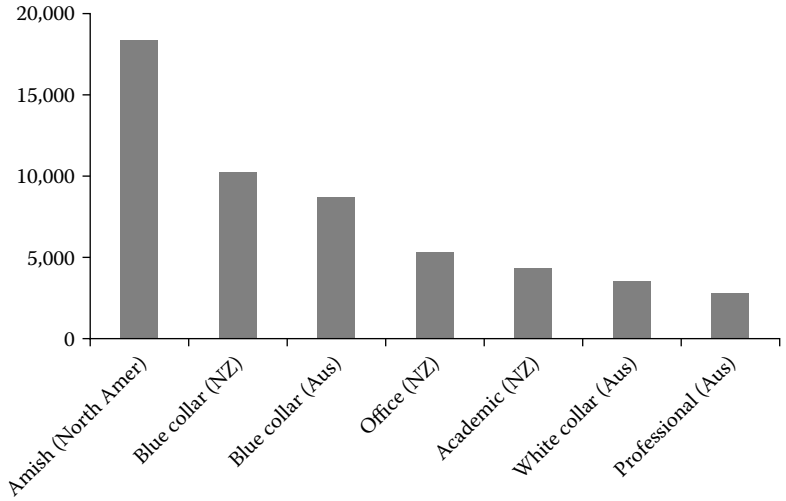

FIGURE 34.1 Average daily step counts in Amish farmers[15] and in Australian[17] and New Zealand[18] workers.

An additional purpose of this original article was to consider what value of energy expenditure could be used to represent a sustainable maximum work capacity. The authors concluded that as a general rule 5 kcal/min represented the upper limit of work that could be sustained day after day, week after week. They suggested that this value, which represented the energy expenditure of work in heavy industry, was roughly equivalent to walking 30 mi./day and, together with the assumed energy expenditure of sleep and nonworking time, corresponded to a total daily energy expenditure of approximately 4300 kcal.

The compendia of physical activities published in 1993,[24] 2000,[25] and 2011[26] have included and expanded on these original occupational energy expenditures, reporting values in METs. Recent occupational work additions to the compendia include treadmill workstation desk (2.3 METs), cook/chef (2.5 METs), property manager (1.8 METs), and laundry worker (3.3 METs).[26]

Recently, Tudor-Locke et al.[27] used the compendia to assign MET values to the 2002 Census Occupational Classification System, a coding system used by U.S. federal statistical agencies and other users to classify and organize 509 separate occupations. Since the U.S. Bureau of Labor Statistics' ongoing American Time Use Survey (http://www.bls.gov/tus/) uses this occupational classification system, Tudor-Locke et al.[27] were able to apply this coding system to the survey data and report population estimates of occupational activity intensity. Overall, as many as 33% (men) to 41% (women) of U.S. workers were engaged in sedentary occupations (<2 METs), with up to 88% engaged in sedentary or light-intensity occupations (<3 METs).

Gilson et al.[28] used accelerometers to measure the proportions of time that Australian office workers spent in different energy expenditure categories (sedentary: <1.6 METs; light: <3.0 METs; moderate: ≥3.0 METs). The sample was small ($n = 11$), but measurement protocols used accelerometer time stamps to identify workplace arrival and departure points. Out of a typical 8-hour day at the office, these workers spent 76% of their time sedentary, 15% in light-intensity activities, and 9% in moderate-intensity activities.

Based on time-use studies, Tudor-Locke et al.[1] reported that U.S. workers employed in sedentary occupations (<1.6 METs) spent approximately 11 h/day sedentary (including working and nonworking time), leaving little time to achieve the recommended levels of PA considered important for overall health. These time-use data are United States centric, but still reflect occupational trends in other developed countries such as Australia[29] and Finland,[30] as well as developing countries such as China[31] where populations are rapidly transitioning from an agrarian to an urban lifestyle and adopting more and more sedentary occupations.

34.4 EVIDENCE LINKING OBESITY WITH LOW OCCUPATIONAL ENERGY EXPENDITURE

In a narrative review of China's growing obesity epidemic, Bauman et al.[32] proposed that low work-related energy expenditure increases the risk of becoming overweight or obese. This section considers evidence relative to this hypothesis by reviewing cross-sectional and longitudinal studies that have examined the relationship between occupational work and overweight or obesity.

34.4.1 Cross-Sectional Studies

Survey-based studies conducted with Polish[33] ($n = 508$) and Spanish[34] ($n = 12{,}044$) workers have reported no associations between occupational energy expenditure and body mass index (BMI). Other survey studies have identified gender differences. For example, occupational PA, BMI, and waist circumference were associated only in women workers in the Swedish population[35] ($n = 1745$). Conversely, Choi et al.[36] reported that low-activity occupations increased the risk of high BMI and waist circumference in U.S. men ($n = 1001$) but not women ($n = 1018$). This risk was particularly pronounced for men who reported working more than 40 h/week.

Survey data from the U.S. National Health and Nutrition Examination Study (NHANES) indicate associations between obesity and occupational energy expenditure, with no gender differences. King et al.[37] evaluated NHANES (1988–1994) BMI and occupational PA in 4889 U.S. adults and found that obesity was 42% higher in workers reporting no leisure-time PA and low levels of occupational PA (e.g., typists) compared to those reporting no leisure-time PA and high levels of occupational PA (e.g., construction trades). Using more recent NHANES data (1999–2004) and the same occupational classifications, Steeves et al.[38] found similar results with workers ($n = 3539$) in high-activity occupations being 37% less likely to be abdominally obese (>102 cm in men and >88 cm in women) compared to workers in low-activity occupations.

An extensive systematic review of the literature (covering 1980–2009) on occupational sitting and health risks by van Uffelen et al.[39] identified 10 cross-sectional studies that evaluated associations with obesity. All these studies relied on self-report measures of both sitting time and BMI. Five out of 10 studies reported positive associations, 4 reported no associations, and 1 reported a negative association. In a subsequent study, not captured in this earlier review, Chau et al.[40] evaluated workers' data from the 2007–2008 Australian National Health Survey ($n = 10{,}785$). Findings showed that the relative risk of being overweight or obese (BMI ≥ 25 kg/m^2) was 12% higher in workers reporting mostly sitting occupations compared to workers reporting mostly standing occupations. This risk was independent of PA and reported leisure-time sitting.

34.4.2 Longitudinal Studies

We identified two longitudinal studies examining relationships between occupational energy expenditure and overweight and obesity over time. Evaluating data from the China Health and Nutrition Survey (1991–2000; $n = 9405$), Monda et al.[41] used detailed interview data to classify participants into light (<2 METs), moderate (<4 METs), and heavy (>6 METs) energy expenditure occupations. Longitudinal analyses based on annual measures carried out over a 9-year time span

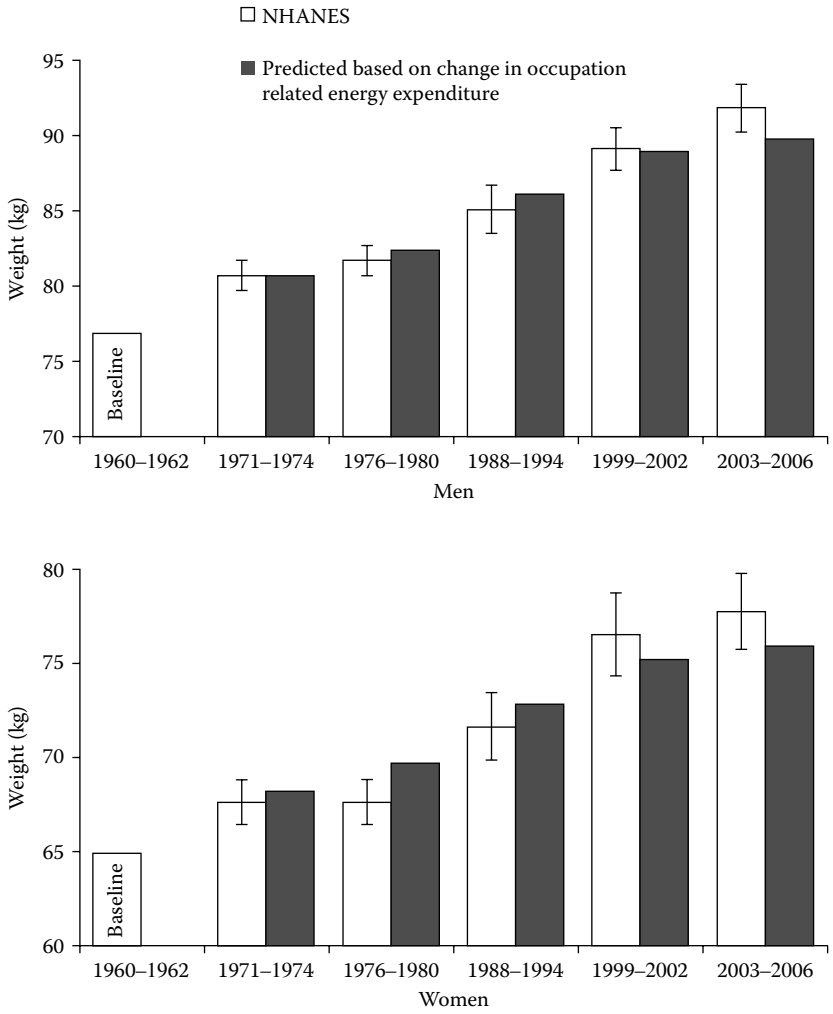

FIGURE 34.2 Predicted (based on change in occupational energy expenditure) and actual (based on National Health and Nutrition Examination Study [NHANES] data) weights of 40- to 50-year-old U.S. men and women from 1960 to 2006. (From Church TS et al., *PLoS One*, 6, e19657, 2011.)

showed that increases in the prevalence of overweight men (12%) and women (9%) coincided with decreases in occupational energy expenditure (22% and 24%, respectively).

A comprehensive, retrospective study by Church et al.[42] used an energy balance model to predict trends in weight gain for working U.S. adults from estimated decreases in occupational energy expenditure from 1960 to 2006. Figure 34.2 shows these predictive trends for men and women relative to actual weight gain as objectively measured by NHANES for the same time period.

The mean predicted weight gain attributed to decreases in occupational energy expenditure closely matched the actual weight gain of 40- to 50-year-olds across five survey time points. This was an ecological analysis, and it cannot be determined whether specific people who decreased their occupational energy expenditure also increased their body weight. However, the authors concluded that occupational energy expenditure alone declined by more than 100 cal/day over the past 50 years in the United States and that this decline was associated with concomitant population levels of weight gain over the same time period.

34.4.3 Summary of Evidence

Cross-sectional evidence supporting a link between occupational energy expenditure and obesity is equivocal and limited by a predominant reliance on subjective measurement of occupational activities and, at times, by self-reported anthropometric data. Longitudinal findings, on the other hand, present more compelling, albeit largely ecological, evidence that reductions in occupational energy expenditure over time have contributed to societal weight gain.

34.5 INCREASING ENERGY EXPENDITURE IN LOW ENERGY EXPENDITURE OCCUPATIONS

Given the current high prevalence of low energy expenditure occupations (i.e., those characterized by relatively low levels of PA and high levels of sedentary behavior), researchers in recent years have started to consider how modern occupational practices and environments could be enriched to facilitate, rather than discourage, increased energy expenditure.

Studies have principally focused on office workers. For example, an early initiative to replace sitting on an office chair with sitting on an exercise ball was dispelled somewhat by research demonstrating that there were no significant differences in muscle activation between the two types of sitting and that sitting on a ball was associated with increased discomfort.[43–45] Eves and Webb[46] reviewed studies of stair-climbing interventions delivered at the workplace. The interventions typically consisted of "point of decision prompts" in the form of strategically placed signage. There was some modest evidence of increased stair usage across studies, but it appeared to be more in favor of going downstairs rather than climbing stairs.

Gilson et al.[28] evaluated the impact of shared access to sit–stand desks (i.e., height-adjustable desks that workers can use in either a sitting or a standing position) in an open-plan office on the percentage of time spent being sedentary at work (<1.5 METs). Desk use varied between employees, with no overall effect on the proportion of sedentary work time. In 2007, McAlpine et al.[47] described a "stepping device" (built with hydraulic resistance tubes) that could be stored under a standard desk, plugged into an office computer for self-monitoring purposes, and pulled out for use at opportune times (e.g., during a telephone call, while reviewing a document, during a work break, and while talking with a colleague). Piloted in 19 sedentary volunteers, of whom 10 were obese, the stepping device was associated with a mean energy expenditure of 289 kcal/h (and greater for obese vs. normal-weight persons) above that expended while sitting in an office chair.

Levine and Miller[48] introduced the "walk-and-work desk" or workstation in 2007. This workstation allowed an office worker to use a computer while walking at a self-selected speed on a treadmill positioned underneath and perpendicular to a desk. On average, the energy expenditure of 16 obese and sedentary office workers while seated at work was 72 kcal/h and while walking at 1.1 mph was 191 kcal/h, that is, effectively a mean increase of 119 kcal/h.

Subsequently, Thompson et al.[49] described a feasibility study with nurses, clinical assistants, and secretaries using the treadmill workstation. Researchers collected objectively monitored PA and demonstrated an average increase of 2000 steps per day, equivalent to approximately 100 kcal/day. They also reported that the workstations were well received and could be used in a real-life work setting. In a follow-up study, Thompson and Levine[50] reported that the accuracy of transcription did not differ between working while sitting and working while using the treadmill workstation; however, the speed of transcription was reduced by 16% with the workstation, suggesting that additional training and/or familiarization would be necessary to prevent a significant drop in employee productivity. John et al.[51] also conducted a study focused on the performance of simulated work tasks while treadmill walking. They documented a 6%–11% decrease in measures of fine motor skills and math problem solving while treadmill walking, but there was no difference in selective attention, processing speed, or reading comprehension relative to the seated condition.

Finally, John et al.[52] reported the pre–post impact of a 9-month treadmill workstation pilot intervention on PA and anthropometric, cardiovascular, and metabolic variables in 12 overweight/obese and sedentary office workers. Participants were not given any recommendations regarding duration or speed of walking while working, but rather they were allowed to use the workstation as they preferred. Between baseline and 9 months, median steps per day increased from 4352 to 7080, average waist circumference decreased by 5.5 cm, and hip circumference decreased by an average of 4.8 cm. However, body weight and mean percentage body fat did not significantly change.

In summary, studies aimed at increasing energy expenditure in office workers have focused on integrating low-intensity, incidental movement strategies into the working day. With the exception of stair climbing, solutions have typically been delivered through an adaptive working position or condition. Studies tend to be small, preliminary, and uncontrolled but also novel and creative in their approaches. Results show promise, and more rigorous studies in this area are likely to be performed.

34.6 ENERGY BALANCE: A SUMMARY OF WORKPLACE INTERVENTIONS

As we stated in Section 34.1, most adults spend a great deal of their time and attention at the modern workplace, making it an obvious delivery channel to intervene on body weight–related behaviors, specifically PA and dietary behavior. Therefore, it should not be surprising that a number of qualitative and quantitative reviews of workplace behavior interventions have been published in recent years. These reviews have reported effects on body weight–related behaviors (e.g., PA, sedentary behavior, and diet) and weight-related outcomes (e.g., weight, BMI, and body fat percentage). Each was conducted according to different aims, behavioral and outcome definitions, search strategies, inclusion and exclusion criteria, and analytic strategies. Although there is some overlap, we offer here, in the penultimate section of our chapter, a short summary of the most salient reported findings.

In one of the first reviews, Dishman et al.[53] in 1998 identified 26 studies of workplace PA interventions and determined that overall they did not report statistically significant increases in PA or fitness. Any small observed effects were not sustained over time. The authors cautioned that conclusions about the ineffectiveness of workplace PA interventions were premature, given the generally poor scientific quality of the research up to that time, including a reliance on subjective assessment of behavioral change.

In 2003, Proper et al.[54] reviewed the literature again, looking at the effects of workplace interventions on PA and health (including body weight–related outcomes). They concluded, on the basis of two high-quality randomized controlled trials (RCTs) published since the previous review, that there was a significant intervention effect on PA level. They also determined that there was inconclusive evidence of a workplace

PA intervention effect on body weight or body composition. A lack of effect was attributed to the observation that participants in the reviewed studies were generally healthy and nonobese and therefore anticipated changes would be small. An alternative explanation presented was that the behavioral changes resulting from the interventions were too small to effect a change in body weight or body composition. The authors of this review noted that adherence to programs was generally poorly reported, and they pointed out a lack of objective measurement of PA behaviors.

Engbers et al.[55] assembled RCTs of workplace health promotion programs with environmental modifications targeting several health behaviors. They located 13, primarily multicenter, trials focused on stimulating healthy dietary behavior, with only 3 focused on PA. Based on the number of studies and the strength of the evidence obtained, it was concluded that workplace health promotion programs including environmental modifications have the potential to positively influence dietary behavior. However, they found no evidence that the identified workplace health promotion programs had an effect on health outcomes, including BMI. The authors of this review called for more high-quality studies, especially those focused on PA in the occupational setting.

Matson-Koffman et al.[56] included workplace-specific interventions in their literature review of experimental and quasi-experimental policy and environmental interventions. They noted that fewer policy and environmental interventions were aimed at PA ($n = 5$) than dietary behavior ($n = 56$). However, they concluded that workplace policy and environmental strategies may promote both PA and good nutrition. The strongest evidence was for interventions including prompts to increase stair use, education, employee and peer support for PA, incentives, access to fitness facilities, availability/labeling of nutritious foods, and point-of-decision purchase placement/promotion/pricing strategies.

In a review of workplace PA interventions, Dugdill et al.[57] specifically sought to identify which types of interventions were most effective in inducing behavioral change. They concluded that the effectiveness of stair-climbing interventions was limited and short-lived, workplace counseling increased PA, and public sector workplace pedometer interventions showed evidence of increasing steps per day (if accompanied by facilitated goal setting, diaries and self-monitoring, and walking routes). Uniquely, the review also included an intervention demonstrating some positive changes in increasing the frequency of walking to work. A limitation of this review was that it did not include U.S./Asian studies as it was commissioned, and therefore focused, on the United Kingdom.

Kremers et al.[58] conducted a systematic literature review of overweight and obesity prevention interventions in adults and included five workplace PA and/or dietary behavior interventions among 46 identified studies. When the primary aim of the interventions was weight management, intervention effects were stronger. The inclusion of formative evaluation was also associated with a stronger effect. The age of participants was negatively associated with effect. The authors noted that longer interventions are required to form conclusions about the sustainability of behavior change and effects on weight.

Anderson et al.[59] reviewed the effectiveness of workplace interventions controlling for employee overweight and obesity, and they included interventions focused on changes in body weight, BMI, and percentage body fat. They concluded that there was a modest reduction in weight as a result of workplace interventions aimed at improving PA, dietary behavior, or both. Generally, those programs offering more components or more intensive components realized the greatest effects. They reported no important differences in effects for programs delivered by lay versus professional group leaders.

Most recently, in 2011, Verweij et al.[60] conducted a meta-analysis of the effects of workplace PA and dietary behavior interventions on weight outcomes, including only RCTs and excluding studies focused on weight loss and those conducted only among overweight and obese samples. Thus, the focus was more on primary and secondary prevention of weight gain. They concluded that there is moderate quality of evidence that combined interventions (i.e., targeting both PA and diet) have moderate effects on weight outcomes. There was low quality of evidence that interventions focused only on PA have similar effects and no evidence on those focused on dietary behavior, only because of a lack of this type of study. Subgroup analyses did not show a relevant change (>20%) in body weight by follow-up duration (6 or >6 months). Analysis by intervention components showed a greater effect on body weight from combined PA and dietary behavior interventions that also had an environmental component versus those that did not. The catalog of environmental components ranged from walking routes, maps, friendly competitions, reminders/prompts, and family involvement to business goals and management commitment.

The literature reviews of PA interventions in the workplace have primarily focused on promoting exercise (e.g., access to fitness facilities). There is less evidence to inform the effectiveness of workplace interventions seeking to reduce a fundamental behavior of many modern occupations—sitting time—although a small body of literature has studied point-of-decision prompts, notably taking the stairs at work. Chau et al.[61] undertook a systematic review of interventions to reduce sitting time. They located six PA intervention studies that also included reducing sitting as a secondary study outcome. All studies relied on self-reported sitting. Only one specifically focused on occupational sitting behavior[62]; the rest used a general measure. None of the workplace interventions had a documented effect on sitting behaviors. Given the notable associations of prolonged sitting with deleterious health outcomes, and the fact that the modern workplace is largely characterized by such a behavior, the authors called for more research into the effectiveness of workplace interventions to reduce occupational sitting time. This recommendation should also logically extend to intervention effects on a range of theoretically associated health behaviors including weight-related outcomes.

A number of points about workplace PA and dietary interventions can be gleaned from this collection of reviews. There continues to be a need for theory-based program design based on contemporary theories of behavioral and organizational change. There also appears to be a need to expand the spectrum of what constitutes a PA intervention to include not only exercise but also nonexercise PA (e.g., the emergence of treadmill workstation desks), reducing/breaking up sitting behaviors, and the energy balance–promoting opportunity of the daily journey to and from work. Multicomponent interventions may indeed provide the largest effect, but they also obscure important component effects, potential redundancies, unintended effects, and possibly opposing effects. Strategy development should recognize that the workplace is not isolated from the greater lifestyle of the individual, which also includes the home, family, and community.

There is also little evidence at this time to inform behavioral mechanisms of change, including mediating/moderating effects on intervention effectiveness. There has been an almost unanimous call to move measurement approaches beyond the subjective assessment of change. This will include objective monitoring of PA and sitting behaviors and tracking actual sales or individual food purchases. Longer term follow-up is also required for all behaviors that are intervened on, as well as associated body weight–related outcomes. Finally, it appears that formative and process evaluation are necessary in addition to outcome evaluation and that participatory action research strategies would help to engage collaboration with employers, personnel, and management.

34.7 CONCLUSIONS

Subjective and objective assessments indicate that the PA and sedentary behavior requirements of occupational work vary widely, and together these contribute to occupational energy expenditure. There is evidence to suggest that low energy expenditure occupations are now the norm in society and that workers engaged in these types of occupations are at increased risk of obesity. Recognition of this risk has spurred research into workplace interventions that have evolved from program-focused exercise opportunities outside of working time to more recent attempts to modify working conditions, workstations, and environments to facilitate increased energy expenditure. More and more, it also appears that efforts to address occupational energy imbalances are moving beyond interventions that look only at the energy expenditure side of the equation, shifting to multicomponent interventions that aim to maximize benefits through concomitant changes in PA, sedentary behavior, and diet.

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35 Leisure-Time Physical Activity and Obesity

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CONTENTS

35.1 INTRODUCTION

Central to body weight regulation is the delicate balance between energy intake and energy expenditure, typically referred to as energy balance. The interest in physical activity (PA) as an important lifestyle behavior in part stems from the understanding that PA is a means to increase energy expenditure. PA behavior is in fact the largest modifiable component of energy expenditure[1] and is assumed to be one of the major behavioral determinants affecting the dramatic increase in obesity over the past decades.[2–6] According to definitions by the World Health Organization[7] and Centers for Disease Control and Prevention (CDC),[8] PA refers to all bodily movement produced by the contraction of skeletal muscle that substantially increases energy expenditure. Specifically, leisure-time physical activity (LTPA) is referred to as all physically active hobbies, exercises, and sports performed in one's leisure time.[8]

35.2 CHILDREN

Most children are presented with opportunities for being physically active in school and out of school. Schooling is mandatory in most countries and, as such, physical education (PE) in school is not considered part of child LTPA. However, as recess and out–of-school hours are part of a child's leisure time or free time, activities performed during those times may be considered as LTPA. Nevertheless, child LTPA is not always well defined[9,10] and various definitions have been used. For example, in a 2009 review of school-based PA programs, LTPA was defined as all PA performed outside of school hours excluding PA performed during recess.[11] Another example used the definition of LTPA as PA occurring outside of school hours excluding recess and also excluding organized sports outside of school hours.[12] For the purposes of this chapter, child LTPA is defined as PA performed during leisure time, thus both during recess and occurring outside of school hours. Additionally, as there are different but distinct types of activities performed during leisure time (e.g., organized sports, active transport, and free play), and as different types of activities may be affected by differing behavioral and environmental factors, which are possibly independently associated with obesity among children, the potential association of types of activities and obesity is reviewed.

In general, child PA patterns vary greatly from those displayed by adults. Typically, PA among children is sporadic and varies in intensity, as children seem to have a preference for interval-type activities over more sustained types of activities.[13] Children thus have less structured activity patterns than adults and their natural PA patterns are more likely to consist of short-duration bouts, especially during play, although as they mature and develop their activity patterns become increasingly more structured and similar to adult patterns of PA. For elementary-school children, it has been estimated that the majority of their activity bouts last between 3 and 22 seconds,[14,15] which has considerable implications for accurately measuring, processing, and

interpreting child PA data and indicates a need for using short-interval-type measures administered over a period of a few days in child PA research (such as accelerometers with small epoch capabilities). Among children, even more than among adults, relying on self-reported data can be questionable and, although increasingly objective methods such as accelerometers are being used in child PA research, much of the current evidence has been derived from self-reports, which may threaten the accuracy of that data.

35.2.1 Secular Trends of Child Leisure-Time Physical Activity

Limited data exist on changes in levels of PA among children and adolescents over time, and specifically on changes in LTPAs (e.g., active transport, organized sports, and unstructured PA during recess and after school). Varying definitions and types of PA, differing methodologies (instruments used and administration modes), and the age range of youth studied make general conclusions about changes over time problematic. This issue is highlighted by the conclusions of two recent reviews on time trends in general levels of PA among youth over time. The authors of the first review,[16] which included nine studies mostly relying on self-reported data, concluded that although the results from the studies varied, overall, levels of PA seemed to have declined over time. The authors of the second review,[17] including eight more studies with three using objective measures of PA, concluded that the methodological problems and issues surrounding self-reports did not lend themselves to accurate assessment of temporal trends in children's PA levels over time. They concluded that available data do not support that PA levels have declined in youth during the past two decades. Data on the secular trends of general child PA levels therefore remain inconclusive.

We can also examine time trends in the specific types of PA (active transport, sports, and unstructured PA). Data seem to support a decline over time in active means of transport as more children are being driven from one place to another instead of walking or riding bicycles, a finding that has been documented in numerous countries around the world.[18–21] In the United States specifically, rates of active transport among schoolchildren aged 5–15 years dropped dramatically between the years 1969 and 2001, that is, from 48% to 16%.[22,23] For time trends in sports participation, study results include an observed decrease in participation in organized sports over time,[24] no changes observed over time,[25] as well as an observed increase in sports participation over time.[26–28] Potentially, the lack of a unified definition of organized sports, the variability in the methods and measures used, and the particular age range of the children under study in addition to the various cultural environments wherein the studies take place may complicate matters and partly explain why no consistent patterns in time trends for sports participation have been found over time.

For changes in unstructured PA (physically active free play), declines over the last few decades are commonly assumed. The major contributing factors implicated are the ever-increasing time spent on electronic and screen-based entertainment, reduced access of children to free play, and especially reduced outdoor play both at school and in out-of-school contexts. According to a recent review, child self-reported time spent in screen-based and non-screen-based sedentary behaviors ranges from 4.7 to 8.0 h/day (3.6–8.1 h/day as measured by accelerometers).[29] Also, according to the American Academy of Pediatrics the average child watches nearly 3 h/day of television (TV).[30] Screen-based sedentary behaviors thus take up a considerable amount of children's time otherwise available for unstructured PA. This conclusion is supported by findings from studies on child leisure-time activities, which show sedentary behaviors such as TV and homework to be the most common leisure-time activities of elementary schoolchildren.[31,32] Notably, since the 1970s children in the United States have lost about 12 hours a week of free time, including a 25% decrease in play and a 50% decrease in unstructured outdoor activities.[33] For school-aged children recess can be an important source of opportunity for daily PA,[34] and some data suggest that children can be highly physically active during school playtime.[35,36] However, the No Child Left Behind Act of 2001 prompted school districts in the United States to allocate more time and resources into reading and mathematics and, as a result, school programs such as art, physical education, and recess have suffered cutbacks.[37] Changes in the built environment, such as limited access to open space, playgrounds, and sidewalks, have additionally affected the amount of opportunities available to children for outdoor activity, which has been shown to significantly contribute to child PA levels.[39] It thus seems plausible that these factors and others may have contributed to a decrease in active play over time and potentially contributed to the rise in childhood obesity, but studies directly tracking changes in unstructured PA and free play over time have not been reported.

Instinctively, it seems plausible that changes may have been occurring concomitantly in levels of PA and obesity among children. However, methodological difficulties in capturing reliable baseline data pose challenges to such studies. Much remains unknown about changes over time in child PA and LTPA specifically. Current evidence shows that a large percentage of children around the world are not meeting the recommended levels of general PA of 60 minutes on at least 5 day/week,[17,40] which is of concern given the vast data documenting the beneficial effects of PA on physical health,[41–50] cognitive development, academic achievement,[45,51–62] and mental health.[63] Therefore, this remains an intriguing area of study; but ultimately other types of studies may be more helpful in elucidating the association between PA, and LTPA specifically, and obesity among children.

35.2.2 Cross-Sectional Studies

Most studies to date on the association of PA and obesity have been cross-sectional studies. In those studies, child and adolescent PA levels have consistently been negatively correlated

with weight status.[64–68] Specifically, according to findings from cross-sectional studies lower weight status seems to be significantly associated with increased time spent in vigorous PA and not lower intensity PA.[50,68–71] The cross-sectional association between higher levels of PA and lower weight status has been reported by a large number of high-quality studies. For example, a 2010 systematic review included 48 cross-sectional studies all published in the years of 2004–2008. In the studies reviewed, PA levels of children in the age range of 0–18 years were analyzed regarding an association between objectively measured PA and weight status/adiposity.[72] Consistent evidence was found for negative associations between PA and weight status, providing strong evidence[73] in favor of the existence of such an association.

Despite the vast evidence documenting a cross-sectional association of weight status and general PA levels among children, limited information exists on the cross-sectional association between child LTPA specifically and obesity. Most studies have only considered weight status in relation to a global measure of PA, such as daily minutes of moderate to vigorous physical activity (MVPA), leaving it open to question how the different types of activities may contribute to the observed association. Yet some data are available to support that lower levels of PA among overweight and obese children than among normal-weight children may be related to their lower participation rates in organized sports.[74–77] Still other sources of data do not confirm these findings, and a recent review of 19 studies comparing sports participants with nonparticipants on weight status and PA found no clear pattern of association between body weight and sports participation.[78] Although in 17 studies of the 19 reviewed sports participants were found to be more physically active than those who did not participate, association with weight status was inconclusive.

Active transport (in this case, cycling to school) has been found to be associated with a lower weight status in adolescents in the Netherlands and in Norway.[79] Also, from reviews of the association between active commuting to school and PA or weight in children[80,81] and from a recent large study on adolescents from 10 European cities,[82] a positive association between active commuting and overall PA levels is suggested. However, only a few of the studies that examined the association of active commuting with weight status found consistent results for association with weight status, indicating that there might not necessarily be an association between active transport and reduced weight or body mass index (BMI).[80,81] Current findings on the cross-sectional association of active transport and childhood obesity thus do not lead to a definite conclusion.

No studies were located that directly assessed the cross-sectional association of free play and overweight/obesity among children, although one study was found that documented the association of free play and general levels of PA. The results of that study suggest that children who spend more time outdoors are more active.[39] Also, another study found that adolescent boys and girls categorized as highly active reported more outside activities than those categorized as less active.[83] Thus, outdoor play and its contribution to child general PA levels and association with overweight/obesity warrants further study.

In summary, child general levels of PA seem to be negatively correlated with weight status and, although the various types of activities may contribute in different ways to the general levels of PA and this in turn may be important for informing intervention efforts, limited evidence exists on the role of child LTPA and the various types of PA in contributing to the association observed.

35.2.3 Cohort Studies (Longitudinal Studies)

Compared to the vast number of cross-sectional studies examining the association of PA and weight status among children, only a few longitudinal studies have been undertaken and only a handful of studies have described associations between child LTPA and obesity. A 2010 systematic review of the association of PA and obesity among children was limited to studies with objectively measured PA.[84] In that review, seven longitudinal studies (published between 2004 and 2008) were included in which children aged 3–15 years at baseline were followed for 2–3 years. In six out of the seven studies, higher levels of PA were predictive of lower weight/adiposity status over time. A study published in 2009 also reported an inverse association between MVPA and BMI and fat mass,[85] consistent with the conclusions from the review. Moreover, a newly published review on studies of the association of PA levels and overweight and obesity among preschoolers only (aged 4–6 years at baseline) reported strong evidence for an inverse association between total PA and overweight.[86]

As cross-sectional studies do not demonstrate causality, and as PA may be both an antecedent and a consequence of obesity, corroborative findings from longitudinal studies are important. The available evidence from longitudinal studies confirms the findings of cross-sectional studies, indicating an association between higher levels of PA and decreased relative weight and less fatness. A higher level of PA thus may be concluded as protective of excessive weight gain during childhood.[72,85–89]

Longitudinal studies of associations between child LTPA and obesity are scarce. Three studies were located examining the role of active transport in the prevention of excessive weight gain. Rosenberg et al.[90] found that for elementary school students boys who actively commuted to school had a better weight status than nonactive commuters at baseline. Yet active commuting to school over 2 years was not associated with a change in weight status. The authors concluded that active transport to school may contribute to preventing excessive weight gain, or leaner children may walk or cycle to school. The second longitudinal study, in which children were followed for over 6 years,[91] found that participants who did not cycle to school at baseline but who had changed to cycling at follow-up had a significantly better weight status than those who did not cycle to school at either time point. In the third longitudinal study assessing the effects of active transport for adolescents aged approximately 13 years at

baseline,[92] those who stopped cycling over the time of follow-up (2 years) were more likely to be overweight at follow-up, whereas those who continued cycling were less likely to be overweight compared to other groups. Although data are limited, the results from these studies support a potential beneficial effect of active transport on child weight status over time.

Additionally, two longitudinal studies on the role of sports in preventing excessive weight gain[93,94] were located. Lajunen et al.[93] found that among boys (aged 11 or 12 years at baseline) participation in sports reduced the later risk of being overweight (followed up at ages 14 and 17). Also, Ara et al.[94] found that boys aged 9.4 years at baseline who were classified as physically active (3 hours or more of sports activities during leisure time) were protected against total and regional fat mass accumulation 3.3 years later. The limited longitudinal data available on the role of LTPA in childhood obesity suggest both active transportation and sports participation may be protective of excessive weight gain over time; but more studies are needed, including studies of the role of active play and specifically outdoor play.

35.2.4 Intervention Studies

As PA has been identified as a correlate and a predictor of childhood obesity from cross-sectional as well as longitudinal studies, it lends itself as an obvious target for childhood obesity prevention and intervention. A number of intervention studies aimed at increasing general levels of PA have been performed in educational settings.[11] However, according to reviews made in 2009[11,95] school-based intervention studies that solely focus on increasing levels of PA usually have not had an effect on weight status. Multicomponent school-based interventions including a PA component have been found effective in helping to lower child weight,[96] but the relative contribution of including a PA component has not been assessed. PA components are also frequently included in weight management programs for children who are already overweight or obese, but the effects of those specific components, and their relative contributions to the interventions, have not been studied. As no studies have assessed the relative contribution of either PA or LTPA in the prevention or treatment of overweight and obesity among children,[87] the relative effects of PA in multicomponent childhood overweight/obesity interventions is largely unknown.

Very few intervention studies have been undertaken with the aim to specifically increase LTPA or the different types of LTPA. Two sports-related intervention studies for children who were already overweight or obese were located. One study on overweight fourth and fifth graders detected significant increases in PA and decreases in BMI at 3 and 6 months after participation in a soccer group compared to a health education group.[97] The other study included a week-long sports camp and a 6-month support program. Compared to a waiting-list control group, no differences were found in changes in weight status between the groups.[98] No conclusions in relation to the role of PA in the treatment of childhood overweight and obesity can be drawn from this limited data, and additional research is needed. As sports participation seems to be longitudinally associated with better weight outcomes,[93,94] more research on sports and sports participation among children may foster an understanding about how sports, and youth sports settings, can help promote energy balance and healthy body weight.[78]

Increasing PA during recess has been suggested as a helpful way to increase child general levels of PA, and some data are available to suggest that schools that facilitate PA by maintaining playgrounds and providing PE classes have more active children and that children at such schools are less overweight.[99,100] Playground intervention studies aiming to increase child PA levels nevertheless show conflicting results. One study among children in U.K. elementary schools did not find statistical short-term differences for child PA levels between children at intervention and non-intervention schools,[101] and a study at the preschool level was not able to detect significant intervention effects either.[102] However, other studies intervening at the elementary school level have shown significant effects for recess-/playground-based interventions;[103–106] but more studies are needed, especially studies looking into the determinants of effective interventions.

Some data support longitudinal beneficial effects of active transport on child weight status over time,[90–92] and active transport has been suggested as a means to provide a source of habitual PA for children. It has been suggested that habitual PA may be especially important for adolescent girls, among whom low and declining PA levels have been reported all over the world.[107] Active transport might provide exactly this sort of habitual PA. A recent study found that a decline with age in MVPA was associated with a greater increase in weight status in boys but not girls.[108] Sports settings that provide MVPA might thus be the intervention of choice to prevent a decline with age in PA for boys, whereas active transport may be more sustainable as a way to provide habitual PA and reduce decline in PA with age among girls. Alternatively, interventions at either settings may work equally well for both genders. Most likely, using the different types of PA to avoid mid-to-late childhood reductions in MVPA by effectively intervening at that age may reduce excessive weight gain and positively impact both boys and girls. However, the mechanisms, determinants, and barriers of change may vary across gender and are areas that require further study.

Several interventions with the established aim of increasing active transport have been successful, such as the Safe Routes to School Program in Marin County, California,[109] that helped communities to identify and create safe routes to schools. In 2 years, this program was successful in increasing school trips made by walking and biking by 64% and 114%, respectively, as reported by the participating public schools. A recent review on intervention studies related to active transport found 14 interventions (including the Marin County intervention) that focused on active transportation to school. These interventions mainly focused

on elementary school children. Out of the 14 studies, 6/12 interventions reported a small effect size on active transport, 3/12 reported larger effect sizes (including the Marin County intervention), and 3/12 reported a trivial effect size (effect sizes were not calculated for 2 studies with insufficient data). It was concluded that more research with higher quality study designs and measures should be conducted as low methodological quality of many of the interventions likely contributed to the generally small intervention effects observed.[110]

Data from cross-sectional and longitudinal studies support the association of PA and weight status among children, but they are less clear about the role of different types of PA. In general, more intervention studies are needed to further our understanding of the role of PA and LTPA in childhood obesity.

Most intervention studies aiming to prevent or reverse excessive weight gain have been performed in school-based settings. Intervening in schools where children spend a large part of their day may incorporate the notion of importance of PA in a child's daily life and help enforce PA as a lifelong habit. However, as a number of studies have demonstrated that parents' levels of PA and child levels of PA are associated,[111–115] especially mothers' levels of PA and child levels of PA,[116] including parents in interventions and increasing their levels of PA may be equally important in studies of PA levels in children. Specifically, intervening at the family level may be important for preschoolers where parental involvement may be critical for improving PA levels.[117] In general, comprehensive interventions that focus on multiple behavioral settings and provide abundant opportunities for PA across settings may be what is needed to enhance youth health and arrest the obesity epidemic.[11] In addition to school-based intervention efforts, studies aiming at after-school programs and out-of-school settings are suggested. Data support that a large proportion of PA in children occurs after school.[118] Some evidence has shown that after-school programs can improve PA levels,[119] which may be important as activity levels in after-school programs are oftentimes well below recommendations.[120] However, current findings from after-school interventions to increase PA in youth are mixed,[121] so further studies are needed to explore the potential of intervening in after-school settings.

Intervening in child-care centers also requires more research as a body of high-quality evidence is consistent in suggesting that PA levels within child-care centers are typically very low and levels of sedentary behavior are typically high.[84] Other potential settings for future intervention include sports clubs and recreation centers in the community, health clubs/fitness centers, getting the community involved in organizing PA at a local park, initiating walking school buses, as well as breaking down environmental barriers for active lifestyles in the community. Much remains unexplored and intervening at multiple socio-environmental levels and engaging the community to increase levels of PA for the entire family may be the route to child and adolescent wellness and lifelong health.

35.2.5 Methodological Challenges and Future Research on Leisure-Time Physical Activity and Obesity among Children

Research is scarce on the association of LTPA and obesity among children, preventing firm conclusions from being drawn. The major challenge in assessing the association of child LTPA and obesity is the general lack of attention to LTPA, but beyond that another challenge is limited attention to the role of specific types of PA in child PA research. Methodological challenges include the varying definitions of LTPA (with even organized sports being defined in a number of different ways), the different types of outcome measures used for PA, and the use of prone-to-bias self-reported data. As no questionnaires have been found to have both acceptable reliability and validity,[122] objective measures of PA, and more accelerometer data in particular, are needed for future studies for valid and reliable PA measures.

In general, there is a need for a clear and uniform definition of LTPA and the different types of PA. Also, there is a need for established best practice, standardized measurements of PA and LTPA, as well as weight status, in PA studies. When looking at PA levels, specifically participation in sports, and their relationship with weight status, using BMI as the only outcome measure may bias results, as children and adolescents who participate in sports may be more muscular than those who do not. As such, differential body composition may cause a systematic error in findings reported for differences in weight status between sports participants and non–sports participants toward no difference being detected.[78] Additional weight status outcomes are encouraged to address changes in body fat and lean body mass and not just BMI.

Without a doubt, methodological challenges play a part in the heterogeneity of results observed from the few published studies on the association of LTPA and childhood obesity. More studies and methodological improvements in future studies will advance our understanding of the role of PA in childhood obesity. Studying the effects of increasing different types of PA may enhance our knowledge on how PA may serve to prevent and/or treat excessive weight. Currently, intervention studies among children include a variety of approaches. This fact, combined with the heterogeneous measures used to assess the impact of interventions, limits our ability to draw firm conclusions about the best interventions for effective behavior change. There is a strong need to assess the relative value of PA in multicomponent interventions and to include longer term follow-up as such data are almost entirely lacking. A variety of positive intervention impacts have been reported from different studies; but only a limited number report postintervention follow-up, which makes it difficult to have confidence that the outcomes of often short-term interventions are sustained over the longer term. Maintaining new behavior is challenging, although it is what is most important for sustained behavior change and improvements in health outcomes in the longer term.

PA seems to be an important determinant of weight status among children. However, very limited data are available on the specific association of LTPA and obesity among children,

and much work is needed in this area. Studying the different types of PA, and not just general PA levels, at different ages and across gender to establish the role of PA, as well as effective types of PA interventions for different age groups and gender, is warranted. In general, levels of PA seem to decline as children get older,[123] and gender seems to be a significant predictor of PA levels across age with boys being more active than girls from preschool and throughout adolescence.[14,123,124] Different determinants may apply across gender and at different ages. Furthermore, different types of PA may appeal to different groups. Assessing these factors may allow for more effective development of prevention and intervention as well as tailoring of already established interventions. Effective interventions are needed to reduce the observed decline in PA levels with higher age and among girls especially. Assessing the determinants of PA and the different types of PA is important, and mediation analysis should be performed in intervention studies to help in the development and revision of interventions. Exploring whether increasing the different types of PA during intervention studies is warranted, as well as intervening in more varied settings, as most studies to date have been performed in school-based settings. Finally, lower weight status seems to be significantly associated with increased time spent in vigorous PA as opposed to lower intensity PA.[50,68–71] Yet, little is known about the dose–response effect of PA on young people's health and weight status. More information on the potential dose–response effects of different types of PA and on weight status is needed.

35.3 ADULTS

35.3.1 Secular Trends of Adult Leisure-Time Physical Activity

Secular changes in patterns of PA over time have been reported among adults. Brownson et al.[125] performed a review of data from the United States, describing patterns and trends in activity levels, occupation, and transportation over time. They concluded that LTPA had remained relatively stable and perhaps even increased slightly over time, whereas work-related activity, active transport, and activity in the home had decreased over time, leading to an overall trend of declining total PA levels. Consistent with the conclusion of Brownson et al., Ng and Popkin,[126] in a more recent review on patterns across the globe, also concluded that levels of PA had declined with the exception of LTPA.[125] In both of these studies the definition of LTPA did not include active transportation, but rates of active transportation were found to have decreased over time.

The results of these reviews indicate a general decline in levels of PA over time occurring concomitantly with the increased rates of obesity observed across the globe. However, the role of LTPA in reducing levels of PA is not supported. Rather, changes in levels of PA over time may be attributable to changes in other specific types of physical activities such as an observed decline in work-related PA, active transportation, and activity in the home.

35.3.2 Cross-Sectional, Cohort, and Intervention Studies

PA is considered a key lifestyle behavior to prevent and treat overweight and obesity in adults.[127] Evidence from both epidemiological and interventional studies has demonstrated an inverse association between PA and obesity.[128] Among adults, all PA behavior outside of work is considered LTPA and although active transportation may intuitively fall under this category, it is most often given specific consideration and categorized on its own.

A cross-sectional inverse association between PA levels in general and weight status has been demonstrated by both Lee et al.[129] and Jakicic et al.[130] Lee and colleagues[129] reported that people who achieve levels of PA that are consistent with public health guidelines have a lower body weight than those not reporting this level of PA. Also, Jakicic and coworkers[130] have reported an inverse association between BMI and objectively measured PA (defined as achieving an intensity of >3 metabloic equivalent (MET)/min consistently for a period of >10 minutes). The findings of Jakicic et al. moreover showed that individuals classified with higher levels of BMI were engaging in PA less frequently and for a shorter duration, and potentially at a lower intensity, when they do engage in PA compared to individuals classified with a lower level of BMI, which appears to contribute to lower energy expenditure from PA as BMI increases. King and colleagues[131] furthermore explored the interaction between LTPA and occupational activity on obesity prevalence in a cross-sectional U.S. national sample (National Health and Nutrition Examination Survey [NHANES] III). Their findings indicated that once the frequency of LTPA was sufficient to meet daily recommendations of PA the likelihood of obesity was 50% less than if a person did not reach the daily recommendations of PA through LTPA regardless of his or her daily level of occupational/work-related activity.

Cause and effect cannot be determined from the findings of these cross-sectional analyses, but associations between PA and obesity have also been documented through longitudinal studies. For example, in the Nurses' Health Study[132] it was reported that for each 1 h/day of brisk walking there was a 24% reduction in the risk of becoming obese over a period of 6 years. Also, DiPietro et al.[133] estimated that weight gain would occur in men who had a decrease in PA level over a period of 5 years, with modest weight loss occurring in men who increased their activity from low (<1.45 METs per 24 hours) to moderate (1.45–1.60 METs per 24 hours) or high (>1.60 METs per 24 hours). Additionally, data from the NHANES I follow-up study, from 1971–1975 to 1982–1984, provide evidence that low levels of LTPA specifically may be linked to weight gain and overweight/obesity in both men and women.[134] In this study, the relationship between self-reported recreational PA levels (low, medium, and high) and measured weight change after 10 years among 3515 men and 5810 women, aged 25–74 years, was studied. Cross-sectional analyses at both baseline and follow-up surveys revealed that LTPA was inversely related to body weight. The risk of significant

weight gain over time was lower in individuals who increased their level of PA compared to those who decreased their level. These results indicate a beneficial role of LTPA in combating overweight and obesity.

Further support for the beneficial role of PA on weight comes from the Pound of Prevention Study,[135] which examined various strategies to prevent weight gain in a community sample of adults. In this study, analysis of data collected across a 3-year period revealed that PA was predictive of change in body weight. Analysis of data for women showed that an increase in moderate-intensity (i.e., activities such as walking and home maintenance activities), high-intensity (e.g., running/jogging, biking, swimming, and exercise classes), or occupational activity was prospectively associated with a lower body weight. Body weight at follow-up was lower by 0.10 kg for each additional moderate-intensity exercise session per week and by 0.15 kg for each high-intensity exercise session per week. In men, each additional high-intensity exercise session per week resulted in lowering the body weight by 0.54 kg. These data further support both the role of PA in general and the specific role of LTPA in the prevention of weight gain in adults. Moreover, these results indicate that a higher intensity activity (e.g., running/jogging, biking, and swimming) may be more beneficial than less intense activities for the prevention of weight gain, particularly in men.

35.3.3 Intervention Studies

Data from intervention studies also support the role of PA in the prevention of weight gain and obesity. For example, Slentz et al.[136] reported that PA resulted in a modest decrease in body weight and measures of body fatness, whereas control subjects not participating in PA had a modest increase in body weight in the STRRIDE Study. Systematic reviews and meta-analyses have been conducted to describe the influence of PA, without a prescribed reduction in energy intake, on weight loss.[137–140] The Advisory Committee for the 2008 Physical Activity Guidelines for Americans[139] concluded that 150 min/week of moderate- to vigorous-intensity PA (e.g., brisk walking) result in approximately 1%–3% reduction in body weight. However, in another systematic review of the literature,[137] the magnitude of weight loss has been reported to increase as the dose of PA increases. This review[137] reported that PA of >150 min/week results in 2 to 3 kg of weight loss, with weight losses of 5 and 7.5 kg occurring with 225 and 420 min/week of PA, respectively. These findings suggest that PA, when not combined with a concurrent reduction in energy intake, results in modest weight loss, with the magnitude of weight loss being associated with the amount of PA performed. The specific effects of leisure-time activity on weight loss, however, are less clear. Nevertheless, from adult studies it seems that positive effects of PA on weight status are realized by the accumulation of total energy expenditure throughout the day, whether it comes from work-related activity, LTPA, or some other types of activity such as active transport.

35.4 SUMMARY

PA is estimated to account for 20%–30% of total daily energy expenditure,[1] and this can vary considerably between individuals based on their activity behaviors. For example, in adults those who are physically active in their occupation may have a greater level of energy expenditure in PA than those who are seated at a desk most of the day. However, even an individual with a relatively sedentary occupation can participate in leisure-time and structured forms of PA to enhance total daily energy expenditure. Children, in the same manner, can engage in various forms of physical activities throughout the day to reach a sufficient level of PA to enhance daily energy expenditure and improve their health. In theory, all forms of PA can affect energy balance, and it is important to engage in sufficient amounts of PA to positively impact body weight and health. PA can potentially contribute to improvements in body weight regulation and weight loss and therefore should be included in clinical and public health approaches to the prevention and treatment of overweight and obesity in adults as well as children.

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36 Sustained Short Sleep and Risk of Obesity
Evidence in Children and Adults

Michelle A. Miller, George Smith, Andrew O'Keeffe, and Francesco P. Cappuccio

CONTENTS

36.1 INTRODUCTION

Sleep is affected by a number of different cultural, societal, historical, and environmental factors. These determine where, how, and with whom a person sleeps, along with the value placed on sleep. Likewise, they may affect the duration and quality of the sleep obtained.

The recent introduction of longer working hours, more shift work, and 24–7 availability of commodities has been paralleled by the trend to curtail sleep[1] and an increased reporting of tiredness and fatigue.[2] The societal importance of sleep has recently been recognized[3] alongside evidence that both poor quality and duration of sleep may be determinants of health.[4] There is an epidemiological link between quantity of sleep (short and long duration of sleep) and obesity.[5] In addition, sleep deprivation has deleterious effects on metabolism,[6,7] endocrine functions,[8,9] and immune and hemostatic pathways.[10–12] Given the potential significance of sleep quantity and quality, it is important that these variables are determined accurately.

36.1.1 Sleep Stages and Measurement of Sleep Quality and Quantity

There are four different stages to sleep. The first three (N1, N2, and N3) make up nonrapid eye movement sleep (NREM) and represent increasingly "deep" sleep states. The last stage (dreaming stage) is made up of rapid eye movement sleep (REM). Different brain activity is observed in the different stages, and in general, a person will cycle through the phases approximately every 90–100 minutes during the night. N3 (formerly known as stages 3 and 4) has the highest proportion of slow-wave sleep

(higher amplitude, lower frequency brain wave activity), which is highly correlated with prior time awake and is a measure of sleep deprivation.[13] The proportion of NREM and REM in each cycle varies throughout the night, with proportionally more REM in the latter part of the night. REM can be detected by the associated eye movement in an electrooculogram (EOG) and by the associated inhibition of muscle activity, which can be seen on an electromyogram (EMG). In the REM phase, the brain is very active, and this activity can be detected on an electroencephalogram (EEG). The accepted gold standard for the measurement of sleep quantity and architecture is polysomnography (PSG), which comprises at least three distinct types of data (EEG, EOG, and EMG); these jointly determine whether a person is asleep or awake and provide an objective assessment of the sleep–wake cycle over the entire sleep period.[14]

For reasons of practicality and cost, many of the large epidemiological studies have utilized self-administered questionnaires and/or sleep diaries. There are many different types of sleep logs and sleep questionnaires.[15] The Pittsburgh Sleep Quality Index,[16] for example, is a useful tool to measure sleep quality in different patient groups.

Actigraphy measures movement, not sleep, to differentiate when someone is asleep or awake, but its advantage is that it can be used to record data for long periods of time.[17] Many wristwatch-style actigraphs have light monitors and auxiliary channels (e.g., EEG) incorporated into them, and while actigraphy is not appropriate for the diagnosis of certain sleep disorders, it is appropriate for examining sleep variability.

For large epidemiological studies, a simple and cost-effective alternative to PSG is to use actigraphy in combination with sleep diaries. However, the possibility that sleep estimates may be confounded by "time in bed," naps, and the normal distribution of sleep quantity needs to be considered.

36.1.2 Overweight and Obesity

Overweight individuals are defined as having a body mass index (BMI) of 25–30 kg/m^2. An elevated BMI is a major risk factor for heart disease, stroke, type 2 diabetes, and other chronic diseases. The ever-growing rate of obesity (BMI > 30 kg/m^2), particularly among children, is of great concern.[18] In the United Kingdom, 44% of men and 35% of women are overweight, and 23% of men and 24% of women are obese.[18]

36.2 EVIDENCE LINKING SLEEP AND OBESITY

A growing body of evidence supports an epidemiological link between sleep duration and adverse health outcomes, including obesity.[5] In this section, the effect of ethnicity and gender as potential confounding factors is briefly addressed, along with consideration of underlying sleep disorders and the effect of shift work. Finally, the evidence for an association between sleep and obesity in adults and children is reviewed.

36.2.1 Ethnicity and Gender

To date, most sleep research has been conducted in white males of European descent, thus making generalization of the findings to other ethnic and racial groups and to women difficult. Furthermore, there may be gender differences in the association between sleep and adverse health outcomes[19] and in the potential underlying mechanisms.[11] A recent prospective study of 1343 white, 355 black, and 128 Hispanic mother–child pairs showed that black and Hispanic children were less likely to sleep at least 12 hours per day in infancy. Furthermore, weight gain was more rapid in black and Hispanic children during infancy.[20]

36.2.2 Sleep Disorders and Obesity

Obesity and sleep-related breathing disorders, such as obstructive sleep apnea (OSA), are contributing factors to the development of cardiovascular disease and are associated with an increased risk of morbidity and mortality as well as reduced life expectancy.[21] Obesity is a risk factor for OSA, and the associated lack of sleep in these patients may also contribute to the development of obesity, thus potentiating a vicious cycle (see review by Miller and Cappuccio[22]). Night eating syndrome has recently been recognized for its role in the development and maintenance of obesity (see review by Vander Wal[23]). Likewise, obesity hypoventilation syndrome is defined as a combination of obesity, daytime hypercapnia ($PaCO_2 \geq 45$ mmHg), and sleep-disordered breathing when all other causes of alveolar hypoventilation have been excluded.[24]

36.2.3 Sleep and Obesity in Shift Workers

Endogenously generated circadian rhythms occur with a periodicity of approximately 24 hours and play a fundamental role in the survival of organisms. Behavioral and biochemical processes within the body are aligned with the day/night cycle through the intrinsic circadian clocks. These clocks are controlled by the central pacemaker in the suprachiasmatic nucleus of the hypothalamus. Normally, the signals from these clocks control the processes that regulate hunger and satiety. In shift workers, however, circadian desynchronization occurs as the individuals consume food and sleep out of phase with the normal clocks, with adverse metabolic effects.[25] Adverse alterations in the oscillating clock genes, within human adipocytes, have also been associated with obesity.[26]

In a recent study, the effect of sleep duration on risk of new-onset obesity was determined in Japanese adults by using self-administered sleep questionnaires. In male shift workers who reported sleeping ≤5 hours, there was a significant increased relative risk of obesity (odds ratio [OR] = 1.30, 95% CI: 1.14–1.49) as compared to those who slept 5–7 hours. By contrast, there was no significant increase in obesity in the men who slept ≤5 hours who were not shift workers (OR = 1.09, 95% CI: 0.94–1.25).[27] This evidence highlights the need to document shift work in studies of sleep and obesity.

36.2.4 Sleep and Obesity in Adults and in Children and Adolescents

In the United States in the past 50 years, there has been an increase in obesity and a concomitant decrease in the average

self-reported sleeping time (~1.5–2 hours), leading to speculation that the two phenomena might be linked.[28] Here, we review evidence in both adults and children to determine whether it supports this hypothesis.

36.2.4.1 Cross-Sectional Studies

In 2008, we conducted a meta-analysis of studies in both adults and children.[5] The meta-analysis used data from 36 population samples and comprised 30,002 children and 604,509 adult participants from around the world. The association between sleep and obesity was consistent across different populations and was observed in both children and adults. In children, the pooled OR for short duration of sleep (≤10 hours per night) and obesity was 1.89 (95% CI: 1.46–2.43; $p < .0001$) (see Figure 36.1a). In adults, the pooled OR for short sleep (<5 hours per night) was 1.55 (95% CI: 1.43–1.68; $p < .0001$), and there was no evidence of publication bias (see Figure 36.1b). As these studies consisted mainly of cross-sectional data, temporal sequence or causality could not be determined.

Subsequent studies have shown that, in children, greater sleep duration is associated with a lower BMI.[29] In a recent study of 3497 Australian children ages 5–15 years, there was an almost twofold increase in obesity among those who slept ≤9 hours per night compared to those who slept ≥10 hours (OR = 1.97, 95% CI: 1.15–3.38). As with other recent studies, this association was independent of confounders such as physical inactivity, diet, and socioeconomic status (SES). In addition, this link was stronger in children under 12 years of age; the authors commented on this age being a potential "threshold" beyond which sleep duration may not have an effect on body mass. Indeed, analyses in this study of children ages 13–15 years showed no relationship between sleep and BMI, leading the authors to suggest that possible obesity interventions involving sleep duration should target younger age groups.[30]

The Quebec Adiposity and Lifestyle Investigation in Youth study is an ongoing longitudinal study of 550 Canadian children. Mean sleep duration is determined using actigraphy. When correlating this data with measures of adiposity such as BMI Z-score and waist circumference, researchers found a U-shaped relationship, suggesting that both short and long sleep duration result in increased body mass.[31] However, they noted that long sleep resulted in smaller increases in adiposity than short sleep. Short sleep alone was significantly related to overweight and obesity, with an OR of 2.08 (95% CI: 1.16–3.67), even after adjusting for confounding variables such as Tanner stage and parental BMI, corroborating the results from other studies.

These cross-sectional studies have limitations. There was considerable variation in adjustment for potential confounders; such studies cannot address whether an individual's sleeping habits may change over time or what effect this may have, and the majority of the studies used sleep questionnaires as well as various methods to measure obesity.

36.2.4.2 Prospective Studies

In adults, the findings from prospective studies have been inconsistent; while some have demonstrated an association,[32,33] others have failed to support the view that short sleep duration predicts the future development of obesity (e.g., Refs. 34–37; see Table 36.1). In the Whitehall II study, for example, both short and long sleep duration were cross-sectionally associated with higher BMI and an increased OR for obesity in men. But, by contrast, the prospective analysis failed to show any effect of sleep duration on BMI or any increase in the risk of obesity over the following 5 years.[37]

Age may be an important confounding factor. One study showed that while sleep was associated with obesity in young adults (age 27–34 years), the association was not present in adults older than 40 years.[32] A 2010 study investigated the effect of baseline sleep on the accumulation of fat over a 5-year follow-up period in individuals of African-American and Hispanic-American descent who participated in the Insulin Resistance Atherosclerosis Family Study.[38] The extremes of sleep duration (≤5 hours or ≥8 hours) were related to increases in BMI, subcutaneous adipose tissue, and visceral adipose tissue in persons younger than 40 years but not in those older than 40 years. While this study measured body composition by computed tomography and used an acceptable length of time for follow-up, its limitations are that sleep duration was obtained by self-reported questionnaire and confounders such as depression were not adjusted for.

Gender may also be important: In a study of more than 60,000 women who participated in the Nurses' Health Study, a small effect of reduced sleep on incident obesity was observed (OR = 1.15 and 1.06 for those sleeping ≤5 hours and ≤6 hours per night, respectively).[33] However, in a more recent study of more than 35,000 Japanese electric power company employees (31,477 men and 3770 women), while there was a cross-sectional association between obesity and sleep in women, there was no significant prospective association. By contrast, in men who slept ≤5 hours, there was an increased risk of obesity over a 1-year follow-up period (OR = 1.91, 95% CI: 1.36–2.67).[39] Such findings warrant further investigation, but the gender difference may be due in part to the relatively small percentage of woman (~10%) in the cohort.

Gender differences were also described in the Helsinki Health Study. Short sleep duration was associated with major weight gain in women but not in men (OR = 1.52, 95% CI: 1.08–2.14) during the 5–7-year follow-up period. This association persisted after adjustment for covariates. Long sleep duration in women was also associated with major weight gain after adjusting for age (OR = 1.35, 95% CI: 1.00–1.81). In this study, 80% of the participants were women ($N = 5729$ women vs. 1298 men).[40] In the same cohort, sleep problems (trouble falling asleep, waking up several times per night, and trouble staying asleep) were associated with major weight gain during the 5–7-year follow-up in women but not in men.[41]

In children and adolescents, emerging data from prospective studies support the view that short sleep duration predicts future obesity (see Table 36.2). In a nationally representative study of over 2000 American children and adolescents (ages 3–12 years at baseline), children who slept less at the time of the first assessment had higher BMIs 5 years later.[42] In a separate study, short duration of nighttime sleep in children ages 0–4 years at baseline was strongly associated with increased

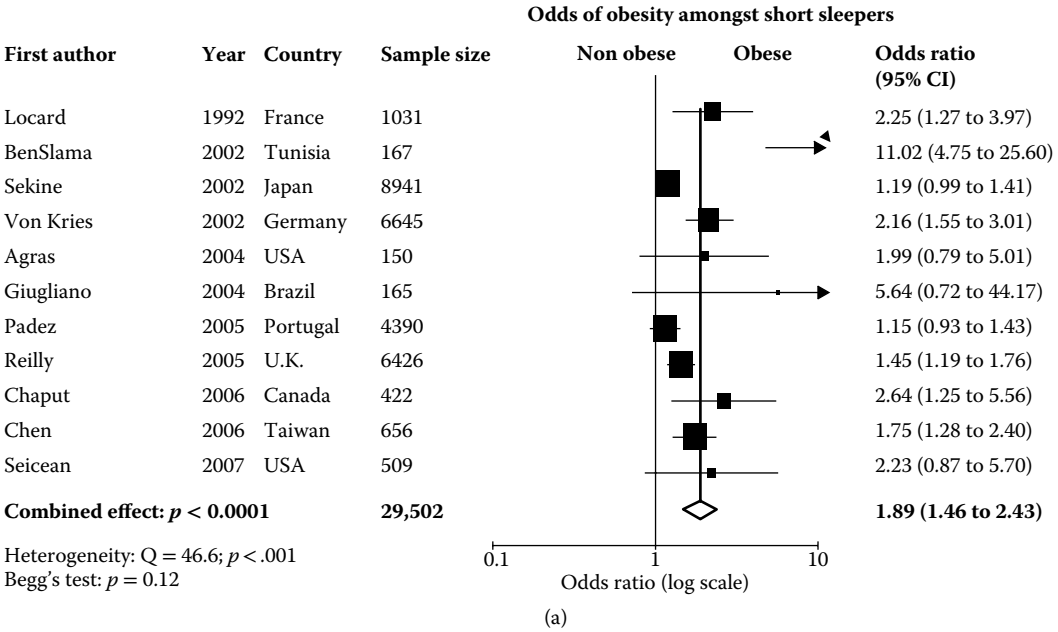

FIGURE 36.1 Meta-analyses of cross-sectional studies of short duration of sleep and obesity in (a) children and adolescents (age 2–20 years) and (b) adults (age 15–102 years). (Data modified from Cappuccio FP et al., *Sleep*, 31, 619–26, 2008.)

risk of subsequent overweight or obesity (OR = 1.80, 95% CI: 1.16–2.80). For older children (ages 5–13 years), however, baseline sleep was not associated with subsequent weight, but their current sleep duration was associated with current weight.[43]

A prospective study of 1916 preadolescent children in Canada found that compared with children sleeping 11 hours, children with a 1-hour decrease in the time spent in bed at 10 years of age had an increased risk (about two times higher) of being obese at age 13 years. Likewise, the short-sleeper

TABLE 36.1
Summary of Prospective Studies Showing Association between Sleep and Obesity in Adults

Author	Year	Country	Study Design & Population	Sample Size	Age (Years)	Definition of Sleep (Short) & Obesity	Major Outcomes & Conclusions
Hasler et al.	2004	Switzerland	13-year prospective single-age cohort study of young adults	496	27 at baseline; 40 at final follow-up.	Self-reported sleep duration Short sleep = <6 hours. Subjective quality of sleep recorded (not impaired, moderately impaired, severely impaired) Obesity = body mass index (BMI) ≥ 30. Self-reported height and weight	Positive association between short sleep and obesity found (odds ratio [OR] = 7.4, 95% CI: 1.3–43.1 [age 27 years]). Negative association between sleep duration and BMI found. Associations between sleep duration and obesity diminished after age 34 years
Bjorkelund et al.	2005	Sweden	Prospective population study in women; 32-year follow-up in Gothenburg	1462	38–60 at baseline; 70–92 at last follow-up	Sleep duration obtained by questionnaire Sleep <6 hours per night. Height, weight, and waist and hip circumferences	Sleep complaints increased across age groups: 16% (age 38) and 30% (age 60). No significant difference found in weight gain for those with or without sleep problems
Gangwisch et al.	2005	USA	Longitudinal and cross-sectional analyses of the National and Health Nutrition Examination Survey I Follow-up Studies	9588 (cross-sectional). 8073 for the 1987 and 6,981 for the 1992 longitudinal analyses	32–49 at baseline	Sleep duration obtained by questionnaire Sleep at baseline <7 hours BMI was dichotomized between obese (≥30) and nonobese (<30)	Obese category had the highest percentage and the lean had the lowest percentage of subjects between the ages of 32 and 49 years who reported getting <7 hours of sleep per night
Lauderdale et al.	2009	USA	Cross-sectional and longitudinal studies of early middle-age adults; nested within the Coronary Artery Risk Development in Young Adults Study	612	33–45 at baseline; 38–50 at follow-up	Sleep duration was measured with actigraphy Sleep = <4.5 hours, 4.5 to <6 hours, 6 to <7.5 hours, or >7.5 hours BMI used to define obesity	Both shorter sleep and greater fragmentation were strongly associated with higher BMI. After adjustment, BMI decreased by 0.78 kg/m^2 (95% CI: 1.6–0.002) for each increasing sleep category. No longitudinal associations between sleep measurements and change in BMI found
Stranges et al.	2008	U.K.	Prospective cohort of white-collar British civil servants	10,308	35–55 in 1985–1988. Data were gathered in 1997–1999 and 2003–2004	Sleep duration was elicited by questionnaire Sleep = ≤5 hours, 6, 7, 8, or ≥9 hours. Short sleep ≤5 hours Obesity = BMI ≥ 30	Short sleep was not associated with significant changes in BMI (beta = 0.06, 95% CI: −0.26–0.14) or waist circumference (beta = 0.44, 95% CI: −0.23–1.12) or with the incidence of obesity (OR adjusted = 1.05, 95% CI: 0.60–1.82). There is no temporal relation between short sleep and future changes in measures of body weight and central adiposity
Patel et al.	2006	USA	Prospective study of female nurses free of comorbid disease. Median follow-up was 12 years	68,183	39–65 years	Sleep duration was obtained by questionnaire Short sleep = ≤5 hours Two discrete outcomes were also assessed as measures of weight gain: the development of clinical obesity (BMI > 30) and a weight gain of 15 kg or more	In analyses adjusted for age and BMI, women sleeping ≤5 hours gained 1.14 kg (95% CI: 0.49–1.79) more than those sleeping 7 hours over 16 years, and women sleeping 6 hours gained 0.71 kg (95% CI: 0.41–1.00) more

(*Continued*)

TABLE 36.1 (*Continued*)
Summary of Prospective Studies Showing Association between Sleep and Obesity in Adults

Author	Year	Country	Study Design & Population	Sample Size	Age (Years)	Definition of Sleep (Short) & Obesity	Major Outcomes & Conclusions
Watanabe et al.	2010	Japan	Prospective study of electric power company employees with baseline in 2006 and 1-year follow-up	35,247 (31,477 men, 3770 women)	Working age. Specifics not given	Sleep duration was obtained by questionnaire Reference category = sleep duration 7–8 hours, short sleep = <5 and 5–6 hours, long sleep = ≥9 hours Obesity = BMI ≥ 25	Higher incidence of obesity was observed among the groups with shorter sleep. Adjusted OR for the development of obesity were 1.91 (95% CI: 1.36–2.67) and 1.50 (95% CI: 1.24–1.80) in men who slept <5 and 5–6 hours, respectively. No association in women
Hairston et al.	2010	Three U.S. communities	Prospective study. Abdominal fat accumulation measured at 5-year intervals	African-Americans ($N = 332$) and Hispanic-Americans ($N = 775$).	18–81	Sleep duration assessed by baseline questionnaire Sleep = ≤5 hours, 6–7 hours, or ≥8 hours Obesity = BMI ≥ 30	BMI and computed tomography–derived visceral adipose tissue and subcutaneous adipose tissue were determined. Extremes of sleep duration were related to increases in BMI and subcutaneous and visceral adipose tissue in persons <40 years old but not those >40 years old
Lyytikaineen et al.	2011	Finland	The Helsinki Health Study prospective cohort. Baseline survey data 2000–2002 for municipal employees. Follow-up survey data from 2007	7332	40–60	Sleep duration was obtained by questionnaire Major weight gain ≥5 kg over a 5- to 7-year follow-up	50% of the participants reported occasional sleep problems at baseline. Frequent sleep problems were reported by women (20%) and men (17%). Major weight gain was reported by women (25%) and men (24%). Trouble falling asleep (OR = 1.65, 95% CI: 1.22–2.22), waking up several times per night (OR = 1.49, 95% CI: 1.22–1.81), and trouble staying asleep (OR = 1.41, 95% CI: 1.13–1.75) were associated with major weight gain during the follow-up in women but not in men. Associations attenuated by adjustment for common mental disorders at baseline
Itani et al.	2011	Japan	Prospective study of employees of local government organization; involved a medical checkup	21,693 males and 2109 females	Working age. Specifics not given	Sleep duration was obtained by questionnaire Short sleep = <5 hours. Obesity = BMI ≥ 25 kg/m^2	Among the male shift workers, the relative risk (RR) of new-onset obesity for those sleeping <5 hours was 1.30 (95% CI: 1.14–1.49) higher than for those with sleep duration of 5–7 hours. Analysis using both engagement in shift work and sleep duration as dependent variables showed that the RR of new-onset obesity for those with a sleep duration of <5 hours was 1.20 (95% CI: 1.09–1.32) for men and 1.7 (95% CI: 1.11–2.87) for women

TABLE 36.2
Summary of Prospective Studies Showing Association between Sleep and Obesity in Children and Adolescents

Author	Year	Country	Study Design & Population	Sample Size	Age	Definition of Sleep (Short) & Obesity	Major Outcomes & Conclusions
Snell et al.	2007	USA	Prospective study (6 years): Child Development Supplement of the Panel Survey of Income Dynamics (PSID)	2281 total. 1441 for sleep and weight analysis	3–17	Seep duration was obtained from diaries (completed by parents of younger children) Sleep duration = <8 hours, 8–8.9 hours, 9–9.9 hours, 10–10.9 hours, or >11 hours Obesity = body mass index (BMI) ≥ 30	Each hour increase in sleep resulted in an average of 0.75 kg/m^2 decrease in BMI at follow-up. An assumed linear association between sleep duration and BMI showed a predicted 5.6% increased chance of overweight at follow-up with each hour decrease in sleep time
Landhuis et al.	2008	New Zealand	32-year prospective study of birth cohort	1037 (502 female, 535 male)	0 at baseline; 32 at final assessment	Sleep duration was obtained from parental reports Individual mean childhood sleep time (ages 5–11 years) recorded and compared with population mean. Short sleep = <11 hours. Obesity = BMI ≥ 30	Shorter sleep in childhood was associated with increased adult BMI and hence greater chance of obesity at age 32 years, even after accounting for confounders (e.g., socioeconomic status, parental BMI, physical activity)
Touchette et al.	2008	Canada (Quebec province)	Prospective study (6 years)	1138	2.5–6	Sleep duration was obtained by questionnaire Short persistent sleep pattern = <10 hours. Obesity defined by standard BMI measures	Persistent short sleepers were at greater risk of overweight or obesity compared to >11-hour sleepers (OR = 4.2, 95% CI: 1.6–11.1, p = .003), independent of confounders
Bell and Zimmerman	2010	USA	Five-year prospective study: PSID	1930	0–13 at baseline	Sleep duration was obtained from diaries Short sleep = <25th percentile of sleep for age of an external sample of Swiss children Obesity = ≥95th weight percentile for age and sex of a national sample of 2000 growth charts	Short sleep in children aged 0–4 years was associated with greater risk of overweight or obesity at follow-up (OR = 1.8, 95% CI: 1.16–2.8), but this effect was not observed for children aged 5–13 years
Rutters et al.	2010	The Netherlands	Prospective study of a Dutch cohort	98	7–16	Sleep time was obtained from self-reported questionnaires between ages 12 and 16 years Short sleep not explicitly defined Obesity defined using standard BMI thresholds	Fewer hours' sleep at night was correlated with higher BMI through Tanner stages 1–5 ($r = -0.33$, $p < .05$). Sleep duration decreased with progression through Tanner stages ($R^2 = 0.38$, $p < .02$) independently of confounders
Seegers et al.	2011	Canada	Longitudinal prospective study: Quebec Longitudinal Study of Kindergarten Children (Canada)	1916	6 at recruitment; 10–13 when assessed	Sleep duration was obtained by questionnaire Sleep = <10.5 hours (short), 10.5 hours, or 11 hours Obesity defined by standard BMI measurements	Being in the short sleep trajectory increased chances of being in the obese BMI trajectory (OR = 3.26, 95% CI: 3.20–3.29) compared with the 11-hour sleep trajectory. One hour less of sleep at age 10 years increased chances of being obese at age 13 years (OR = 2.07, 95% CI: 1.51–2.84)

trajectory was associated with an increased risk (about two times higher) of being overweight or obese at age 13 years compared with the 11-hour trajectory.[44] In young children, sleep may therefore be an important and modifiable risk factor for (or marker of) future obesity.

A prospective cohort study of a representative sample of infants born in 1997–1998 in the Canadian province of Quebec measured BMI at ages 2.5 and 6 years and collected yearly sleep duration data on 1138 children. After controlling for confounding factors, a striking increase in overweight or obesity was observed, at age 6 years, for children who exhibited a persistent sleep duration of <10 hours as compared to those sleeping 11 hours (OR = 4.2, 95% CI 1.6–11.1; $p = .003$).[45]

Using data from 1037 participants (502 female) in a New Zealand birth cohort study, the relationship between childhood sleep time and adult BMI, at age 32 years, was examined. Following adjustment for multiple confounders (including early childhood BMI, SES, and adult physical activity), a lower OR for adult obesity was associated with more sleep time during childhood, suggesting that sleep restriction may increase the risk for obesity.[46]

A longitudinal Dutch study showed an inverse relationship between sleep duration and progression through Tanner stages between the ages of 12 and 16 years, which is in keeping with the general view that the required hours of sleep decrease as adolescents transition into adulthood. Furthermore, there was an additional inverse correlation between sleep duration and BMI change ($r = -0.33$, $p < .05$ through Tanner stages 1–5), which was independent of other confounding factors. Sleep duration, however, was self-reported using a questionnaire.[47]

36.3 METHODOLOGICAL CONSIDERATIONS

The previous studies have shown that while in children short sleep duration is consistently associated with the development of obesity, the same may not be true for adults. Possible reasons for these differences include the methodological problems associated with the measurement of obesity and sleep as well as adjustment of different confounding factors.

Subjective assessment of sleep parameters such as duration is a common feature in many sleep research studies. Using objective measurement may help to improve reliability and validity of results since discrepancies exist between subjective and objective evaluation of sleep,[48] particularly when sleeping time is irregular.[49] In many of the studies in children, it is the parents who reported children's sleep duration rather than the children themselves; this is necessary for young children, and depending on parents' level of awareness and attention to their child's sleep schedule, this may be more reliable than allowing children to self-report sleep duration.

Clearly, it is necessary to establish a temporal sequence for the association between sleep and obesity, which necessitates the use of data from longitudinal studies. Furthermore, repeated measures of variables of interest at different time points may enhance the study design and provide a more robust outcome measure. The effect of sleep on obesity, particularly in adults, may be small and take a long time to appear, and this may warrant the use of a large number of individuals in studies and thus make the use of detailed sleep and obesity measurements difficult and costly. Measurement errors, however, also reduce the effect size, and consideration needs to be given to whether total sleep time or the timing of sleep is important. Likewise, what is the effect of naps or sleep quality? Improved estimates of sleep quantity and quality may be provided by prospective studies in which sleep is measured by PSG or actigraphy in combination with diaries and by recording daytime naps.

For the measurement and classification of obesity in the context of sleep, it may be necessary to consider whether total weight gain or the accumulation of fat mass and depot-specific fat is more important. The adjustment for known and as yet unknown confounders such as sex, social class, and physical activity is important.[50] It is possible that potential "confounders" may in fact be "mediators" on the causal pathway between sleep and obesity. Any adjustment for such factors may therefore affect the analysis and attenuate any potential observed relationship between sleep and obesity. Finally, other comorbidities, such as depression, should be identified, as these may affect the observed relationships.

36.4 MECHANISMS

Sleep, alongside other factors, may contribute to the development of obesity, especially in young children. Obesity may, however, also lead to short sleep duration, especially in individuals with OSA.[51] There are a number of possible mechanisms that might underlie these associations (see review by Miller and Cappuccio[22]), and some of these are discussed in this section (see Figure 36.2).

36.4.1 Regulation of Energy Balance

Short sleep duration may lead to obesity through changes in the hormones that regulate appetite. In a randomized crossover clinical trial of extreme acute sleep, Spiegel et al. reported that sleep deprivation was associated with decreased leptin and increased ghrelin levels.[52] Caloric intake was maintained by a glucose infusion, but the observed change in the ghrelin-to-leptin ratio was associated with an increase in hunger. On a long-term basis, this could lead to the development of obesity. Changes in the light/dark cycle and meal timing have also been shown to alter plasma leptin levels.[53]

Hypothalamic orexin (hypocretin) neurons are pivotal in sleep/wake regulation, energy balance, and appetite control (see review by Burt et al.[54]). Orexin A and orexin B (hypocretin A and hypocretin B) have potent wake-promoting effects and stimulate food intake, and the orexin system activates the appetite-promoting neuropeptide Y. While in animal models experimental sleep deprivation results in increased orexinergic activity, it is unclear as yet in humans whether sleep deprivation, resulting from watching television for example, would have similar upregulating effects.

Animal studies have suggested that sleep loss leads to changes in the circadian clock, alters metabolism, and affects

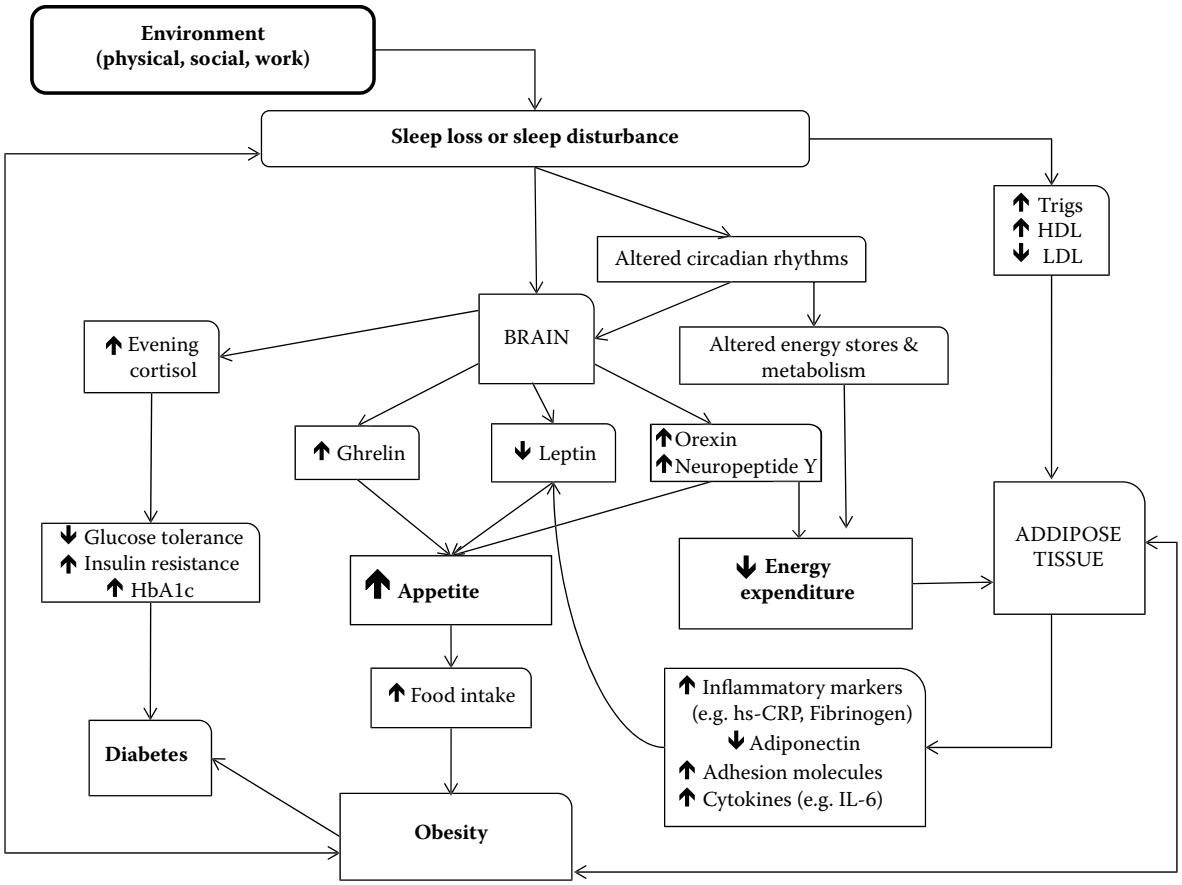

FIGURE 36.2 Potential mechanisms underlying the association between sleep and obesity. HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein.

energy stores, but these effects may also be the result of a stress response rather than of sleep loss per se.[55] In the Nurses' Health Study, short sleep duration led to an increase in weight without affecting appetite, suggesting that a change in energy metabolism may have occurred.[56] It is not clear, however, whether all short sleepers have a reduction in their energy expenditure.[6]

36.4.2 Hormonal and Metabolic Factors

To date, the majority of studies on sleep and metabolic risk factors have been cross-sectional but have demonstrated an association between short sleep duration and higher cholesterol in both men and women[57–58] and with lower high-density lipoprotein concentrations in short-sleeping adult women with type 2 diabetes.[59] In a recent study conducted in 308 community-recruited children (age 4–10 years), sleep duration in obese children was shorter and showed more variability on weekends compared with schooldays. In the obese children, the variability of sleep on schooldays was positively associated with triglyceride levels.[60]

In another recent study, two traditional risk factors for the development of excess body weight/obesity (high dietary lipid intake and nonparticipation in high-intensity physical exercise) were compared with three nontraditional risk factors (short sleep duration, high-disinhibition eating behavior, and low dietary calcium intake) in adults (age 18–64 years) from the Quebec Family Study in a cross-sectional ($N = 537$) and longitudinal ($N = 283$; 6-year follow-up period) design. The prevalence and incidence of overweight/obesity was best predicted by the combination of the nontraditional risk factors.[61] An additional follow-up study indicated that short sleep duration in adolescent females (grade 7–12 at baseline) could be a significant risk factor for high cholesterol in young adulthood (age 18–26 years).[62]

In young adults, sleep curtailment has been shown to result in a constellation of metabolic and endocrine alterations, including increased evening concentrations of cortisol.[63] Many metabolic pathways display circadian cycles, for example, 24-hour variation in leptin, glucose, and insulin levels.[64] It has been suggested that the observed increase in diabetes, obesity, and cardiovascular events in shift workers[25] may in part be due to the resulting circadian misalignment of the control of glucose metabolism and energy balance.[65]

36.4.3 Inflammatory Pathways

Short sleep duration has been implicated in the development of obesity through activation of inflammatory pathways, and the associated increase in adipose tissue may increase the production of cellular adhesion molecules, cytokines, and hormones such as resistin and leptin.[66–67] The latter regulate appetite and

may also have inflammatory effects possibly through actions on C-reactive protein (CRP).[6] Short-term sleep deprivation has been associated with an increase in high-sensitivity CRP (hs-CRP) concentrations in some[68,69] but not all studies.[70]

In a study of more than 4000 individuals from the Whitehall II study, the relationship between sleep duration, interleukin-6 (IL-6), and hs-CRP was examined. There were no overall linear or nonlinear trends between sleep duration and IL-6. But for hs-CRP levels, there was a significant nonlinear association in women but not in men.[11] The level of hs-CRP was significantly higher in short sleepers (≤5 hours) after multiple adjustments ($p = .04$) (interaction $p < .05$).[11] In another study, sleep disturbances were associated with higher fibrinogen and inflammatory biomarkers in women but not in men.[71] One study suggested that it may be possible to subtype obese individuals according to whether they display an activation of proinflammatory cytokines with or without activation of the hypothalamic-pituitary-adrenal axis.[72]

Longitudinal studies are required to investigate fully the possible temporal relationships between short sleep duration and markers of inflammation in both males and females. Ethnicity as well as gender may also be important. A recent study showed that following sleep restriction (4 hours in bed for 5 nights), adiponectin levels were unchanged in men; however, in Caucasian women, they were decreased ($Z = -2.19$, $p = .028$), and in African-American women, they were increased ($Z = -2.73$, $p = .006$).[73]

36.4.4 Food Intake

A two-process model of sleep regulation was first proposed in 1982.[74] It suggests that one's drive to sleep is governed not only by the regular 24-hour circadian pacemaker but also by an hourglass-like homeostat. The circadian pacemaker (defined as Process C) governs the timing of many behavioral, physiological, and metabolic processes. The homoeostatic pressure (Process S) predicts the propensity to sleep, increases the longer one has been awake, and is determined by the amount of slow-wave activity (stage N3) during sleep. These processes are particularly important in shift workers who may be required to sleep at a time when their homeostatic pressure is low and, hence, have difficulty in initiating or maintaining sleep. This may in turn lead to excessive daytime sleepiness and increased risk of errors and accidents. Likewise, the shift work may demand that they need to stay awake when the homeostatic pressure is high and to be awake and eat at a time that is out of phase with their circadian clock, resulting in adverse metabolic effects.

A recent study showed that sleeping patterns can alter the timing of food intake and affect the type of foods consumed. The tendency to eat during conventional eating hours decreased with decreasing sleep duration, and there was an increase in snacking in short-sleeping women. Furthermore, these were related to increased intake of fat and sweets for energy and decreased intake of fruits and vegetables.[75] Another study showed a lower prevalence of obesity (~40%) in preschool-aged children ($N = 8550$) who were exposed to a routine that included regularly eating the evening meal as a family, obtaining adequate nighttime sleep, and having limited screen-viewing time.[76] In a separate study of 240 adolescents (mean age 17.7 ± 0.4 years), those sleeping ≤8 hours on weekdays consumed a higher proportion of calories from fats compared with those sleeping 8 hours or more.[77]

36.5 CLINICAL SIGNIFICANCE AND PUBLIC HEALTH IMPORTANCE

Sleep deprivation may be a risk factor for the development of obesity and may represent a new, as yet unmet, public health problem.[78] As with many public health initiatives, there is a call for the changes to be implemented across one's lifetime. Furthermore, the greatest potential targets for public health modification are those activities that we do most frequently, and sleep is something that an individual does every day. With such a frequency, if the evidence for harm is accepted, then modifying sleep duration could prove beneficial at a societal level.

Wingard and Berkman described a U-shaped relationship between mortality risk and different sleeping patterns in 1983.[79] They demonstrated that, following adjustment for confounders such as sex, weight, SES, smoking history, and physical inactivity, the relative mortality risk was lowest for those individuals sleeping 7–8 hours per night, whereas those sleeping for 6 hours or less or 9 hours or more had a significant increased relative risk of 1.3. Since then, a number of publications have considered these relationships, and in a recent systematic review and meta-analysis of the available prospective studies, a U-shaped relationship was found for cardiovascular morbidity and mortality.[80] However, the underlying mechanisms for the associations in short and long sleep duration might be different. For example, Ferrie at al. found that a decrease in sleep duration among participants sleeping 6, 7, or 8 hours at baseline was associated with cardiovascular mortality (hazard ratio = 2.4, 95% CI: 1.4–4.1).[81] However, an increase in sleep duration among those sleeping 7 or 8 hours at baseline was associated with noncardiovascular mortality (hazard ratio = 2.1, 95% CI: 1.4–3.1). It is possible that while subclinical or undiagnosed comorbidity may be the contributing factor in long sleepers, metabolic, endocrine, and behavioral factors associated with cardiovascular risk may be more important in short sleepers.

From a public health perspective, it is of interest that when asking the question, "Have you had difficulties falling asleep in the last month?" Redline and Foody found that those who answered "almost every night" had a 40%–50% increased multivariate-adjusted hazard ratio for acute myocardial infarction.[82] Furthermore, there was a stepwise graded relationship between self-reported sleep disturbance and increased risk of acute myocardial infarction. This suggests that the incorporation of such a question into a general practitioner consultation may be important, but such a practitioner may not have received the specific training to adequately address a positive response.

36.5.1 Sleep, Obesity, and Abnormal Maternal and Fetal Outcomes

Disturbed sleep in pregnancy and increased inflammation may be associated with adverse pregnancy outcomes through the prevention of the required vascular remodeling.[83] OSA, which has an underlying inflammatory component, is a common but often unrecognized condition in women of childbearing age. It is more common in women with a past or current history of obesity and increases in pregnancy.[84] Therefore, sleep and obesity may be of particular clinical importance during pregnancy.

36.5.2 Sleep and Weight Loss

While short sleep duration has been associated with obesity, the observed U-shaped relationship between sleep and all-cause mortality suggests that the relationship between sleep and health may be complex. A recent study suggested that insufficient sleep may undermine the body's ability to lose weight as fat.[85] Ten nonsmoking individuals with a BMI in the range of 25–32 kg/m^2 who usually slept between 6.5 and 8.5 hours per night were studied. They underwent a period of either 5.5 or 8.5 hours of sleep per night in conjunction with moderate caloric restriction. Each sleep schedule and restricted caloric intake resulted in a weight loss of approximately 3 kg, but further analysis revealed that those individuals sleeping 8.5 hours lost most of their weight as a result of a loss of fat mass, unlike those sleeping 5.5 hours, who lost mainly fat-free mass. These results may be important in ensuring that weight-loss regimes are effective.

36.6 POSSIBLE LIFESTYLE AND THERAPEUTIC INTERVENTIONS

Given that sleep may be a key public health issue in the context of its association with increased obesity, possible intervention measures should be considered.

36.6.1 Sleep Extension as a Treatment for Obesity (Natural and Drug-Assisted)

It is important to consider the effectiveness of "prescribing" additional hours of sleep to tackle obesity. Even though it may be possible to alter the sleeping environment to induce an extra hour of sleep, if an individual tries to sleep for longer but in fact only lies in bed for an hour longer, then it could be that this time should be spent undertaking other pursuits such as exercise or preparing a healthier breakfast, which may produce an even greater weight loss.[86]

The sleep-obesity hypothesis is complicated by the possible bidirectional causality pathway[51] Furthermore, the practicality of extending sleep may prove unfeasible. Initiating earlier sleep may be more achievable than extending sleep through avoiding alcohol and stimulants before bedtime, removing light and distractions from the bedroom, and taking melatonin supplementation. Notwithstanding, a randomized clinical trial of the effect of sleep extension on obesity could represent a proof of concept and is currently under way.[87] To date, the study has reported that through behavioral modification their intervention group has acquired an additional 30 minutes of sleep duration per night; the participants have also reported better mood and energy, improved ability to focus, less sleepiness during the day, decreased caffeine intake, more willingness to exercise, and less craving for sweets or salty snacks, especially in the evening. The change in eating habits highlights how sleep duration may have an indirect effect on weight by influencing dietary habits, and further detailed analysis of any weight change occurring as a result of the sleep extension is planned, along with the determination of endocrine and cytokine factors.

It is also important to consider lifestyle factors that might affect the number of hours that an individual may sleep and therefore the ability to heed the advice to increase sleep duration. If people do not get as much exercise as they would like, then the reasons they cite (e.g., work commitments, family pressures, and lack of motivation) are probably the same reasons why they do not get as much sleep as they would like either, and these factors may need to be addressed.

The possibility of increasing sleep by use of drugs has also been considered. However, drugs such as benzodiazepines have many potential side effects and are addictive and would not be advocated for the general population. The possible therapeutic use of melatonin has been recently considered. This is used to correct disturbed sleep–wake rhythm and may have associated positive effects on metabolism. Melatonin at a low dose (2–5 mg/day) has been used to improve sleep in patients with insomnia and circadian rhythm sleep disorders. Several studies support the idea that melatonin can prevent hyperadiposity in animal models of obesity.[88]

36.6.2 Sleep and Lifestyle Intervention for the Treatment of Obesity

While sleep duration is reported to have an impact on obesity, it would not be prudent to ignore the influence that the demands of work and family have on an individual. In cultures where sleep occurs once a day, most often at night, individuals typically attempt to initiate sleep at the end of the day and stop sleeping when the new day begins. Therefore, our schedules can dictate when we are able to make time for sleep. If we are unable to go to bed until we feel we have met the demands we or others have set for ourselves, then it is likely that the initiation of sleep will be delayed. Likewise, the time that our working day starts will influence when we have to get up. Not surprisingly, Yiengprugsawan et al. discovered an occupational travel time effect: in 2005, short sleep duration was reported by 17%, 14%, and 12% of those traveling more than 1 hour, between 30 minutes and 1 hour, and 30 minutes to work, respectively.[89]

The Control, Evaluation, and Modification of Lifestyles in Obese Youth program is a unique 2-year health-wellness program of physical activity and health education aimed at tackling the problem of obesity in young adults. So far, it has

been shown that a program of enjoyable physical activity can significantly improve sleep quality and quantity and have beneficial effects on obesity and academic performance.[90]

36.7 SUMMARY

There is a possible bidirectional association between sleep and obesity,[51] and while the consequences of short sleep duration and ensuing excessive daytime sleepiness are recognized, more evidence is required to establish a causal link between short sleep and obesity. Notwithstanding this, the potential public health implications of a causal association have been widely disseminated in the media. It is therefore important to conduct rigorous prospective studies of sleep and obesity. Furthermore, randomized controlled clinical trials of the effects of sleep on the development of weight gain and the effects of sleep extension on body weight are required.

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Part IV

Environmental, Social, and Cultural Determinants of Obesity

37 Role of Agriculture and the Food Industry in America's Obesity*

James E. Tillotson

CONTENTS

37.1 ISSUE

A productive and reliable agriculture system coupled with an efficient food-processing and distribution system is a basic requirement for the smooth functioning of an industrial nation such as the United States. Since the mid-nineteenth century, the growth and development of modern American agricultural and food-processing systems—their industrialization—have been, and are, a shining achievement of generations of industrious and innovative men and women under supportive governmental policies and programs that have afforded us a dependable, varied, economical, convenient, and delicious commercial food supply.

Much to the credit of food industrialization, and particularly of agricultural industrialization, centuries-old fears of starvation and hunger have largely disappeared in the industrial countries; in America, food has become ever more plentiful, varied, and available, with the result that food has now taken on new social roles—eating for enjoyment and amusement—beyond solely survival [1].

Industrialization also allows the majority of us to devote a minimum of our waking hours, activities, and income to satisfying our daily need for nourishment. This is no small achievement, considering the food history of the United States.

Starting at the tail end of the twentieth century, the very success of the American commercial food system in feeding us began to be questioned on a number of fronts; questions started to be raised concerning the possible negative environmental, social, and human health effects that commercial food supply may be responsible for, either directly or indirectly. Over the previous century and a half, Americans had readily endorsed the achievements of the commercial food supply—its agriculture and processing—by their unquestioning purchase of its multitude of food and beverage products.

However, questions are currently being asked: is the present commercial food supply environmentally sustainable, is it socially fair to all, and above all is it good for our health? This chapter focuses on only one facet of the last question: the role of the modern commercial food system in the prevalence of overweight and obesity among Americans today.

During recent decades, as the industrial transformation of the food supply has gathered speed, overweight and obesity have markedly increased among Americans. This raises the health issue of the "degree of association" between food industrialization and the occurrence of higher levels of population-wide overweight and obesity in America.

What specific role does the food industry play in Americans' daily food selection and consumption? Is the commercial food sector merely a passive feeder with a ravenous, unchecked appetite, or is it a compelling commercial force stimulating Americans to eat ever larger amounts of unneeded food? Or more likely, does it play a mixture of both roles?

A major controversy, still unresolved, revolves around the relative contribution of personal responsibility versus other factors in the etiology of overweight and obesity. Hard evidence is lacking. However, personal responsibility and other individual-related activities do not occur in a social vacuum. They occur today under diverse environmental conditions resulting from food industrialization, conditions that have significant influence on an individual's ultimate eating behavior and, in turn, his or her weight.

When considering the causes of overweight and obesity, the relative importance of different factors is commonly stressed depending on whether these conditions are being considered at the individual level or at the population level. At the individual level, the importance of personal diet, food habits, and lifestyle (physical activity) are commonly thought to be more significant factors. At the population level, greater attention is given to environmental conditions (industrialization,

governmental policies and programs, economics, and cultural factors).

All will agree that commercial food supply over the past century has become a dominant factor in feeding Americans. The commercial food sector, with its varied and ubiquitous food offerings, coupled with its aggressive marketing methods, is a leading "environmental condition" suspected to have been a powerful force in recent decades in the marked increase of overweight and obesity among Americans, both young and adult.

In the 2010 *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans* [2], the role of the present food environment, which is based on commercial food supply, was identified as a major factor in overweight and obesity:

> An emerging body of evidence has documented the impact of the food environment and select behaviors on body weight in both children and adults. Moderately strong evidence now indicates that the food environment is associated with dietary intake, especially less consumption of vegetables and fruits and higher body weight.

The purpose of this chapter is to examine the role of the commercial food supply chain—the supply side of our food—starting with agriculture through processing to ultimately food delivery to the consumer. Although people's organoleptic desires and their purchase of food—the demand side of food—are important factors in shaping the immediate commercial food supply chain, the food industry and the government with its institutionalized programs and policies are also key factors in determining the long-term nature of the commercial food offerings on which Americans depend and from which they choose their diet.

Beyond the influence of demand-side factors (eating behavior), there is growing recognition of the importance of supply-side factors (the amount, nature, and cost of commercial food) in the obesity pandemic: the role of social, economic, technological, and political environmental conditions that assist or deter an individual in maintaining his or her desirable weight. Confirming the need to better understand the supply-side influence is a conclusion reached by the previous *Report of the Dietary Guidelines Advisory Committee on Dietary Guidelines for Americans* [3]:

> In conducting the research on which this report is based, the Committee was struck by the critical and likely predominant role of the environment in determining whether or not individuals consume excess calories, eat a healthful diet, and are physically active.

Further, the committee added the observation that environmental influences tend to be "beyond the control of individuals," implicitly recognizing the dominance of the supply-side role in the obesity pandemic.

Among future public policy challenges are determining what supply-side policies might, or should, be and what the role of government should be in developing the environmental conditions necessary for Americans to attain and maintain optimum weight. These yet-unresolved issues will require research in the area of nutrition and policy (challenging and difficult) and also promise to be a matter of great public controversy because of the lack of hard evidence–based research on agriculture and the food industry's role in the weight pandemic.

The following analysis rests heavily on anecdotal and observational information (partly based on the author's 50-plus years of observing the commercial food sector from within the industry and, more recently, as an academic studying the food sector). Recognizing that there are many views but unfortunately little hard evidence, this chapter is meant more to raise questions than to provide a definitive answer to the commercial food supply's role in overweight and obesity.

37.2 INDUSTRIALIZATION

Industrialization of the food supply is a relatively recent event in humankind's long history, occurring mainly during the past century and a half. The industrialization of food involves the innovative application of mechanization, land, labor, technology, and capital in its production, with the objective of producing sufficient food to justify the investments involved.

Ongoing food industrialization has increasingly removed the majority of the population from the growing, processing, and even preparation of our daily food. As the U.S. food supply became industrialized, the mode that produced daily nourishment evolved from one based largely on subsistence to one increasingly based on a large-scale commercial food sector.

In addition, broad industrialization—in food production and other commercial activities—gave rise to ever-greater labor "differentiation." Fewer and fewer U.S. workers were needed or involved in food production, whereas increasingly more were employed in other types of labor, enabling them to purchase commercially processed foods with their wages. Along with these social and economic changes, food was no longer exchanged or bartered but sold.

With food industrialization, Americans have increasingly delegated the production, processing, and final delivery of food to the commercial sector, often today buying fully prepared and ready-to-eat meals. As a result, Americans have become increasingly dependent on the commercial sector's food and beverages for their daily nourishment.

With food industrialization (particularly during the latter half-century), Americans were also faced with great changes in their diet. Harvey Levenstein [4], the noted food historian, has labeled this transformation as nothing less than a "revolution at the table" in the United States.

Germane to this change in the kind of food that Americans eat is the extensive commercialization of the food supply that occurred. With this rise in commercial activities between producers and consumers, the commercial sector had ever-stronger economic incentives to keep increasing Americans' food consumption. Food industrialization has proved to be an increasingly strong force in forming Americans' daily diet. For most Americans today, commercial food supply is their

daily food. In addition, food industrialization has proved to be a powerful environmental condition allowing widespread "overconsumption" of food.

Industrialization results in a paradox: Food (calories) becomes more available because of industrialization; however, because of ongoing industrialization and its reduction in manual activities, the individual's caloric requirement generally lessens.

37.3 GOVERNMENTAL POLICIES

Guiding the United States' agricultural and food-processing activities—between "consumer demand" and "supply" conditions—is a framework of "public policies" (agricultural, economic, and industrial, as well as public health) that shape the population's eating behavior, influencing their diet and, in turn, their weight.

First, we need to recognize that the majority of present U.S. policies affecting food supply were developed decades ago with valid objectives far different from those that might be applied if these policies were being developed today. These policies were largely developed at a time when a growing segment of the population was leaving rural agricultural life to enter a new urban lifestyle, dependent on fewer and fewer of their fellow citizens to feed them.

One of the primary challenges of these public policies "at their inception" was to ensure adequate and affordable food for all Americans by ensuring the economic support of the agricultural sector. It is probable that the genesis of the present obesity problem is partially rooted in the public policies and policy decisions of the past that were so instrumental in forming and shaping the dynamic and powerful commercial food sector.

Historical "timing" has also played a role in the unforeseen weight dilemma we now find ourselves in. Two major factors have had great influence on the obesity problem in the twenty-first century: industrialization of the U.S. economy (including the food supply system) and the increasing knowledge of the role of diet in human health.

Significantly, these factors have come into play at different times in history: the basic industrialization of food supply was largely completed and entrenched prior to much of the discovery of our present knowledge concerning the relationship between chronic diseases and diet, particularly overnutrition, and certainly prior to the occurrence of high levels of overweight and obesity among Americans, young and adult.

In America, obesity and overweight have become a significant, growing, population-wide problem only in very recent decades; throughout much of the country's development, food and public health concerns have mainly focused on securing food (during the Great Depression of the 1930s) and proper subsistence for all (feeding programs for needy women and children). During this earlier period, obesity among Americans was a rare occurrence. As a result, providing adequate food for Americans has been the leading objective of public health and agricultural policies from their inception until very recent decades.

In the period from the 1900s to the 1950s, the causes of many nutrient-deficiency diseases were uncovered. These discoveries were soon followed by government-initiated nutritional policies aimed at adequate food consumption to eliminate these diseases, particularly in low-income households. During this era, governmental policies were aimed at increasing food consumption to eliminate deficiency in the diets of many Americans.

In the period from the 1950s to the 1980s, great advances were made in the understanding of nutrient-related, noncommunicable diseases (e.g., diabetes and cardiovascular diseases). Policy makers incorporated this new information into nutrition policies aimed at eliminating or reducing from the American diet imbalances and excesses of certain nutrients associated with such diseases (fats, oils, and saturated fatty acids). In this era, the government's health policies were aimed at the "composition" of the American diet and were largely silent on total food consumption. It was during this period that the Senate Select Committee on Nutrition and Human Needs released the first *Dietary Goals for the United States* [5]. This was followed soon after by the 1980 *Nutrition and Your Health: Dietary Guidelines for Americans* [6]. Consumption of the appropriate diet rather than weight control was the core message of these policy documents.

Our current public policy challenges are far different from (and more difficult than) those of the past; we suffer not from a lack of food but more often from an oversupply of "calorie-rich" food supplied by industrialization. However, the legacies of the U.S. governmental policies of the past—particularly the calorie-rich food supply (sugars, oil and fats, dairy, grains, and meats) that these policies helped create and favored—are still with us today, successfully and aggressively functioning.

The present widespread caloric overnutrition is a new concern in the long history of U.S. public food policies. Only at the end of the twentieth century did health policies shift to obesity-related issues, stressing "reduced food consumption" by advising prudent caloric balance.

The twentieth century (particularly the latter half) saw nutritional science making monumental progress in its understanding of the relationships between diet and long-term human health. As these new findings became available, the government attempted to implement this new health knowledge into its public health policies (Figure 37.1). This has resulted in an ongoing change in nutrition-based public policies with changing public health objectives.

In spite of the government's attempts to put this new knowledge into broad use by Americans (assisted by the public's intellectual interest in nutrition), the latter part of the century saw a rapid rise in a serious nutrition-related problem: widespread and increasing overweight and obesity throughout the United States. Policy makers were faced with a paradox: during a period in which there were large increases in nutritional information (as well as wider public understanding of its meaning for human health), there occurred one of the United States' most serious nutritional crises; now, at the start of the twenty-first century, more than two-thirds of adult Americans are overweight or obese.

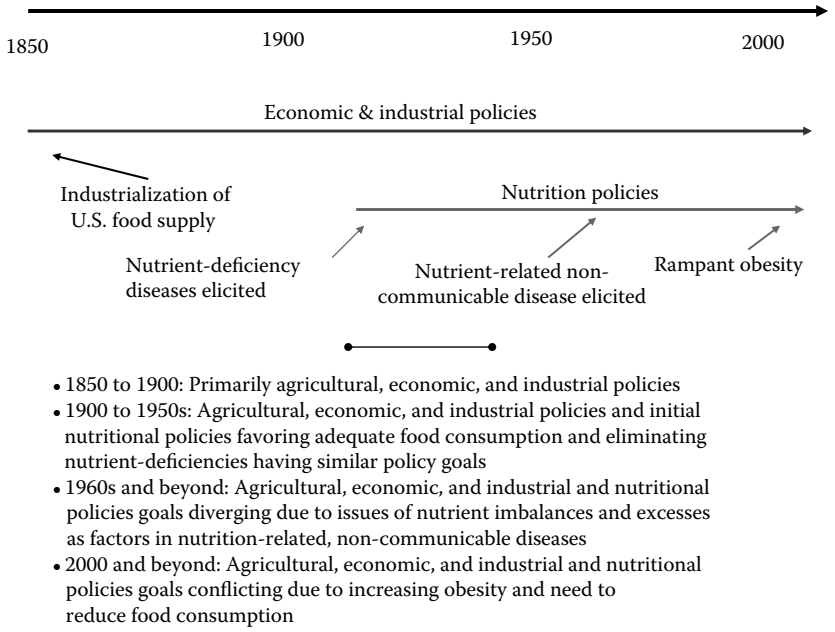

FIGURE 37.1 Economic and industrial policies. (From Tillotson JE, *Annu. Rev. Nutr.*, 24, 617–43, 2004.)

An analysis of twentieth-century public health policy initiatives is not the purpose here; nevertheless, the constantly changing thrust of these health policies is potentially one of the significant factors explaining why agricultural and industrial policies were so successful, whereas diet and health policies were not, especially in relation to the weight issues of Americans. As we attempt to craft new public health policies to control overweight and obesity, we need to understand better why past nutritional policies have not been effective in dealing with the pandemic. Many reasons have been advanced for the inability of these policies to check rampant overweight and obesity. The following have been advanced as some of the likely (but not proven) causes.

Looking back, it is obvious that governmental health agencies were slow to react to the fast-rising pandemic, only acknowledging by the 1990s that many Americans—both adults and children—were becoming dangerously overweight and obese. The reasons for the government's slow reaction remain an open question. Yet, even today, in governmental circles where there is much rhetoric about Americans' overweight and obesity problems no formal nationwide coordinated public program has emerged to deal with this pandemic.

Still another topic for consideration is how the U.S. government's organizational structure has been a contributing factor. Governmental nutritional initiatives have been historically scattered throughout various agencies (Department of Health and Human Services, U.S. Department of Agriculture [USDA], Food and Drug Administration, and Federal Trade Commission). As a result, their overall effectiveness may have been diminished by not being centralized in one governmental agency with a strong primarily nutritional mandate and authority.

During the past century, as a dramatic increase in the understanding of nutrition and its relation to health occurred, governmental policy makers, operating under different—and sometimes conflicting—laws and legal mandates, attempted to incorporate this new knowledge into America's health policies. This new, but changing, nutritional knowledge required ongoing changes in public health responses. The result has been "unintended" and "unforeseen" conflicts in governmental directives to Americans on health-related food consumption, which no doubt diluted the effectiveness of any nutritional advice given to the public [7].

Underlying these constantly shifting health policies was the basic shift in the energy requirements of the American population. The increasingly widespread use of physical labor–sparing technologies (industrialization) and the resulting increasingly sedentary lifestyle of the average American during the twentieth century have actually reduced the caloric requirement for most Americans.

Another important factor to consider is the different financial resources used to accomplish the mission of these differing governmental policies. Nutrition and related activities received "a few million" dollars annually, whereas agricultural and food-sector programs were funded with "many billions" of dollars annually, as recent annual federal budgets reveal.

Still another salient factor to be considered is the traditional approach taken by U.S. governmental agencies in advising its citizens on issues concerning their health. Up to the present time, the predominant governmental nutritional philosophy has been for governmental agencies to serve in an "advisory role" to the citizens in matters of diet and health (food pyramids, guidelines, and food labels), believing it is the responsibility of the individual to use this advice to maintain his or her nutritional health and body weight. Historically, governmental nutritional advice to Americans has been long on what they should eat, but short on how they might eat the right foods while living with an increasingly enticing commercially supplied food and drink diet. This policy philosophy has been actively endorsed by commercial agricultural

and food interests and aggressively supported in their lobbying efforts.

Obviously, this laissez-faire nutritional philosophy has not prevented the nationwide occurrence of overweight and obesity. As described later in this chapter, agricultural and other food policies relating to the commercial sector were far from laissez-faire.

Further, the government's responses to the rising obesity problem could be identified as "tactical" (labeling, guidelines, food pyramids, etc.) in nature rather than "strategic" (i.e., coordinated policies and programs aimed to reach health objectives). This, no doubt, also hampered the overall effectiveness of the initiatives.

Compounding the government's organizational, philosophical, and strategic problems, the agricultural and food-industry sectors were generally resistant to the application of new nutritional science in governmental policies, being concerned about the potentially negative influence of new health science on the businesses of the commercial food sector.

Agricultural and other food policy objectives involving the commercial food sector did not suffer this policy vacillation; as outlined later, these supply-side policies stayed basically the same during the twentieth century to the present. Their singular, unwavering objective was continuously increasing selective food production (with the government subsidizing commodities such as grains, fat and oils, dairy, and cattle), resulting in an American food diet that was very favorable to the overconsumption of "high-calorie" foods.

These earlier agricultural policies—and the food crops they favored—apparently act even today as an impediment to creating an environment that can maximize the opportunity for an individual to control his or her own weight. Unfortunately, we do not yet have the necessary research to confirm such beliefs and, in the absence of hard research, we have to rely heavily on anecdotal impressions (always a risky basis for public policy development).

This disjunction between supply-side and demand-side public policies has apparently been a major contributing factor to the rise in overweight and obesity, warranting further study (and ultimately correction, if we hope to make progress with the pandemic).

To summarize, the twentieth century saw both the greatest advances in diet and health knowledge and the greatest changes in Americans' eating behavior (not always in the best interest of nutritional health). However, the public health policies arising from new nutritional knowledge apparently had only a limited influence on long-established and successful agricultural, economic, and industrial public policies, which have focused on ever-increasing food consumption.

37.4 AGRICULTURE, COMMODITIES, AND POLITICS

To understand any relationship between the obesity problem and the agricultural sector, it is helpful to understand the development of American agriculture and its public policies, its accomplishments, and its wide support among Americans.

The United States is one of the world's leading industrial nations; however, agriculture still remains a large, vital part of its economy. Agriculture is, in fact, one of this country's largest and most successful businesses when all elements, including food processing, are included; major agricultural commodities are also an important, reliable part of the nation's export economy [8].

American agriculture supplies the world's largest consumer-food market, which in 2010 reached some $1.2 trillion in retail purchases in the United States, including both in-home and away-from-home food sales. The United States is also one of the world's largest exporters of agricultural commodities (with over $100 billion in export sales in 2011) [8].

Largely because of the availability and low cost of its major agricultural commodities, consumers' food costs were a mere 9.5% of Americans' average disposable income in 2010, according to the USDA [9]; as a result, America has one of the world's most economical, varied, and consumer-enjoyable food supplies.

This inexpensive food and beverage largesse is based on calorie-dense ingredients (corn-derived sweeteners, vegetable oils, dairy, and meat) derived largely from government-subsidized agricultural commodities. As a result of these food supply conditions and consumers' organoleptic preferences, most Americans tend to consume only marginal amounts of more expensive, less-calorie-dense fruits and vegetables.

America's food supply chain starts with farms and ranches of unparalleled agricultural productivity. Agricultural productivity is also greatly assisted by America's unparalleled "comparative advantage" in natural resources (land, climate, and water resources). Historically, the foundation of major agriculture in large parts of the United States involved a sparse population and a rich natural resource base. This agronomic condition lent itself to an agricultural system producing mainly commodity food grains, feed grains, and oilseed crops. In turn, this crop system also lent itself to the development of a large animal-protein and dairy production system. Much of the commercially prepared food in the United States is based on these commodity building blocks, which afford practically all Americans an ample, attractive, and affordable, but calorie-rich, daily diet [10].

The American agricultural system includes more than farmers and ranchers; it also includes the many industries that supply the various agricultural sectors with the necessary inputs and services (agricultural chemicals, equipment, and assorted financial services), as well as the industries that collect, handle, distribute, and process the crops that the agricultural sector grows.

The U.S. food-processing industry is highly dependent on the agricultural sector's commodity productivity. This agricultural supply of grains, oilseed, dairy, and cattle affords food-processing industries low-cost, high-quality, reliable, and basic agricultural commodities to turn into consumer-desired products.

The agricultural system in the United States, with its many related industries, creates strong economic and political pressure for the continuous increase in production and utilization

of the major commodities it produces. Further, the agricultural system and its related governmental policies and programs operate on the implicit assumption that American food demand will continue to increase, for both domestic consumer consumption and export. The long-term economic viability of the agricultural system is based on this growth assumption—ever-greater production and domestic consumption coupled with ever-greater exports.

From a domestic public health perspective, this growth assumption is of less concern in a nation with a rapidly growing population that needs to be fed, as was the case for the United States in the past. However, with the U.S. population growth rate at less than 1% and with most Americans already consuming too much food (calories), this continuous-growth production and consumption strategy—supported by present governmental agricultural policies—becomes more questionable today.

It is important to recognize that American agriculture's supply-side achievements in commodity crops are the result of more than natural resources. They are also due to a favorable combination of governmental policies; the U.S. agricultural education and research system; abundant technology; and, not to be forgotten, industrious and innovative farmers and livestock producers.

Strong, politically backed, and long-active governmental policies have played a key role in shaping American agriculture. Political support for agriculture has its foundation in early U.S. history. At its founding, America was predominantly an agricultural nation, with 90% of its people directly depending on agriculture for their livelihoods [11]. The nation's founders, many having their own agricultural holdings, greatly valued agriculture and its way of life. Many of these individuals hoped that the United States would remain an agricultural nation.

This agrarian orthodoxy fuels American agricultural growth and prosperity up to the present day, and it has given rise to the strong, enduring agricultural tradition of the "family farm." Many Americans still strongly hold these sentiments, which serve as a powerful reservoir of political support for favored agricultural interests and their public policies.

Americans also recognize the uniqueness of agriculture compared to other types of businesses. Farming requires the favorable interaction of a unique and complex set of environmental conditions (weather, temperature, etc.) with varying degrees of unpredictability. As a result, agriculture is commonly recognized as a high-risk undertaking, worthy and necessary of public support. This uncertainty coupled with the economic variability of commodity markets results in economic risks to farmers and is a further reason why agriculture has long been favored with public policies that attempt to provide economic stability to much of the agricultural sector.

Historically, Americans have overwhelmingly approved of governmental policies supporting agriculture and for decades have been willing to fund the government's great involvement in agriculture through their taxes. As a result, agriculture and its production-oriented governmental policies—particularly for major commodities—have had, and continue to have, wide political support. Fruit and vegetable crops have not been so favored.

Since the Civil War, the U.S. government has been increasingly involved in agriculture. Congress created the USDA in 1862. In this same period, it also enacted the Morrill Land-Grant College Act, commonly considered the most important piece of agricultural legislation in American history, which provided for the appropriation of public land for the establishment of agricultural and industrial colleges in each state. In 1887, the Hatch Act, in combination with the previous act, established agricultural experimental stations at the United States' land-grant universities. This sequence of congressional legislations resulted in the establishment of what is commonly acknowledged to be the world's leading national agricultural education and research system. Much of the production technology for commodity-subsidized crops in the United States is, and has been, developed at the research-oriented institutions founded in the wake of the Hatch and Morrill acts.

Because of the creation of this government-sponsored system, American agriculture continues to be supplied with a constant stream of world-class, cutting-edge technologies, allowing it to become more efficient and productive in its chosen agricultural commodities. These scientific resources have favored and been predominantly applied to the crops that the United States was historically most proficient in producing (grains, oilseed, dairy, and livestock). These crops have enjoyed a broad market demand both domestically and internationally, which has resulted in a continuous cycle of increased productivity, efficiency, and economic improvement in their production. At the consumer level, foods produced from commodity-subsidized crops are very cheap, relatively speaking, because of both the effect of actual subsidies and the increased efficiency of agricultural production resulting from government-sponsored research. This has resulted in an ongoing relative reduction in the cost of growing major commodity crops both through technology and a multitude of governmental crop-subsidy programs over the past 80-some years. Through no fault of American agriculture, this dominant system and its commodities favor the supply of economical, high-quality, and consumer-liked, but high-caloric-density, foods, an unintended, unplanned outcome of historical agricultural production policies.

American agriculture has continued to be supported by governmental policies. Between 1902 and 2013, Congress passed at least 70 major federal acts that were highly beneficial to production agriculture. These congressional actions have, over time, created a favored agricultural economy within the broader U.S. economy, strongly supported and financed by federal governmental programs.

As outlined previously,

> As a result U.S. agriculture developed its own agricultural regime of market institutes and public investment and finance—subsidies, marketing assistance programs, special taxation, a farm credit system, market regulations, commodity programs, and trade policies. All of these were highly favorable to U.S. agriculture. It also included a nationally supported rural infrastructure encompassing country roads, drainage systems, flood controls, postal service, as well

> as technical assistance in the form of market information sources, extension education and assistance, and federally funded world-class production agricultural research. [7]

The overarching objectives of this powerful regime are constantly increasing agricultural efficiency and continued production of major commodities. Historically, public policies aimed at furthering these objectives had great social utility for a nation that was rapidly industrializing, accelerating in population growth, desiring food security at reduced cost, and wanting processed foods favored by its citizens. American agricultural policies have been phenomenally successful in meeting these original production objectives through the agricultural commodities they have championed.

During the twentieth century, agriculture's congressional political power played a significant role in the growth of American production agriculture. No other business sector has equaled the ongoing "bipartisan" political power of the agricultural interests in Congress. The power centers of these interests are the agricultural committees in both houses of Congress. Historically, these powerful committees, staffed and controlled by congressional members from predominantly agricultural states, are where U.S. food policy is formed and then implemented through Congress' control of the public purse. (What senator or representative from an agriculture-oriented state seeking reelection can be anything but supportive of present agricultural production policies?)

The political system by which this comes about has been described in the following manner:

> A "structural" view of farmers' political power focuses on a "gold triangle" of members of the committees that authorize legislation and appropriate funds, the executive branch department that administers the programs (USDA) and the lobbyists representing farm interests. [12]

As a result, the U.S. Congress and its agricultural committees have strongly favored, funded, and protected commodity agricultural interests. In this mission, Congress has been backed by American voters' support, the acceptance of the "special business" status of farming, and the agricultural sector's electoral power in predominantly agricultural states. Under this American agricultural regime, agricultural interests have dominated and directed much of this policy to its production objectives—ever-greater commodity yields of favored crops and livestock and increased consumer utilization of these commodities. At this point, it is projected that these agricultural production policies will continue to be successful, as they were in the past, and that Americans will continue to consume large amounts of these commodities in their diets.

The successful results of these policies can be judged by the amount of food now available and ultimately consumed by Americans. At the beginning of the twenty-first century, as per the most recent available data from the USDA's Economic Research Service, aggregate food supply provided Americans with some 3800 calories of food on average daily per person prior to roughly some 1100 calories lost to spoilage, plate waste, cooking, and other losses. Their actual dietary intake of calories was therefore estimated by the USDA at just less than 2700 calories per person per day. Historically, the Economic Research Service data suggest that Americans on average have increased their dietary intake of calories by 24.5% in the period of 1970–2000 or approximately 500 calories daily [13].

Although ample and economical agricultural commodities by themselves are not a "direct causal factor" of the obesity pandemic, U.S. agriculture—with its supportive governmental policies—does create a commodity supply that makes it possible for us to have more-than-ample food (processed and supplied as food products); this, in turn, allows Americans, if they wish, to overconsume commodity-based foods while underconsuming fruits and vegetables, which many have done and continue to do.

The lifestyles of many Americans are shaped by this plentiful, inexpensive, commodity-based food supply. Americans, if they wish, can enjoy a very affordable diet that includes super-large food portions and voluminous soft drinks and sweet treats; they can find fast-food dollar deals and go to all-you-can-eat restaurants, as well as shop at supermarkets offering some 38,000 tasty food items today compared to only 10,425 items in 1977, according to the Food Marketing Institute [14].

Today, food is everywhere in our daily lives: at home, in our social lives, and at work. The American lifestyle is extremely food oriented, resulting in ubiquitous opportunities for Americans to overeat. The temptation to eat high-calorie foods is ever-present. And it is the United States' agricultural commodity prowess that is the starting point for the supply-side condition that makes such a food-based American lifestyle possible.

U.S. agriculture and its governmental commodity policies have only recently been questioned concerning their negative influence on Americans' health and weight. Agricultural policies are commonly recognized as pivotal to the United States' great agricultural abundance but have often been overlooked when analyzing supply-side factors that could be contributing to the obesity pandemic [7].

In summary, overproduction—and the consequent inexpensiveness of high-caloric-density foods—is now being increasingly questioned as one of the potential supply-side factors in the occurrence of overweight and obesity. Today, the greater productivity of U.S. agriculture in a number of high-calorie-yielding commodities, increasing technological innovation that supports agriculture, generous governmental crop subsidies and public policies favoring production agriculture, and the country's comparative advantage in natural resources are all contributing elements to varying degrees in creating an environment that contributes to the obesity problem—excess food commodity production.

37.5 FOOD INDUSTRY'S DEVELOPMENT AND PRODUCTS

To understand the association between the nation's current obesity problem and the food industry, it is helpful to also understand the development of the industry and its accomplishments, products, and business methods, as well as the governmental policies affecting the industry and its relationships to the U.S. agricultural sector.

A commercial food supply revolution began in the mid-nineteenth century that would increasingly affect Americans' daily diets to this day. Aided by a fast-growing demand for food, new food-processing technologies, an expanding transportation network (railroads, and later trucking), and new communication systems (telegraph, newspapers, and magazines), a commercial industry started, developed, evolved, and prospered to answer Americans' growing need for processed food [15]. The rapid growth of the food-processing industry was also aided by the growing numbers of retail stores and chains; new business methods (marketing, branding, and advertising); eager entrepreneurs (sensing great economic opportunities backed by ample venture capital); and, most importantly, very favorable growth-promoting governmental policies.

The remarkable industrialization of food supply over the past century and a half is largely attributable to its economic orientation under the United States' capitalistic system. Under this economic agenda, the food-processing sector has attracted great financial investment, based on the expectation of continuing growth and profitability, which the industry has generally achieved through most of its history. Economic return through market growth rather than social goals like human nutrition has been the paramount objective of the food-processing industry since its founding.

During its development, the food-processing sector was widely accepted—along with the overall industrialization of the nation—as a necessary part of overall U.S. industrial and economic growth. The food industry's economic importance and well-being are to this day major factors in all public policy considerations affecting the food sector.

The government's economic, industrial, and agricultural policies have been highly supportive of the industry's economic growth, and such economically oriented public policies have historically shown little or no attention on the possible health-related problems (overweight) that could occur from this largely economics-driven industrial development.

The United States is one of the world's most capitalistic nations, being so since its founding. Its capitalism is based on the principle of open markets driven by market conditions rather than governmental regulation, resulting in an economic system that promotes economic growth as its overriding (if not sole) business objective. The food industry has thrived under this capitalist system, resulting in the industry becoming collectively the world's leading food-marketing juggernaut.

The food industry's development would be further shaped and expanded by evolving food needs, which were affected by changing American social trends; importantly, the nation's almost continuous economic expansion during the twentieth century also generated consumer purchasing power for processed foods, among other industrially produced products. As with the agricultural sector's strategy with regard to commodities, the food sector's strategy assumes a continuously increasing market for its products, which Americans endorse by their increasing purchases of the industry's food and beverage products.

Key also to its phenomenal growth was, and is, the industry's great ability to sell food and beverages that Americans like; answer their eating needs; and provide affordable, widely distributed products that respond to Americans' ever-changing lifestyles and food wants. The industry prospers by supplying large volumes of low-cost, appealing processed foods produced largely from the governmental policy–favored commodity crops (grains, oilseed, dairy, and animal products) that the United States is most proficient in growing. The industry's continuing success depends on satisfying Americans' immediate food wants—taste, convenience, and good prices—and not on governmental health policies that might recommend what Americans should eat.

The development of the commercial diet in the United States can be divided into three historical industrial eras based on the principal type of food produced during the period (Figures 37.2 and 37.3). During the formative stage from the mid-nineteenth century to the 1930s, the first food-processing plants produced basic food ingredients (flour, sugar, salt, fat and oils, dairy, meat, and other food staples, as well as processed vegetables and fruits) packaged in economic, convenient, and consumer-acceptable units. The agricultural products chosen for processing by technologies such as canning, freezing, drying, milling, and other food engineering unit operations represented a balance between those suitable for processing and storage and those that people would purchase for consumption.

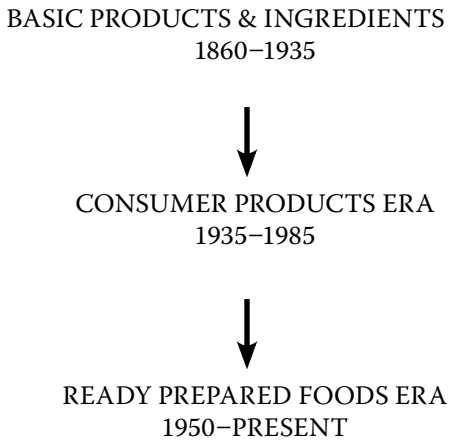

FIGURE 37.2 Eras of food industry development. (From Tillotson JE, *Annu. Rev. Nutr.*, 24, 617–43, 2004.)

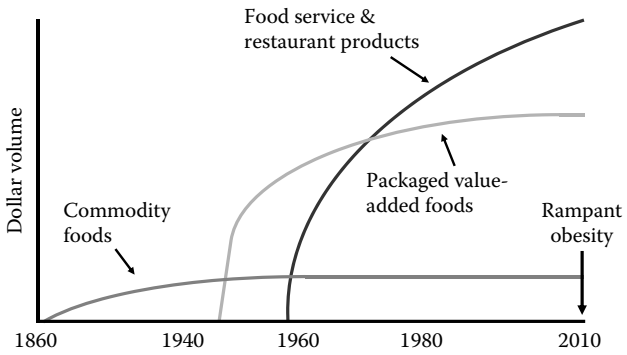

FIGURE 37.3 Industrialization eras of U.S. food supply. (From Tillotson JE, *Annu. Rev. Nutr.*, 24, 617–43, 2004.)

This era also saw the growth of long-distance distribution (railroads and trucking) and long-term storage of commercial food products (warehouses and frozen and chilled storage), as well as the first establishment of urban retail sales outlets (grocery stores). Product branding and salesmanship were introduced as aids in the sale and distribution of manufacturers' products. The manufacturing strategy was production of high volumes using predominately low-cost, governmental policy–favored commodities at low unit costs, as well as efficient processing plants to minimize labor inputs.

As Americans purchased and used the commodity-based products in their meal preparation in ever-increasing amounts, they became accustomed to these products as ongoing components of their daily diet. This was the beginning of the American commercial, high-calorie diet, which from the first was often high in sugars, salt, white flour, fats and oils, dairy, and animal-source ingredients. It was in this initial product stage that the food industry began to exert market and social influence on the nutritional nature of the American diet, an influence that would increase as the food industry developed during the twentieth century [7].

While the earlier commodity-type food products continued to be sold, a second era began, extending from the 1930s to the 1980s, during which the food industry started the development of numerous packaged convenience foods. Aided by advances in food science and technology, increasing numbers of food companies successfully transformed themselves from processors and sellers of undifferentiated, low-profit, and commodity-type foods into producers and marketers of branded, highly profitable packaged convenience foods (TV dinners, cake and dessert mixes, fully frozen prepared items, crackers and snacks, and frozen and bottled beverages of all types). Again, these products were largely based on the commodities favored by the government's agricultural policies.

With vast numbers and amounts of these new food products being produced, the industry found the growing new supermarket chains to be perfect distribution channels to a public that increasingly lived in the suburbs and drove automobiles to shop at these new, large, and consumer-acceptable retail outlets.

The germane strategy used by these companies was to develop new and unique, attractively packaged foods that were based on taste, low cost, and convenience and that met the fancy, needs, and budgets of consumers. The companies then built their products into a national brand, using skillful advertising and promotion, which were aided greatly by the newly available commercial TV. As the public grew to know of and want the new branded products through compelling marketing programs, sales increased, yielding both profits for the stockholders and, more importantly, funds for additional market development. This development era signified an increase in the role of the food industry's products in Americans' daily diet.

Companies successful in using this strategy came to, and still, dominate America's shopping carts and diets. Further, their products acculturated Americans to commercial foods that very often are energy dense or have low nutrient content, are high in fat and sugar, and are high in animal-source content; these products also further extended consumers' acceptance of commercial food products into their diet [16,17].

Industry economics, distribution, and marketing power favored increasing industry consolidation of the companies supplying us with packaged convenience products. Being both larger and fewer in numbers, these companies gained increased marketing power. This industry consolidation trend has been occurring at increasing rates in all food-industry sectors up to the present. A relatively small number of food-processing companies supply a great deal of Americans' food. In 2012, the largest 25 food processors sold products for $294.9 billion in an overall retail market of some $500 billion [18]. Because relatively few companies supply much of the food that Americans currently purchase at retail, these few consumer-goods companies and their popular branded products have a great influence on the American diet; to a very large extent, what they sell is what Americans eat [19,20].

Starting in the 1950s with the founding of one of the first modern national fast-food chains—McDonald's—a new type of convenience food started rapidly entering the American market: ready-prepared foods that offered the public the ultimate in utility and convenience at very affordable prices. This new convenience food, again based on commodities supported by the government's agricultural policies, required no preparation. The food and beverages that were offered, as both handheld snacks and full meals, could be purchased in fast-food outlets or restaurants, as well as in supermarkets and stores of all kinds. The food and beverages were developed to be eaten at the site of purchase, in the home, or on the move. This trend would diminish the previously high growth rate of consumer packaged food products that occurred between the 1930s and the 1980s, whereas the new ready-prepared, ready-to-eat foods experienced rapid market growth as Americans began to favor them.

The rapid and extensive growth of these modern ready-prepared foods was without parallel. By the early 1990s, Americans were spending approximately half of their total food purchase dollars on ready-prepared, ready-to-eat foods

TABLE 37.1
U.S. Annual Expenditures for Food

	Food at Home		Food Away from Home[a]		
	Billions	Percentage of Total	Billions	Percentage of Total	Total (Billions)
1990	$325	57	$245	43	$570
1995	$370	55	$308	45	$678
2000	$443	53	$394	47	$837
2005	$548	52	$512	48	$1060
2010	$639	51	$612	49	$1251

Source: U.S. Department of Agriculture, Economic Research Service. Food Expenditures Series, http://www.ers.usda.gov/data-products/food-expenditures.aspx. Accessed November 13, 2012.

[a] Includes both meals and snacks.

TABLE 37.2
Major Strategic Objectives of the American Food Industry

- Great innovation in products, processing, distribution, and marketing
- Organoleptic quality of products
- Consumer convenience of products
- Better product economics
- Improving product distribution
- Market growth and development of large market share for products

Source: JE Tillotson, *Annu. Rev. Nutr.* 24, 617–43, 2004.

and beverages eaten in and out of their homes, largely high-caloric-density offerings (see Table 37.1).

Throughout the nineteenth and twentieth centuries, major food-processing companies had an ever-increasing influence on the American diet because of their economical, tasty, and convenient products coupled with their innovative promotional and distribution methods [7].

The major influence of the food industry on the diets of many Americans rests in its composite structure, products, and marketing methods (see Table 37.2). The food industry's power in defining the American diet is believed to have arisen from the domestic environment under which it developed and currently operates.

Michael E. Porter [21], the well-respected Harvard economist, has extensively studied the basis for the world prominence that various nations have in various industries, including the prominence America has in the food-processing industry. To explain this industrial prominence—both domestically and globally in any industry—Porter has identified, through his extensive research, four broad, nationwide environmental conditions (Figure 37.4). In the case of the American food industry, these environmental conditions are the following:

Factor conditions: This refers to the necessary factors of production such as labor, arable land, natural resources, capital, and infrastructure (road and transportation), which America has in abundance to support its agriculture and commercial food production.

Related and supporting industries: These are the necessary industries and companies that supply the food industry with equipment, supplies, and services (financial, marketing, etc.), as well as the educational system that trains employees and serves as a source of intellectual capital for the industry. The United States exceeds at these industrial inputs.

Demand conditions: The United States is a large market for processed food and a market that is highly receptive to new food products, as well as being highly competitive. All these market conditions motivate American food companies to be highly innovative and to continuously seek a competitive advantage versus their competitors through new products and services. It is through this dynamic and intense market competition that food companies become ever more competent in answering consumers' changing food desires.

Firm strategy, structure, and rivalry: The United States is recognized as being a nation that is highly encouraging of business activities (the founding, expanding, and profitability of businesses) under the nation's capitalistic economy. Under America's positive business culture, the food industry has grown and prospered.

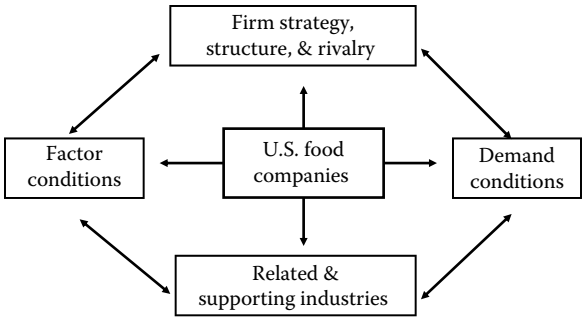

FIGURE 37.4 Derived from national advantage. (From Porter ME, *The Competitive Advantage of Nations*, Free Press, New York, 1990.)

During the past century and a half, all the economic conditions that Porter identifies have been strongly present in the United States for the food-processing industry and arguably present to a greater degree in the United States than in any other nation. These four domestic environmental conditions have nurtured a score of very large, highly successful American food companies operating in the different major food sectors (foods, beverages, and restaurants). They are successful both financially and in terms of their ability to market their food products in great amounts to Americans. Based on the scope and size of their food products in the American marketplace, these companies highly influence the daily diets of most Americans. The food industry has thrived under these

four economic environmental conditions in the United States, resulting in the industry becoming collectively the world's leading food-marketing juggernaut.

At the start of the twenty-first century 8 of the world's 10 largest food companies were founded, and they continue to operate in the United States [22]. It is important to remember that consumer acceptance—"consumption"—of a food company's production—"food products"—goes hand-in-hand with a company's capability for market dominance—"market share."

During the course of the aforementioned century-long, three-stage industrial development, a small number of very large food companies that market consumer food products and ready-prepared, ready-to-eat foods (chain restaurants) have evolved. With the following operating characteristics, these companies no doubt have great supply-side influence on the American diet [23,24]:

- They produce commercial food products that are offered at convenient delivery sites and that the majority of the population finds enjoyable to eat, affordable, and convenient as major sources of their daily diet through repeated purchases.
- They heavily offer foods and beverages that are predominantly energy dense/have low nutrient content and high added sugar and fat content, as well as products with high animal-source content.
- They produce increasing percentages of finished food products requiring no or very minimal further preparation, distributed beyond traditional food channels.
- They produce attractive, mass-produced, and branded food and beverages that are relatively inexpensive, accounting for a decreasing percentage of consumers' rising disposable income.
- They market and distribute through ever-larger food companies with continuously greater resources, and they compete in markets with markedly decreasing numbers of competing firms, often with only one to four brands dominating food product categories.
- They are skilled marketing firms with historically single business strategies aimed at economic and volume growth based on continuously answering consumers' changing organoleptic and lifestyle needs through ongoing distribution and technical innovation.
- Through innovation, they continuously improve the marketing, promotional, and selling capabilities of their market-leading brands.
- Because of their great size, employment, resources, and pivotal importance in the use and distribution of agricultural products, they are favored by government and financial institutions.

In recent decades, the food industry has become widely acknowledged as an increasingly strong environmental factor in determining what, where, and how much many Americans eat. With its present size, resources, products, and new business methods, the industry is today without question a powerful, if not the most powerful, supply-side factor in determining the American diet.

During much of the development era, the industry's food and beverage products and the consumption of these products were also greatly influenced by consumer demand. Granted, the advertising and promotional methods employed by the industry have stimulated consumer demand for its products; yet in the final analysis, we must also acknowledge that the consumers' inherent food desires—particularly for sugars and fat- and oil-based foods and beverages rather than fruits and vegetables—have also served as a motivating condition in determining the industry's structure and commercial offerings. The food industry thrives by selling food products that consumers organoleptically want and are willing to purchase, not by selling what governmental health policies recommend.

In analyzing the impact the food industry has on the American diet and, in turn, the role the industry plays in America's obesity pandemic, it is common to examine a few of its products (soft drinks and fast food); its marketing methods (advertising and product promotion); or the sugar, fat, and oil content of its products, as well as its political power and financial resources (Table 37.3).

Although these are important factors in themselves in explaining the industry's influence on the American diet, this chapter attempts to show that to fully comprehend the "overwhelming power" of the food industry on today's diet, it is also necessary to understand the industry's "business strategies" and the nature of "its food products," as well as the changing industrial "structure" for implanting these factors. Rather than attempting to explain the obesity pandemic by attributing the dietary influence to one, or even several, environmental factors, one needs to take a broader approach that is structural in nature.

Further, over the past few decades, as outlined here, the food industry evolved from one that largely sells food ingredients for us to use in preparing our own daily food into one that increasingly feeds us completely with ready-prepared, ready-to-eat food and beverages. The industry has moved from supplying us to feeding us. This trend markedly increased the environmental influence that the industry has had in determining what many Americans eat and, no doubt, often how much they eat. This change in commercial food products has helped to create an American eating environment—especially in recent decades—that is highly conducive to overeating.

TABLE 37.3
Factors Commonly Attributed as the Source of the Marketing Power of American Food Companies

- Advertising and promotional activities
- Brands and products
- Financial resources
- Political power

Source: Tillotson JE, *Annu. Rev. Nutr*. 24, 617–43, 2004.

A prime example of this is Americans' increasing consumption in recent years of discretionary caloric foods and beverages in the form of snack foods, most of which are high-calorie, low-nutrient-density products. A study reporting on 1999–2000 data calculated that, on average, one-third of Americans' total daily calories—slightly less than 2700—now comes from snack foods (25% from sweets and desserts, soft drinks, and alcoholic beverages) [25].

Concurrent with this change in consumer snack consumption has been a change in the market structure of companies marketing many of these snacks: eight large food companies (alone or with one of the other seven companies) now market 50%–70% of each major category of snack foods (soft drinks, candy, cookies and crackers, and salty snacks) to Americans. These large companies (6 are among the 10 largest food companies and 2 are among the 20 largest) have great marketing and promotional abilities, as well as the financial resources and distribution capabilities, to aggressively promote their consumer-popular branded snacks. Together, these few snack food companies form a powerful marketing force in shaping Americans' daily, calorie-rich eating behavior [19,20,26].

We have seen similar changes in recent years in consumption at fast-food restaurants and in the market concentration of retail outlets supplying often high-calorie meals to Americans. The Pew Research Center reports that there are currently some 160,000 fast-food restaurants in America serving 50 million customers per day with total annual sales of $110 billion. The Pew Research Center also estimates that, on average, 44% of Americans eat fast food once per week and 20% twice a week [27].

Further, with fast-food restaurants we have the same concentrated market trend as with snack foods. Again, we have a food sector with a few very large companies that have large business resources and an immense ability to shape Americans' eating behavior away from their homes [19,20].

Socioeconomic factors, in particular, were largely responsible for the success of these new ready-prepared convenience foods. Americans were experiencing unprecedented economic growth, affluence was molding their expectations, and ready-prepared foods and beverages became "affordable luxuries" for all.

A major factor in the growth of these foods was the increasing participation by women in the workforce; overworked, time-constrained consumers, often in dual-income or single-parent households (particularly with children), did not have the time, energy, or desire to cook, so they consumed these commercial food products in record amounts. Ready-prepared foods were ideally suited, in both form and price, to the newly developing eating patterns of consumers.

What happened in agriculture also happened in the food industry. Without government-sponsored research, it is doubtful that the food industry would have reached the current range and sophistication of its products or its present industrial structure. During the industry's development—under the nation's public policies—governmental institutions (state and federal) supplied the necessary food science and technology research, while the industry supplied the required innovation, yielding a plethora of attractive new consumer products that defined the American commercially sourced diet [28].

The role of the U.S. government is also clearly visible in the growth of the food industry's increasingly sophisticated food products, products that have required sustained industrial entrepreneurship and innovation. We see great governmental support of the food industry in this innovation. Beyond the general support that it has received from America's agricultural and economic policies, the food industry was further favored in its growth by specific policies to encourage innovation in the food sector (such as product and processing research at land-grant universities and USDA laboratories) [29].

In general, the food industry throughout its history has been highly dependent on government-sponsored research as the basis for its innovation (and it still is). Food companies invest relatively less in research than most other major industrial sectors, spending, on average, the equivalent of only 0.5%–1% of their annual research budget, according to financial filings with government agencies.

Historically, the food industry's research efforts have been directed at applied product development plus quality control efforts, rather than at new industry-reshaping technological innovations. The industry, in general, is not highly technology driven but uses technology as necessary to accommodate the American public's changing wants and desires in food. Academic and governmental research laboratories, as well as the research efforts of suppliers (new processing methods, packaging, and ingredients), have supplied much of the new technology used by the food industry for product innovation, leading to its economic growth [12].

The industry's day-to-day research objectives are in the areas of new products and the "processing," "packaging," and "distribution" of food and beverages to encourage consumer purchase. Although the success of any new product from a single company can be (and always will be) problematic, overall the industry-wide new-product efforts have been highly successful. During much of the food industry's development, Americans chose and bought their food mainly for "taste," "convenience," and "economic motivations" rather than for any health reasons, and the food industry responded with food products that satisfied these consumer desires [12].

Viewed from a historical perspective, the industry's innovation was largely aimed at answering Americans' organoleptic, convenience, and food-price objectives rather than at health and wellness considerations. History also demonstrates that the public showed enthusiasm for the industry's stream of innovations by constantly increasing purchases (as they continue to do) of new processed foods that fulfilled their latest food needs and lifestyle requirements.

Although a detailed, full account of the commercial development of the food industry during the twentieth century is

beyond the scope of this chapter, this very brief overview may be helpful in understanding the diet-determining power that the industry gained through product innovation—from "commodity" to "packaged" to "ready-prepared, ready-to-eat" food—aimed at meeting Americans' changing food needs. The introduction of waves of new products with increasing consumer utility, in turn, gave the food industry greater influence over what Americans ate, and do eat [7].

Never in the long history of food has a nation's population faced such a powerful commercial environmental force as the one Americans have faced during the past few decades from its food industry, with its promotional methods and its large and diverse number of highly capable food marketers. As the present size and diversity of the food industry's products attest, American economic and development policies have been markedly successful in their objective of encouraging great innovation in the food sector. Unfortunately, this great industry accomplishment is marred today by the association of its products and marketing methods with the obesity pandemic.

Were it not for serious, long-term health implications, the development of the commercial food system and its resulting products would be seen as a model example of American industrialization, aided by the country's development-favoring governmental policies. In fact, even today, much of public policy (agricultural, industrial, and economic) still greatly favors the growth of the American processed-food industry, despite the fact that many of the products resulting from the current industrial policies have potentially serious negative health implications for Americans.

Given the environmental commercial conditions that have existed in recent decades in the United States—particularly those associated with the food industry—and given the inherent organoleptic appeal of the American commercial diet and the excess eating behaviors and low physical activity levels of many Americans, it is not surprising that the population's dietary outcome is widespread overweight and obesity.

37.6 CHALLENGE

The prevalence of overweight and obesity in the United States is motivating the new questioning of present public policies that influence the food supply chain. Further motivating this much-needed reevaluation are projections of future human suffering and the economic costs from the unchecked obesity pandemic.

Unless solutions are found, future human suffering will be staggering and the related medical costs astronomical. Estimates of the nation's medical costs from overweight and obesity alone were believed to be in excess of $147 billion annually by 2008 and are projected to double in several decades [30]. Can any nation afford or be willing to bear such suffering for the sake of the unfettered economic interests of one of its commercial sectors?

From our agricultural lands to our mouths, our daily food is shaped, controlled, and marketed by commercial interests. What these commercial interests offer is what Americans largely eat and drink; we have few other options. Commercial interests largely set our table and often promote an overeating culture. This is obvious; this requires no lengthy studies to confirm.

As discussed in Section 37.1, we do not know if the commercial food sector is largely a passive feeder of Americans with ravenous, unchecked appetites; or if it is a compelling commercial force stimulating us to eat and drink ever-larger amounts of unneeded food and beverages; or, more likely, if it plays a mixture of both roles. There is probably no one answer, but many answers, to this question, depending on the individual and his or her particular lifestyle.

We must acknowledge that to date our efforts to control or reduce the obesity pandemic at both the individual and the population levels have been largely futile. This lack of success, at either the individual or the societal level, requires new thinking, new insights, and new approaches. With this new thinking, the role of "commercial sectors" in creating a societal environment that fosters population-wide obesity needs to be more aggressively addressed.

Any solution to the obesity pandemic requires "coordinated policy actions" on both the demand and the supply sides of the food supply chain. In crafting future public policies, we can learn much about what will work and what will not from the governmental policies for other orally used substances—tobacco, alcohol, and drugs—which at one time were completely unfettered in their commercial activities, causing socially unacceptable human suffering and harm and incurring high related societal costs.

A modern industrial nation such as the United States requires a well-functioning and economically sound commercial food supply chain. Changes are needed in the manner in which commercial interests supply our food while still retaining their necessary function of feeding us without motivating overconsumption.

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38 Transportation Policies and Obesity

David R. Bassett Jr.

CONTENTS

38.1 INTRODUCTION

Transportation policies have been shown to impact population levels of physical activity and obesity.[1–5] Governments make many decisions that influence people's choice of transportation modes. In most places there is a wide array of transportation options, but simple behavioral economics may cause people to favor certain modes of transportation over others. In places where governments have invested heavily in public transit and in building cities and towns that are conducive to walking and bicycling, obesity rates are lower than in places that are more car dependent.[3,6] Active transportation has a host of other benefits, including economic savings, energy conservation, reduced vehicle emissions, and decreased requirements for roads and parking lots.[7,8]

In the United States, the percentage of trips taken by walking and public transit has been declining since the 1960s,[9] with only a slight increase occurring during the past decade.[10] Bicycling rates have remained low, at around 1–2% of total trips. In contrast, the percentage of trips taken by private vehicles has gradually risen and now stands between 80% and 90% of total trips. Similar trends have been observed in many other industrialized nations including Great Britain[11] and Finland.[12] The percentages of trips taken by walking and bicycling in developing nations such as China and India are also declining,[13] as these countries are becoming more dependent on automobiles.

Modal shares of walking and bicycling vary greatly in countries around the world. In particular, European countries such as Denmark, the Netherlands, and Germany have high modal shares for bike trips, at 15%, 25%, and 9%, respectively (Figure 38.1).[2] These countries have made concerted efforts to increase the percentage of trips taken by bike or on foot. Pucher and Buehler[14] noted that during the 1950s through the 1970s these countries experienced dramatic declines in modal shares of walking and bicycling and became more and more dependent on cars. During the mid-1970s, however, their governments made a concerted shift in transportation and land use policies to favor active transportation. Not surprisingly, in these nations obesity rates are far lower than in countries that are more reliant on personal automobiles.[2,15]

The transportation modal shares in cities around the world also vary widely, even among industrialized cities with high standards of living.[16] This suggests that the trend toward personal motor vehicles is not just an inevitable consequence of technological development. Indeed, many cities have chosen to embrace "low tech" forms of transportation, such as walking and cycling, for short trips. In contrast, however, the car is the dominant mode of transport in most U.S. cities, even for short trips.[15]

38.2 HEALTH BENEFITS OF ACTIVE TRANSPORTATION

Active transportation refers to walking, bicycling, and the use of public transit to move from one place to another.[2] Researchers in the public health field refer to it as "transportation-related physical activity," and researchers in the energy/environment field often refer to it as "green modes of transportation." Walking and bicycling are nonmotorized forms of transport that generally fall into the moderate-intensity category (3–6 metabolic equivalents)[17] that has been shown to elicit health benefits.[18–20] In addition, the use of public transit is regarded as active transportation since it nearly

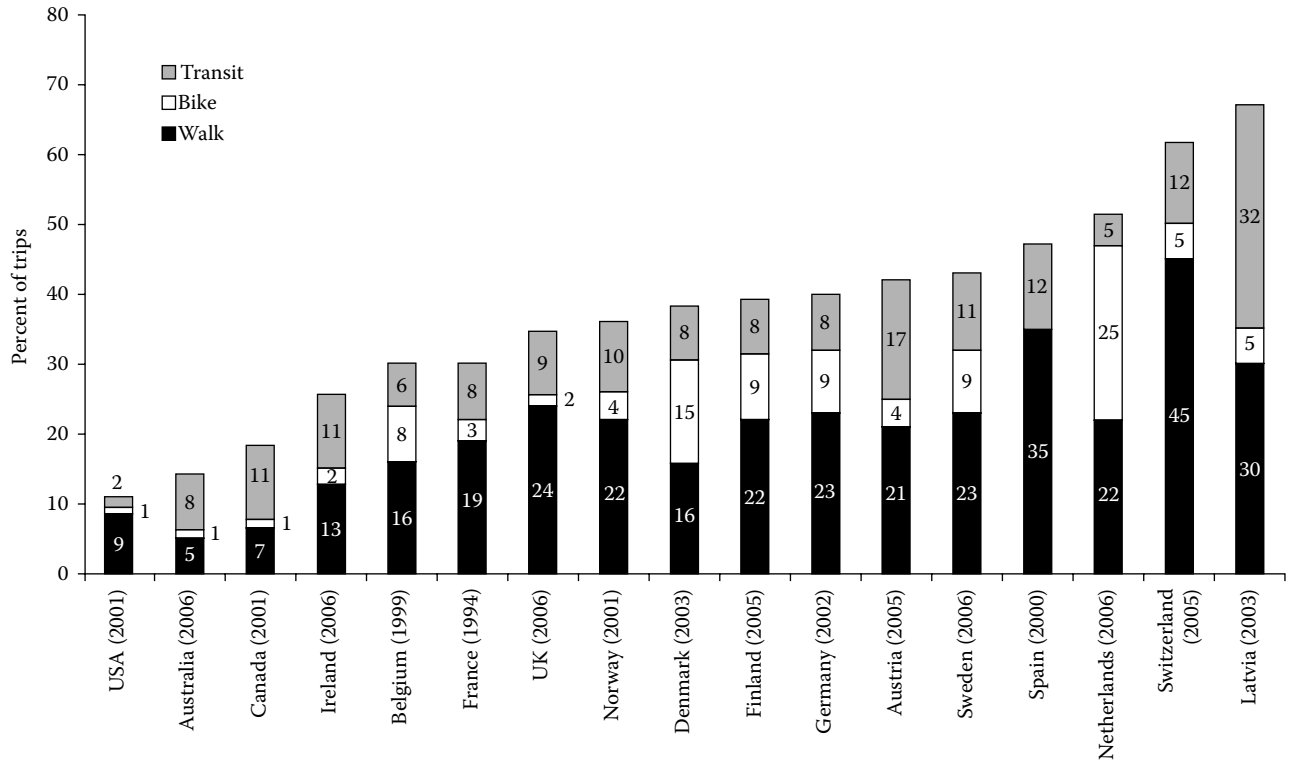

FIGURE 38.1 Percentage of trips taken by walking, cycling, and public transit in countries such as Europe, North America, and Australia. (From Bassett et al., *J. Phys. Act. Health*, 5, 795–814, 2008).

always requires walking or cycling to and from the transit stop.[4] A recent study found that transit users usually walk 19 min/day going to and from transit stops.[21] Nearly one-third of them accumulated the recommended 30 or more minutes of physical activity per day, just by walking to and from transit.[21]

Physical activity has numerous health benefits. It lowers the risk of coronary heart disease, stroke, obesity, hypertension, hyperlipidemia, and some cancers.[22,23] Physical activity also reduces all-cause mortality in men and women.[20,24–28] Therefore, the *2008 U.S. Physical Activity Guidelines*[29] recommend that adults perform at least 150 min/week of moderate-intensity aerobic activity or 75 min/week of vigorous activity. However, despite the widespread knowledge of the health benefits of exercise, fewer than half of U.S. adults meet the recommendation for aerobic activity according to the National Health Interview Survey (1988–2008).[30]

Exercise is a subset of physical activity and is performed for the purpose of improving health, fitness, and/or athletic performance.[31] Engaging in exercise requires a conscious choice on the part of participants and often requires the purchase of special equipment, clothing, and club memberships. As a result, some people regard exercise as a commodity that must be purchased with time, money, and effort.[32] Thus, it is not surprising that exercise, or leisure-time physical activity, is more prevalent among high-income, highly educated social classes.[33,34] The disparity in exercise habits between different social classes helps explain why lower socioeconomic status (SES) groups in developed nations bear a disproportionate burden of obesity and chronic diseases.[35,36]

Most people who bicycle in the United States report riding for exercise/health (41%) or recreation (34%). Only 5% report riding to work as the primary reason for using a bicycle.[37] Active transportation is a key to getting a large segment of the population to be physically active.[38] Walking and cycling are the most socially equitable forms of transportation, since they are readily available to people across the SES spectrum. Why have some countries chosen to embrace active transportation but not others? The reason that some countries elect to promote nonmotorized modes of transportation is largely due to considerations of traffic safety and reduction of congestion, fuel use, and air pollution. (Other countries opt for the personal mobility made possible by automobiles and extensive road networks.) At the time these divergent transportation systems were beginning to develop, the benefits of active transportation for obesity prevention were not fully appreciated. Since that time, however, nations that decided to embrace active transportation have seen its health benefits.

38.3 BUILT ENVIRONMENT, PHYSICAL ACTIVITY, AND OBESITY

Several characteristics of the built environment have been found to influence the levels of active transportation. Urban sprawl is associated with lower levels of walking and an increased risk for being overweight or obese.[39–41] Urban sprawl can be defined in various ways, but it is generally associated with an overall pattern of development where large percentages of the population live in low-density residential

neighborhoods.[40] In high-density urban areas, the population density exceeds 3500 people per square mile. But in sprawling suburban areas, there are single-family homes on large lots and lower population densities (200–3500 people per square mile).[42] In sprawling communities, homes are located many miles from common destinations and this leads to increased car dependency.

Another aspect of land use patterns is land use mix. Since 1950, new developments have often separated buildings into commercial, residential, or industrial uses. Single-use development, which results from zoning ordinances, requires people to drive long distances from their homes to where they work and shop. Mixed-use development enhances the proximity between trip origins and destinations, as amenities are located closer to people's residences.[3]

Street connectivity is desirable for promoting active transportation. Sprawling communities often have cul-de-sac streets that empty out onto a main arterial road with no provisions for walkers and cyclists. In contrast, in communities where streets are laid out in a grid pattern, pedestrians and cyclists can get from one location to another more easily because the distances that must be traveled along street networks are shorter. The presence of sidewalks and bike lanes is also important because without this infrastructure it is hard to engage in active transportation.

The presence of amenities (i.e., shops, schools, post offices, churches, government buildings, restaurants, etc.) located within a short distance from one's residence enhances walkability and increases nonmotorized trips. Walkers are attracted to parks and pedestrian areas that provide easy access to shops, restaurants, and bookstores. High-speed roadways, chain-link fences, and huge parking lots can significantly deter pedestrians from walking to destinations even if they are within close proximity.[3]

38.4 ACTIVE TRANSPORTATION AS A DETERMINANT OF OBESITY: REVIEWING THE EVIDENCE

38.4.1 Ecological Studies Linking Active Transport and Obesity

Nations with high modal shares of walking and bicycling enjoy lower rates of obesity compared to countries that are more car dependent. In 2008, we examined the relationship between active transportation (defined as the percentage of trips taken by walking, bicycling, and public transit) and obesity rates in 15 countries in Europe, North America, and Australia.[2] In this study, national surveys of travel behavior and health indicators conducted between 1994 and 2006 were used. The results showed that countries with the highest levels of active transportation tended to have the lowest obesity rates (Figure 38.2). Europeans walked more than residents of the United States (382 vs. 140 km per capita per year) and bicycled more (188 versus 40 km per capita per year) in 2000 (Figure 38.3).[2] This amounted to a two to threefold increase in the calories expended through active transportation (Figure 38.4). Although the daily impact may seem small, over the course of a year it amounts to a substantial oxidation of body fuel. The results are consistent with the view that variations in the use of active transportation contribute to international differences in obesity rates.

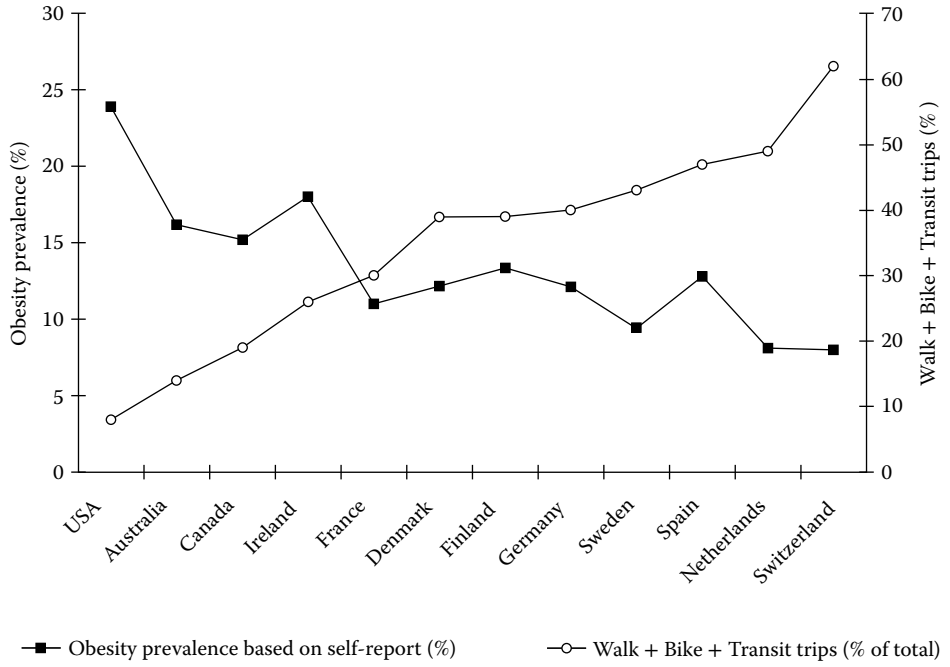

FIGURE 38.2 Obesity prevalence and rates of active transportation (defined as the combined percentage of trips taken by walking, bicycling, and public transit) in countries such as Europe, North America, and Australia: Body mass index was computed from self-reported height and weight. Data were obtained from national surveys of travel behavior and health indicators conducted from 1994 to 2006. (From Bassett et al., *J. Phys. Act. Health*, 5, 795–814, 2008.)

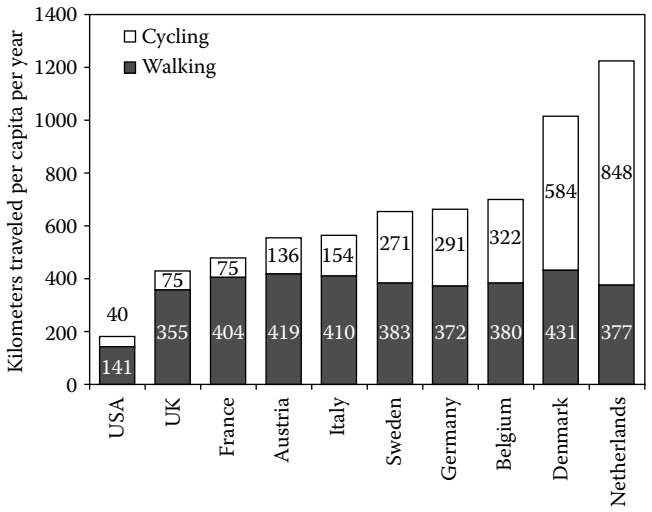

FIGURE 38.3 Walking and cycling distances in selected European cities and the United States expressed in kilometers traveled per person per year in 2000. Source: European Commission's Directorate-General for Energy and Transport, the Danish Ministry of Transport, and the U.S. Department of Transportation. (From Bassett et al., *J. Phys. Act. Health*, 5, 795–814, 2008.)

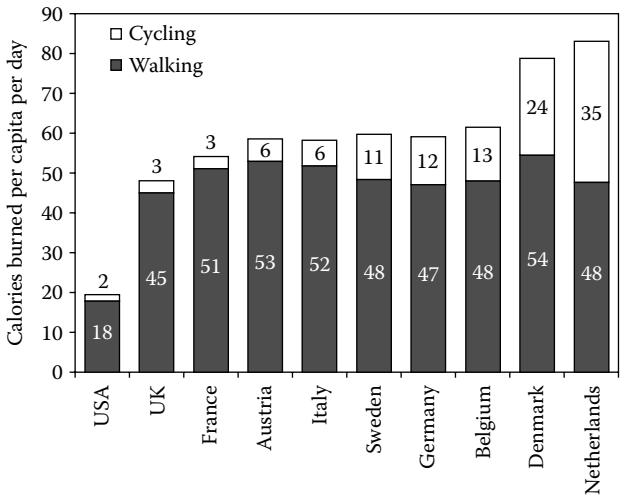

FIGURE 38.4 Estimated energy expenditure by transportation-related walking and cycling in selected European countries and the United States in 2000, expressed as calories burned per person per day. (From Bassett et al., *J. Phys. Act. Health*, 5, 795–814, 2008.)

Pucher et al.[43] reported that active transportation is inversely related to obesity rates for all 50 states and 47 of the 50 largest cities within the United States. They examined aggregate, cross-sectional data and found statistically significant positive relationships between active commuting and overall levels of physical activity. In addition, there were statistically significant negative relationships between active travel and rates of obesity/diabetes. This study provided evidence of the public health benefits of active travel, and the authors concluded that policies on transport, land use, and urban development should be made to encourage walking and bicycling.

One of the limitations of ecological studies such as the aforementioned ones (which rely on aggregate, rather than individual-level, data) is that they can be subject to "ecological fallacy." In other words, it is possible that the relationship between the variables of interest could be due to confounding variables. Although these types of studies are easier to perform and are valuable because they provide a first look at a problem, they should be confirmed by studies using individual-level data.

38.4.2 Individual-Level Studies of Active Transportation and Obesity

Studies have examined the relationship between active transportation or active commuting (i.e., walking or cycling to work) and body weight. Wanner et al.[44] conducted a systematic literature review of this topic in adults and found 36 unique studies, including 17 from Europe; 13 from North America, Australia, and New Zealand; and 8 from other nations. Of 15 studies assessing active transport and overall physical activity levels, 5 found associations in the expected direction (more active transport linked to more physical activity) for all or most of the variables examined, 9 found some associations, and only 1 found no associations. Of 30 studies assessing active transport and body weight, 13 reported associations in the expected direction (more active transport associated with lower body weight) for all or most of the variables examined, 12 found some associations, 2 observed some associations in the expected direction and some in the opposite direction, and 3 reported no associations. The authors concluded that, on the basis of cross-sectional studies in adults, active transport is associated with higher total physical activity levels and lower body weights in adults.

The relationship between active commuting to school and physical activity and body weight has also been examined in children, with quite different results than those found in adults. Lee et al.[45] reviewed the literature and located 32 studies on this topic. Most studies that looked at physical activity found a positive association between active commuting and overall levels of physical activity. However, only 3 of 18 studies examining body weight found consistent results in the expected direction, suggesting there might be no association between active commuting and reduced weight in children. The presence of confounding variables that were not adequately controlled for could have contributed to this finding.

38.4.3 Longitudinal Evidence Linking Transportation Modes and Obesity

Of course, cross-sectional studies can only show associations between active transportation and body weight; they do not indicate whether active transportation is helpful in maintaining normal body weight or whether obese individuals are less likely to use active transportation. Thus, it would be interesting to study adults transitioning from using nonmotorized to motorized transportation to determine if this causes them to

gain weight. Bell and Popkin[46] conducted such a study in the developing nation of China. In the 1980s few households in China owned motor vehicles, but 14% of Chinese households acquired a motor vehicle between 1989 and 1997. A longitudinal study of 2485 adults (aged 20–45 years) was conducted during this time period. The researchers found that Chinese men who acquired a car experienced a 1.8 kg greater weight gain and were twice as likely to become obese compared to men whose vehicle ownership remain unchanged. These findings held even after adjusting for diet and income.

A subsequent study also used longitudinal data from the China Health and Nutrition Examination Survey.[47] They found that from 1997 to 2006 acquisition of a motorized vehicle was related to a 1.2 kg greater weight gain in men ($P < .006$) and a 1.1 kg greater weight gain in women ($P < .008$) after adjusting for age, height, weight, follow-up time, diet, occupation, education, and income.

A longitudinal study was conducted on the effects of using light rail transit on changes in body mass index (BMI) and physical activity.[48] Residents living within 1 mi. of a light rail system in Charlotte, North Carolina, were studied before and after the completion of the light rail. The study cohort was divided into two groups: those who used light rail to commute to work and those who did not. After 6–8 months had passed, the use of light rail transit to commute to work was associated with a 1.18 kg/m^2 reduction in BMI ($P < 0.05$) and an 80% reduction in the odds of becoming obese over time.

In summary, the scientific evidence suggests that regular use of active transportation modes is associated with a lower body weight in adults. Furthermore, the results of longitudinal studies indicate that active commuting is helpful in maintaining normal body weight.[46,47] This is understandable since walking and cycling are aerobic activities that fall into the moderate to vigorous category, and they increase one's rate of caloric expenditure. Furthermore, when individuals perform modest bouts of physical activity (expending 75–150 cal) there is almost no "compensation," which means that they do not increase caloric intake to offset the calories that are expended.[49] Hence, there is a plausible "energy balance" explanation for why active transportation is helpful in the prevention of obesity.

38.5 TRANSPORTATION POLICIES THAT AFFECT WALKING AND CYCLING

Eyler[50] noted that promoting exercise and warning of the dangers of inactivity has not succeeded in increasing physical activity at the population level. Thus, some researchers and practitioners have turned to policy approaches, believing that they can be more effective for increasing physical activity. Policies consist of laws, regulations, and rules that can determine changes in physical, economic, and social environments.[51] Policy approaches have several benefits when addressing public health problems, including a broader scope (i.e., increased "reach") and the potential for causing long-lasting change.[50]

Transportation policies can be implemented at the national, state, or local levels (Table 38.1). Often, policy decisions at different levels intersect with each other.[50] For instance, in the United States the 2005 Safe, Accountable, Flexible, Efficient

TABLE 38.1
Examples of Bicycling Infrastructure, Facilities and Transit Integration, and Programs That Can Increase Levels of Bicycling, Based on an International Review

Travel-Related Infrastructure	End-of-Trip Facilities and Transit Integration	Programs and Legal Interventions
• On-road bicycle lanes	• Bike parking	• Trip reduction programs
• Two-way bike travel on one-way streets	• Bicycle stations (facilities offering sheltered bike parking, repairs, rentals, showers, etc.)	• Individualized marketing (e.g., TravelSmart and SmartTrips)
• Shared bus/bike lanes	• Showers at work	• Travel awareness
• Off-street bike paths	• Parking at rail stations	• Safe routes to school
• Signed bicycle routes	• Parking at bus stops	• Bike to work days
• Colored bike lanes	• Bikes on rail cars	• Ciclovias (recreational events on city streets)
• Cycle tracks (i.e., raised bike lanes)	• Short-term rental bikes	• Bike film festivals, recreational events, and so on.
• Bike boxes at traffic signals		• Education/training
• Separate traffic signals		• Bike sharing
• Route-finding signs		• Helmet laws
• Techniques to shorten cyclists' routes		• Vehicle speed limits
• Traffic calming		
• Complete streets		

Source: Pucher et al., *Prev. Med.*, 50, S106–25, 2010.

Transportation Equity Act: A Legacy for Users provided federal funding for highways, public transit, and pedestrian/bicycle projects.[52] In 2012, it was replaced by the transportation bill called Moving Ahead for Progress in the 21st Century.[53] The new $105-billion, 2-year bill did not significantly alter total funding from the previous authorization, but it reduced funding for pedestrian and bicycle programs from $1.2 billion to $800 million. Furthermore, it allowed states to opt out, or transfer funds from bike and pedestrian programs to other uses like environmental mitigation. A bicycle advocacy organization projects that these changes will lead to a substantial decline in pedestrian and bicycle projects.[54] National-level policy influences state funding, which then helps prioritize and fund local projects. All states and municipalities have their own policies that can impact transportation infrastructure, programs, and enforcement.[50]

38.5.1 Federal Policies

In every country, the Department of Transportation (DOT) or Ministry of Transport is charged with ensuring the availability of safe, economical, and efficient transportation for its citizens. These federal agencies set and enforce safety standards for the design, manufacture, and operation of vehicles; oversee building of highways and railroads; and allocate money to cities for the improvement of public transit systems.

In the United States, the federal interstate highway system was established in 1956, during the Eisenhower administration, after many industry and civic groups joined forces to lobby for improved highways. The Federal Highway Administration provides grants to states through a funding and authorization bill that governs surface transportation spending. The decision to allocate a large portion of transportation funds to interstate and state highways and bridges has resulted in a well-developed network of highways throughout the country that assists long-distance driving, but it has also contributed to sprawl. In contrast, only about 1% to 2% of all transportation funding is allocated to pedestrian/bicycle program improvements.[1] A very small percentage of the transportation budget also goes to support public transit.

In contrast to the United States, many European nations have federal policies that promote walking, cycling, and public transit use and actively discourage the use of personal automobiles.[2,15] An example of a policy that encourages people to use active transportation is the large investment in transit (trains, subways, and buses) seen in Switzerland, Denmark, and the Netherlands.[55] A greater percentage of transportation funds is also allocated to pedestrian and bicycle infrastructure in these places. In addition, some European countries require extensive training on safe walking and cycling for all schoolchildren and extensive driver's education training on how to deal with walkers and cyclists in the road.[5,7,14]

One example of a federal policy that actively discourages the use of cars and encourages the use of public transportation in European nations is high tax rates on private automobiles.[56] In addition, there are annual circulation taxes to use an automobile and high fuel taxes that drive gasoline prices up to $8–$10 per gallon. These disincentives for car ownership and use are so strong that many European families do not own a single automobile. In 2011 car ownership in the United States was 808 vehicles per 1000 residents,[57] but in European countries it ranged from 450 to 690 vehicles per 1000 residents.[58]

38.5.2 State Policies

In the United States, the state DOT, which is headed by the transportation commissioner, determines state transportation policies. The state DOT receives funds from the federal government and is charged with overseeing the allocation of transportation funds for state projects. The DOT is charged with designing a program that balances transportation needs throughout the state, focusing on improving strategic corridors, maximizing economic development opportunities, and providing key safety improvements. Each state's DOT strives to build a quality transportation system, which is seen as being important to the goal of high-quality jobs and economic growth.

The state DOT oversees projects such as new highway construction, bridge repairs, road resurfacing, and road widening. It awards grants to municipalities for the construction of local roads, sidewalks, bike lanes, and greenways. In conjunction with the National Highway Traffic Safety Administration, state DOTs strive to improve traffic safety through enforcement programs targeting speeding, impaired driving, and seat belt use.

38.5.3 Local Policies

Local governments set many policies that impact transportation systems and the built environment. In large cities and metropolitan statistical areas metropolitan planning offices (MPOs) conduct urban planning, whereas in outlying areas rural planning offices (RPOs) conduct the planning. One example of a local policy that can have a tremendous impact on the built environment is an urban growth boundary. Portland, Oregon, is one example of a city that has enacted such a policy. As a result, developers must build within the urban growth boundary, which favors "infill" rather than ever-expanding sprawl. Local zoning and sidewalk ordinances also influence the walkability of communities.

Transportation planning offices are within MPOs and RPOs. These offices receive funding from state DOTs and oversee the planning and construction of regional roads on the federal-aid highway system. (MPOs do not have authority over local roads.) Local highway departments design most local roads, and the state does the designing if it is a state route. In some places, transportation engineers follow the status quo and use a reference called the *American Association of State Highway and Transportation Officials* green book.[59] This reference manual provides specifications for how roads should be built, but a problem is that it is primarily designed with automobile drivers in mind. The green book focuses on increasing vehicle throughput, often resulting in the construction of wider, faster roads.[60]

However, other guidelines exist that consider the needs of pedestrians and cyclists.[61,62] Transportation engineers can

refer to these documents and use them to design streets that are more conducive to active transportation. Many cities have adopted complete street policies, which require transportation infrastructure for a variety of modes and embed that requirement into a policy such as an executive order or design guidelines. Such policies can have a great impact on making the roadways accessible to all types of users, not just car drivers.[63,64] Since local politicians often defer to their transportation planners' expertise, the planners have enormous influence over policies that impact walking and cycling.

RPOs and MPOs typically design long-range transportation plans that are then approved by local elected officials (e.g., mayors). There may be a separate pedestrian and bicycle master plan, which lays out groundwork for improvements to active transportation infrastructure, or it may be contained within the larger transportation plan. These plans vary widely with regard to plan quality elements, including public participation and planning processes, plan goals and objectives, analysis of current trends and conditions, policies and proposals, and implementation.[65] Well-designed pedestrian and bicycle plans, policies, and selection criteria are important for ensuring that the infrastructure is built.[66] Regardless of whether or not an MPO has a bike/pedestrian plan, all projects must be included in the long-range plan to receive federal funds.

Mass transit systems such as those found in Portland; Arlington, Virginia; San Francisco, California; Washington DC; and Boston, Massachusetts, increase the rate of mixed-modal trips. Since people normally walk or cycle to the transit stops, they acquire additional physical activity by using the subways and trains. These systems may be built with a combination of federal funds and local matching funds. Bus transit systems are found in 900 cities in the United States, and they also contribute to an increase in population physical activity levels.

38.6 SUMMARY

Active transportation has great potential for increasing physical activity at the population level and for reducing obesity rates, but to achieve this potential it requires both policies that actively encourage walking and bicycling and policies that actively discourage car use. Bray[67] has proposed the FLUORIDE hypothesis: "for lowering unwanted obesity rates, implement ideas that don't demand effort." Some physical activity researchers refer to this as a "stealth" intervention, that is, getting people to engage in more physical activity without them being consciously aware of it. By making it easier for people to commute to work and run errands using green modes of transport, governments can encourage the populace to obtain more physical activity.

The notion that active transportation is helpful in preventing obesity is consistent with the scientific evidence that daily bouts of physical activity, over long periods of time, can have a large impact on the regulation of body weight.[68] This is due to the fact that the calories expended in modest bouts of physical activity are not compensated for by an increase in caloric consumption.[49] People who live in communities that provide a wide range of transportation options spend more time walking, cycling, and taking public transit. This provides them with opportunities to be physically active on a regular basis and decreases the likelihood of weight gain.

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39 Urban Environment, Building Design, and Obesity

Reid Ewing and Gail Meakins

CONTENTS

39.1 INTRODUCTION

On the Arizona–Mexico border live two different communities of the same native tribe. The Pima share identical genetics and ancestral traditions, yet the two communities occupy land in very different countries with very different cultures. It is no surprise that differences have developed, including language, culture, and food, that set the two subpopulations apart from each other. What may be surprising is that the Arizona Pima have a higher incidence of obesity as well as type 2 diabetes rates that are five times their Mexican Pima relatives.[1] What is the cause of this? Can the physical environment have this much of a direct impact on weight and associated diseases or are other sociocultural and economic factors to blame?

There is a long-running debate in the field of urban planning about the degree to which the physical environment determines human behavior. One view, environmental determinism, ascribes great importance to the physical environment as a shaper of behavior. The counterview is that social and economic factors are the main or even exclusive determinants of behavior. So far, this debate is, at least empirically, decidedly undecided and wide open to personal interpretation. Nearly all evidence of association between the built environment and obesity is based on cross-sectional data, which provide few clues as to cause and effect. From the array of results, one can just as easily argue that physically active and physically fit people choose to live in pedestrian-friendly environments (self-selection) as that those environments cause people to be more physically active and hence healthier (environmental determinism).

It is often the case with social science inquiry, causal direction is difficult to establish. There are simply too many variables to consider. But there are some clues that support the paradigm of environmental determinism. In this chapter, we review what is known about the built environment and its relationship to physical activity and obesity.

39.2 BUILT ENVIRONMENT AT THE MACRO SCALE

Urban planners apply the term "built environment," in contrast to the natural environment, to elements of the physical environment that are man-made. The built environment includes everything from metropolitan land-use patterns and urban transportation systems to individual buildings and the spaces around them.

Land patterns, as part of the built environment, come in varying degrees of two basic forms. Urban (or suburban) sprawl has been the predominant metropolitan development pattern in the United States since then end of World War II. Examples of compact development, the opposite of sprawl, are so few and far between that they seem almost quaint these days. For every New York metropolitan area, there are dozens of areas like Atlanta and Detroit. For every Manhattan,

there are hundreds of Walton and Lapeer counties (counties located on the periphery of the Atlanta and Detroit metropolitan areas).

What exactly is urban sprawl? An early definition emphasized poor accessibility and lack of functional open space as two primary indicators of sprawling development.[2] The potential link of this definition to physical activity and health is clear. In sprawl, poor accessibility of land uses and limited connectivity may leave residents with no alternative to automobile travel. And lack of public open spaces (both natural and man-made) may leave residents with few opportunities for outdoor recreation.

This early definition was a good start, but it was largely conceptual. Before something can be studied quantitatively, it must be measured. So it is with sprawl and its polar opposite, compact development. Density has the big advantage of being easy to measure with available data, and so initial attempts to measure sprawl in the early 2000s focused primarily on metropolitan average population density. However, this produced curious results, including ranking the Portland, Oregon, (complete with a strict urban growth boundary) and New York (the ultimate of American vertical cities) metropolitan areas as more sprawling than Los Angeles, that typical bastion of congestion and development spread.[3–6]

The most notable feature of these early studies was their failure to define sprawl in all its complexity. Judged in terms of average population density, Los Angeles looks compact; it is the endless, uniform character of the city's density that makes it seem so sprawling. Another notable feature of these studies was the wildly different sprawl ratings given to metropolitan areas by different analysts. With the exception of Atlanta, which always seems to rank among the worst, the different variables used to measure sprawl led to very different results. In one study, Portland was ranked as most compact and Los Angeles was way down the list. In another, their rankings were essentially reversed.

If poor accessibility is a common denominator of sprawl, then sprawl is more than low-density development. A subsequent study by the U.S. Environmental Protection Agency and Smart Growth America aimed to better address that complexity.[7] This study examined 22 different land-use and street network variables, producing metropolitan and county indices of compactness for four primary factors: (1) *density*—compact development concentrates activity at medium to high densities; (2) *mix*—compact development mixes homes, shops, and workplaces; (3) *centeredness*—compact development has distinct, thriving activity centers, such as strong downtowns or suburban town centers, as opposed to commercial strips; and (4) *street accessibility*—compact development has streets marked by small blocks and high connectivity.[8] In this study, higher index values were associated with compact development, and lower index values were associated with sprawl. As an example, in the year 2000, the New York metropolitan statistical area had a compactness index value of 178, while Atlanta had a value of 58 and Detroit a value of 80. Manhattan had a compactness index value of 352, while Walton County had a value of 70 and Lapeer County a value of 72.

39.3 BUILT ENVIRONMENT AT THE MESO SCALE

The preceding definition of sprawl may describe metropolitan areas or counties, but is there any comparable way of describing neighborhoods, where people perform most of their active behaviors? In the 1990s, planners began describing neighborhoods in terms of "D variables." The original three Ds, coined by Cervero and Kockelman,[9] were density, diversity, and design. The Ds were later expanded to include destination accessibility and distance to transit.[10] Development scale is a sixth D, included in a few studies. While not part of the environment, demographics are the seventh D, controlled as confounding influences in travel and physical activity studies.

- Density is usually measured in terms of persons, jobs, or housing units per unit area.
- Diversity refers to land-use mix. It is often related to the number of different land uses in an area and the degree to which they are "balanced" in land area, floor area, or employment.
- Design includes street network characteristics within a neighborhood. Street networks vary from dense urban grids of highly interconnected, straight streets to sparse suburban networks of curving streets forming "loops and lollypops." Design is also occasionally measured as sidewalk coverage (share of block faces with sidewalks); average building setbacks; average street widths; or numbers of pedestrian crossings, street trees, or other physical variables that differentiate pedestrian-oriented environments from auto-oriented ones.
- Destination accessibility is measured in terms of the number of jobs or other attractions reachable within a given travel time by different travel modes, including walking and bicycling. Destination accessibility tends to be highest at central locations and lowest at peripheral ones.
- Distance to transit is usually measured from home or work to the nearest rail station or express bus stop. This variable is sometimes operationalized in terms of transit route or stop spacing.

Note that these are rough categories, divided by ambiguous and unsettled boundaries that may change in the future. Some variables overlap (e.g., diversity and destination accessibility). We still find it useful to use the D variables to organize the empirical literature and provide order-of-magnitude insights.

According to the Centers for Disease Control,[11] the two primary modifiable risk factors for obesity are unhealthy diets and physical inactivity, and the greatest areas for prevention and treatment are behavior modification and environmental change.[12–14] The larger-scale sprawl indices and the more local D variables help us measure the built environment and its relationships with healthy attributes and behaviors, including overweight and obesity. As detailed in this

chapter, the design and characteristics of built environments have been widely linked to levels of physical activity and obesity.

39.4 BUILT ENVIRONMENT AT THE MICRO SCALE

For four of the five key D variables, measurement is fairly straightforward. While there are choices to be made, and some D variables overlap, academics who conduct research in this area seem comfortable with these four dimensions of the built environment and the metrics used to operationalize them.

The remaining D, design, is more nuanced. The experience of walking down a given street may have less to do with gross qualities such as average block size and sidewalk coverage than with the micro environment of the street itself. Sometimes referred to as perceptual qualities of the street environment or, alternately, just urban design qualities, these micro qualities are frequently cited in classic readings on urban design.[15–17] Urban designers presume that these qualities are important for active street life, but have little empirical evidence to back the claim.

Focusing on the street-level experience, Ewing et al.[18,19] developed measurement protocols for nine urban design qualities, all related to walkability, cited in the literature—imageability, enclosure, human scale, transparency, complexity, coherence, linkage, legibility, and tidiness. The first five were successfully operationalized. Under the Active Living Research program of the Robert Wood Johnson Foundation, protocols were developed in order to arm researchers with measures that could be used to explain and predict levels of physical activity in urban settings. The measures, while assessed for reliability and face validity, were not assessed at the time for internal validity. That is to say, the measures were not shown to actually predict pedestrian behavior or street life.

The ultimate in "micro" is the individual building. The demonstrated effect of density on physical activity and obesity may have as much to do with stair climbing in multistory buildings as walking or bicycling between buildings. Up to five or six stories, residential buildings often lack elevators, and many taller buildings have been designed to encourage stair walking.

39.5 BUILT ENVIRONMENT AND PHYSICAL ACTIVITY

The built environment is related to both active travel and leisure-time physical activity. Walking is the most common form of active travel, 10 times more common than bicycling. Transit use is less obviously related to public health but is still classified as active travel since it almost always requires a walk at one or both ends of the trip.[20–23] Even if the transit stop is located at the nearest corner, it is likely that the short walk there will be longer than the walk to the garage. Walking and transit use are correlated with the D variables and with the four dimensions of compactness.

Correlations tell us that two or more variables are related, but it is often more helpful to speak in terms of effect sizes. Urban planners utilize elasticities to quantify effect size. An elasticity is a percentage change in one variable with respect to a 1% change in another variable. Ewing found that walking trips increased by 0.93% and transit use by 1.78% for every 1% increase in the metropolitan compactness index.[18] Another study found that, at the neighborhood level, a 1% increase in density or design measures, indicating more compact development, was associated with a 0.45% increase in both walking and transit trips.[10] A 2010 meta-analysis quantified elasticities of active travel with respect to a wide range of built environment variables[24] (see Tables 39.1 and 39.2).

Distinct from the impact of the built environment on active travel is its impact on leisure-time physical activity. Historically, urban planners dealt strictly with travel, while

TABLE 39.1
Weighted Average Elasticities of Walking with Respect to Built Environment Variables

		Total Number of Studies	Number of Studies with Controls for Self-Selection	Weighted Average Elasticity of Walking (e)[a]
Density	Household/population density	10	0	0.07
	Job density	6	0	0.04
	Commercial floor area ratio	3	0	0.07
Diversity	Land-use mix (entropy index)	8	1	0.15
	Jobs-housing balance	4	0	0.19
	Distance to a store	5	3	0.25
Design	Intersection/street density	7	2	0.39
	% 4-way intersections	5	1	−0.06
Destination accessibility	Jobs within 1 mile	3	0	0.15
Distance to transit	Distance to nearest transit stop	3	2	0.14

Source: Ewing R and Cervero R, *J. Am. Plan. Assoc*., 76, 265–96, 2010.

[a] Elasticity *(e)* = percentage change in one variable with respect to a 1% change in another variable.

TABLE 39.2
Weighted Average Elasticities of Transit Use with Respect to Built Environment Variables

		Total Number of Studies	Number of Studies with Controls for Self-Selection	Weighted Average Elasticity of Transit Use (e)[a]
Density	Household/population density	10	0	0.07
	Job density	6	0	0.01
Diversity	Land-use mix (entropy index)	6	0	0.12
Design	Intersection/street density	4	0	0.23
	% 4-way intersections	5	2	0.29
Distance to transit	Distance to nearest transit stop	3	1	0.29

Source: Ewing R and Cervero R, *J. Am. Plan. Assoc.*, 76, 265–96, 2010.
[a] Elasticity *(e)* = percentage change in one variable with respect to a 1% change in another variable.

physical activity researchers focused on leisure-time activity. Recently the two have begun to intersect. The literature on the built environment and physical activity is now so vast that it has produced at least two reviews of the many reviews.[25,26] Leisure-time physical activity studies have shown that the use of trails or bikeways is negatively correlated with distance to the facility, and that leisure walking increases with the presence of sidewalks and perceived neighborhood aesthetics and safety.[25,26,27–33]

For youth, physical activity is most often related to school and neighborhood environments,[34] with physical activity positively correlated with access to recreation facilities, general accessibility, land-use mix, walkability, and transportation infrastructure and negatively associated with local conditions of crime and economic deprivation.[35–38] Traffic speed,[35] distance to school,[39,40] and the number of roads to cross are also inversely associated with physical activity.[36]

At the micro level of the individual block, a recent paper attempted to validate urban design measures against pedestrian counts on 588 street segments in New York City. An effort was made to distinguish which measures, if any, influence levels of pedestrian activity after controlling for the other D variables.[41] The urban design quality of transparency, related to windows overlooking the street, continuous building facades forming a street wall, and active street frontage, proved to have more explanatory power than any other D variable.

At the smallest scale, environmental factors related to physical activity may also be present at the individual building level. Stair use is the most common indicator used to study physical activity and weight gain. Research has shown that more stair use, and thus more physical activity, is associated with four key variables: design,[42] legibility (visibility, stair type, number of turns from entrance), number of nearby potential stair users, and convenience of stairs to an entrance.

One study examined how stair design and elevator programming were related to stair use. Results showed that more open and appealing stairs, teamed with an elevator programmed to stop every three floors, were used 33 times more than enclosed stairs adjacent to a non-programmed elevator.[43] Oleander and Eves recently tested an entirely different approach[44] by simply posting prompts reminding potential users that stair climbing is a viable option. They found that stair use significantly increased above the levels achieved with a simultaneous educational campaign. The authors noted that better results were achieved with the prompts at about 5% of the cost.

We know that compact built environments are related to higher rates of physical activity, and we know that higher rates of physical activity are linked with lower body weights. So it stands to reason that more compact built environments would also be related, perhaps indirectly, to lower rates of overweight and obesity compared to sprawling environments. The next section explores this relationship.

39.6 BUILT ENVIRONMENT AND OBESITY

39.6.1 County- and Neighborhood-Level Analysis

Research has established statistically significant links between elements of the built environment and the risk of obesity.[45] It may be that some neighborhood environments are more "obesogenic" than others.[46] After controlling for age, education, fruit, and vegetable consumption, and other sociodemographic and behavioral covariates, Ewing et al.[47] found that adults living in sprawling counties had higher body mass index (BMI) and were more likely to be obese (BMI > 30) than those living in compact counties. Frank and colleagues have reported similar relationships for adults living in sprawling neighborhoods versus compact, walkable neighborhoods.[48,49] Black and Macinko confirmed these associations but found no clear evidence as to which elements were most important.[46]

Despite the large elasticities found for physical activity, the relationship between sprawl and body weight is small yet significant. Ewing found that a 1% increase on a county sprawl measure (indicating more compact development) was associated with a 0.013 decrease in BMI.[18] The relationship is miniscule, yet it is in the expected direction and is of plausible magnitude. We would not expect the built environment to overwhelm the many genetic, demographic, behavioral, and other environmental influences that contribute to overweight and obesity. Policy solutions that address the built environment are appropriate in concert with behavioral and other interventions.

Feng et al. were less convinced that many characteristics of the built environment are strong risk factors for obesity.[50] By evaluating studies according to their methods of research and analysis, as well as comparing their results, this review found that little can be determined from the available findings. Almost all of the studies considered were cross-sectional, making it difficult to infer causality, and there were various definitions of foundational concepts, such as "place," "walkability," and "sprawl," leaving the authors to wonder whether the studies were really measuring the same variables.

39.6.2 Socioeconomic Status Impacts

The socioeconomic status of an area plays a role in the relationship between obesity and the built environment.[51] Obese individuals of lower socioeconomic status, as well as minority races and ethnicities, are likely to live in neighborhoods with few places to exercise, lower perceived safety, and more calorie-dense food outlets.[52] Living in an economically deprived neighborhood increases an individual's risk for overweight and obesity, even after controlling for individual-level socioeconomic status.[53] Black and Macinko suggested that a shortage of social resources and influential networks among lower income neighborhoods is also related to increased levels of obesity.[46] But it seems as though the design of most lower-income neighborhoods is not the main problem. In fact, though these neighborhoods often have poor access to healthy food options and may face real or perceived safety concerns, their neighborhood environments are often designed to support more active transportation options.[54] Lovasi et al. agreed with these findings, discounting the relevance of walkability and sprawl measures in low-income and racially diverse areas.[52]

One survey of literature on youth found that obesity is consistently associated with socioeconomic disadvantage.[55] Another literature survey found that access to programs and facilities, certain aspects of the neighborhood environment, and urban sprawl are associated with obesity in children.[56] A recent review of the association between the built environment and childhood obesity found that weight gain is more likely to occur when convenience stores are more accessible and when physical activity facilities are less accessible.[57]

39.6.3 Food Environment Impacts

Diet plays an important role in rising rates of obesity, and diet has a spatial component. In the past several decades, as people moved out of urban areas and into the suburbs, so did supermarkets and retail food outlets, leaving many urban residents with very limited access to fresh fruits and vegetables and other healthy foods. These "food deserts," as they are often called, are the result of an interaction between calorie density and population density. Residents of communities with access to healthy foods have healthier diets; proximity of supermarkets is associated with lower rates of obesity; and the presence of convenience stores with less healthy food options is associated with higher rates of obesity.[45,58]

39.6.4 Green Space Impacts

Only a few studies have looked at the relationship between green space and obesity, with mixed results. In 2010, Lachowycz and Jones reported that only 23% of these studies found an unambiguous positive relationship, while another 46% were mixed or weak.[59] The three studies the authors reviewed that looked at obesity-related health outcomes, such as circulatory diseases, found positive relationships with the amount of accessible green space. The authors warned against overinterpreting their results because most studies did not consider the quality of the space, and multiple tests were often used, increasing the likelihood of finding significance from a weak relationship.

39.6.5 Block-Level Analysis

At the block level, Neckerman et al.[51] investigated whether urban design qualities were related to BMI for a sample of 13,102 adults in New York City. BMI was objectively measured. Individual demographics including age, gender, race/ethnicity, and education were controlled. Neighborhood poverty, race/ethnic composition, and, in some models, population density were also controlled. In a multilevel analysis, three urban design qualities—imageability, enclosure, and transparency—proved significantly related to individual BMI in the expected direction. The other two—human scale and complexity—were not significant.

39.6.6 Building-Level Analysis

At the building level, does increased stair climbing decrease weight? Based on a review of eight studies, Dolan et al. predicted that a 2.8% increase in stair climbing would result in a weight loss and/or weight gain prevention of 0.3 kg of weight gain per person per year among new stair users, a small yet significant impact. The authors noted that the effect size of motivational signs prompting stair usage was twice as large for females as it was for males.[60] But another study concluded that while stair climbing can increase cardiovascular fitness and provide cholesterol benefits, there was no association with weight loss.[61] Such a small or nonexistent effect suggests that obesity prevention efforts at the built environment level are best focused on the building's surroundings rather than the building itself.

39.6.7 Study Limitations

Studies reviewing the methodologies of previous research have pointed out some areas for improvement as the discipline matures. Self-reports are often used to evaluate activity behaviors and neighborhood environments, which can lead to perception bias as well as low agreement on neighborhood characteristics. Few studies attempt to verify reported information, an important step in assuring accurate results.[46,54] Booth and associates also suggest that instruments of measurement may present problems. Many studies gather geographical information from indirect sources, such as geographic information system software and publicly available

data sets, which are easy to obtain but may not accurately represent the area at the time of the study. Feng et al. also criticized the often-used method of combining the various environmental factors into composite indices.[50]

39.7 CONCLUSION

Returning to the Pima provides us with a good takeaway from the built environment–obesity literature. It seems likely that the differences in Arizona's and Mexico's built environments play at least a moderate role in the physical activity behaviors of residents. American infrastructure is generally more modern than Mexico's, and wage rates are significantly higher, leading to an assumption that it is physically easier to meet one's basic needs on the Arizona side of the border, leading to fewer bouts of necessary physical activity. As a result, it is likely that the built environment also plays a role in the higher rates of obesity and related diseases among the Arizona Pima, though this relationship is much weaker and likely indirect in nature. Whether the environment causes higher or lower rates of physical activity and obesity is more difficult to establish, yet it is likely that the causal relationship is circular and weak compared to other factors, such as genetics and socioeconomic status. In short, the built environment is no silver bullet when it comes to obesity prevention, yet ignoring the built environment is not sensible either.

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40 Social and Economic Determinants of Obesity

Lindsay McLaren

CONTENTS

40.1 INTRODUCTION

This chapter draws on the extensive research literature documenting patterning of obesity by socioeconomic factors, within and between countries worldwide. The chapter proceeds as follows. I first review what is known about the association between socioeconomic factors and obesity, based on existing reviews. I then extract key summary points, highlighting variation by gender, age (adults and children), over time, country's development status, and indicator of socioeconomic status (SES). Summary points are then interpreted with reference to Bourdieu's multidimensional theory of social class and to four frameworks (behavioral, material, psychosocial, and neo-material) that have been used to understand social inequalities in health more generally.

40.2 RELATIONSHIPS BETWEEN SOCIOECONOMIC FACTORS AND OBESITY

40.2.1 Findings from Existing Reviews

There are at least seven reviews of the literature whose primary focus is the relationship between socioeconomic factors (e.g., income, education, and other indicators of material or social resources) and obesity (overweight, body mass index [BMI], and other indicators of adiposity) in various populations.[1–7]

Sobal and Stunkard[1] published the first major review of the literature on the association between SES and obesity. Based on an exhaustive review of the studies published between the 1960s and the mid-1980s, these authors located 144 pertinent reports that collectively pointed to a strong inverse association (higher SES and lower obesity) among women from developed societies. In brief, 93% of studies from the United States and 75% of studies from other developed societies showed an inverse association for women. Also shown was a strong positive association (higher SES and higher obesity) among men (12 of 14 studies), women (10 of 11 studies), and children (14 of 16 studies for girls; 13 of 15 studies for boys) in developing societies. The relationships for men and children in developed societies were inconsistent.

In a 2004 paper, Monteiro et al.[2] reviewed research on the SES–obesity relationship among adults in developing countries, based on 14 studies published between 1989 and 2003. They built on Sobal and Stunkard's[1] findings (higher SES and higher obesity for both men and women across the developing world) by identifying a more nuanced pattern: rather than obesity being solely an attribute of the rich in developing countries, a gradient was observed, whereby as a country's gross national product increases, obesity tends to appear increasingly among those of lower SES. Gender differences were observed, whereby the shift of obesity to those of lower SES appears at an earlier stage of economic development (i.e., at a lower gross national product) in women than in men.

McLaren[3] set out to update the Sobal and Stunkard review, focusing on adults worldwide, and to build on the earlier review by exploring different indicators of SES. Findings were based on 1914 associations from 333 studies. For women

in countries of high development status (based on the United Nations Development Programme's Human Development Index), the majority of associations were inverse (higher SES and lower obesity), and this was especially true for certain SES indicators (e.g., education, 72% inverse; occupation, 68% inverse). For men in developed countries, the predominant association was nonsignificant/curvilinear (no linear relationship), though some nuance by SES indicator was apparent. For both men and women, there was a general pattern whereby as one moved from countries of high to medium to low development status, the proportion of positive associations increased (3%, 43%, and 94% for women and 9%, 39%, and 100% for men, respectively), and the proportion of inverse associations decreased (63%, 26%, and 0% for women and 37%, 6%, and 0% for men, respectively); this gradient effect is consistent with Monteiro's[2] findings in developing countries. In countries of medium and low development status, positive associations were most numerous when income was the SES indicator.[3]

Shrewsbury and Wardle[4] reviewed studies focused on school-age children (ages 5–18 years) in developed countries. They identified 45 studies containing measured data on adiposity, of which 42% showed an inverse association (higher SES and lower obesity); the inverse association was particularly prominent when parental education was used as the indicator of SES (75% inverse). No positive associations were detected. Shrewsbury and Wardle[4] did not observe striking gender differences: of the studies that presented sex-stratified results, over half found the same association for boys and girls, and there was no difference in the proportion of inverse associations for boys versus girls.

At least three reviews have focused on longitudinal aspects of SES and obesity, all in developed countries. Ball and Crawford[5] examined the relationship between SES and change in body weight over time among adults from developed countries. The review was based on 70 distinct associations from methodologically strong studies (i.e., those that contained measured adiposity data, had a follow-up period of at least 4 years, and contained multivariate adjustment) of predominantly nonblack samples. Among women, an inverse association was observed between occupation and weight gain (89% of associations were inverse) and between education and weight gain (68% inverse), but not for income and weight gain. For men, an inverse association was observed between occupation and weight gain (83% inverse), but there was only marginal support for an association between education and weight gain (50% inverse) and no support for an association between income and weight gain (17% inverse). Positive associations were rare. Collectively, Ball and Crawford's[5] findings suggest that occupational status may influence later weight/obesity status in both men and women. Furthermore, the longitudinal nature of the original studies supports the conclusion that the SES–obesity associations detected in cross-sectional studies cannot be explained by social selection alone (social selection refers to the process whereby obesity leads to lower SES through downward social mobility).

Parsons et al.[6,8] reviewed literature on childhood predictors of adult obesity in industrialized countries and observed that, among the various risk factors examined, SES stood out as one of the most consistent predictors of adult obesity. Based on 12 studies that examined the influence of SES in childhood (i.e., parents' education, occupation, income, or a composite) on obesity in adulthood, with a study duration ranging from 10 to 55 years, the overall pattern of findings was that both men and women from lower socioeconomic origins had a greater risk of obesity in adulthood than those from higher socioeconomic origins. This inverse effect was observed in four of five associations among women, eight of nine associations among men, and three of four associations among combined male/female samples.

Finally, Senese and colleagues[7] updated the Parsons et al.[6] review, focusing on studies published between 1998 and 2008 that examined the association between childhood socioeconomic position (SEP) and adulthood obesity. Forty-eight publications, based on 30 studies from mainly highly developed countries, were identified, most of which used parental occupation as the indicator of childhood SEP. Inverse associations (lower SEP in childhood and higher likelihood of obesity in adulthood) were observed in a majority (70%; 14 of 20 studies) of studies in females, but in only 27% (4 of 15 studies) of studies in males. Adjusting for adult SEP reduced the proportion of studies with inverse effects to 47% in women and 14% in men, which the authors interpreted as suggesting that adult SEP may be one of the pathways through which the childhood SEP–adulthood obesity operates. Because the studies spanned a long time frame, the authors examined findings stratified by year of participants' birth and found that inverse associations were more common for studies in which participants were born since 1950 than for studies in which participants were born before 1950, for both males and females.

40.2.2 Variation by Gender and Over Time for Adults and Children in Affluent Countries

Based on these reviews, which collectively incorporate more than 600 original articles, some summary points may be drawn. First, there is a consistent inverse association between SES (current or during childhood) and obesity (or overweight, BMI, and weight gain) among adult women in affluent countries. The association for men in these countries is mixed. This pattern appears to be stable: it is apparent in reviews published across a 20-year period, with original studies spanning a half-century, and continues to be observed, according to recent multicountry studies.[9–11]

At least two studies have investigated whether there has been any demonstrable change over time in the nature of the SES–obesity association among adult men and women in affluent countries, with somewhat conflicting findings. Molarius et al.[12] examined the association between education and BMI among men and women in 26 countries of mostly high development status in two surveys that were 10 years apart. For women, a majority of populations showed an inverse association at both time points, while for men, there were similar numbers of inverse and nonsignificant associations at both time points. In approximately two-thirds of the populations (19 of 26 for women; 16 of 26 for men), the educational

inequalities in BMI increased (worsened) between the two survey periods. The authors concluded that there was a changing trend over time toward an inverse association in men and toward an increasingly inverse association among women. On the other hand, Devaux and Sassi[11] examined inequalities in obesity and overweight by education among men and women in eight Organisation for Economic Co-operation and Development (OECD) countries over a 7- to 12-year period and reported that they were largely stable, though there was some indication (based on an education × time interaction term) of a reduction (narrowing) in inequalities in England and France. Overall, the nature of change over time—if any—in the SES–obesity relationship among adults in affluent countries is not clear and may vary by country or region rather than show a generalized pattern.

In terms of children in affluent countries, the review findings suggest change over time: whereas Sobal and Stunkard[1] found no clear relationship between SES and obesity for children in developed countries in their 1989 review, Shrewsbury and Wardle's 2008 review[4] observed a tendency toward an inverse relationship. Neither Sobal and Stunkard[1] nor Shrewsbury and Wardle[4] detected sex differences in the nature of the SES–obesity relationship; this absence of sex differences was furthermore reported by Due et al.[13] in their multisite investigation of the SES–BMI relationship among adolescents in 35 countries in North America and Europe. Overall, and unlike in adults, an inverse SES–obesity relationship in children in affluent countries appears to have emerged more recently (i.e., since the 1989 review) and not to be characterized by gender differences (as recently as a 2009 publication[13]). Whether gender differences will emerge when the current cohorts of children reach adulthood, or whether they will be apparent in subsequent cohorts of children, is not known.

40.2.3 Global Variation: A Social Transition?

A second summary point pertains to the global reversal of the association between SES and obesity among adults: whereas it is predominantly inverse (higher SES and lower obesity) in affluent countries, it is predominantly positive (higher SES and higher obesity) in poorer countries; gender differences are evident worldwide. Countries of middle development status are intermediate between richer and poorer countries in terms of the proportion of positive and inverse associations, as demonstrated by McLaren[3] worldwide and more recently by Boissonnet[10] among middle and high Human Development Index cities in Latin America (a region undergoing rapid social and nutritional transition).

Following from the observation of Monteiro and colleagues,[2] noted earlier (Section 40.2.1), that the burden of obesity tends to shift toward the poor as a country's wealth increases, at least three studies have investigated the existence of a hypothesized social transition whereby the proportion of inverse associations may be linked to an indicator of national wealth. Fleischer et al.[9] found that among 70 countries in the World Health Surveys, the relationship between education and BMI became increasingly inverse as level of urbanicity (highly correlated with affluence) increased, particularly for women. Jones-Smith and colleagues[14] examined the SES–overweight association among women in 37 developing countries between 1989 and 2007 and found that as gross domestic product increased, there was a faster increase in overweight among lower SES groups, which also supports the social transition hypothesis. On the other hand, Subramanian et al.[15] found that country-level economic development did not moderate the SES–BMI relationship among women in 54 middle- and low-income countries. Thus, while there does appear to be a gradient whereby the proportion of inverse SES–obesity associations is highest in affluent countries, lowest in poor countries, and intermediate in middle-development countries, it is not clear that the proportion of inverse associations varies in a consistent fashion with countries' economic status. In other words, the extent to which the SES–obesity association is inverse in a given country depends *in part* on its economic status; there are additional factors at play.

40.2.4 Variation by Indicator of SES

A third summary point is that the indicator of SES matters: in affluent countries, the predominantly inverse association seen in women is most prominent when education or occupation is the indicator of SES used[3,5,7]; the pattern is not consistently observed with income. In countries of middle- and low-development status, the predominant positive association is most consistently observed with income or material possessions as the SES indicator.[3,15] The pattern in middle-development and lower-development countries likely reflects, at least in part, the relatively more important role of the economic or material dimension of class in poorer countries: where food is less ubiquitous, the ability to procure food is an important factor that enables weight gain among those of higher SES and allows excess weight to become valued as a marker of affluence or distinction, which is only possible for those who can afford it.[1,3]

40.3 MULTIDIMENSIONAL THEORY OF SOCIAL CLASS

The fact that different indicators of SES are differentially important for understanding the socioeconomic patterning of obesity in different regions suggests that, for interpretative purposes, a multidimensional theory of social class (i.e., one not limited to economic factors) would be helpful. One such theory is that of Bourdieu,[16–20] who asserted that one's social class comprises the amount of *capital* one has on several dimensions: economic (i.e., income, wealth), cultural (i.e., acquired knowledge, experiences, credentials), and social (pertaining to social relationships, engagement, and norms). These forms of capital can take on symbolic value when recognized as having particular value or prestige in a society; for example, having experienced a particular event, or dressing or speaking in a particular way, may have prestige or distinction that is not entirely reducible to its economic basis. Furthermore, Bourdieu put forth the notion of *habitus*, which refers to the embodiment of one's status.[16–20] According to

Bourdieu, a lifetime of exposure to social status axes (e.g., class and gender) results in one's body (including size/shape, appearance, behaviors, and mannerisms) becoming a social metaphor for, or a marker of, one's status, which as noted comprises different forms of capital. From this perspective, the socioeconomic patterning of obesity, whereby body weight is consistently associated with particular SES indicators (dimensions of capital), is a literal example of *habitus*.

Furthermore, because of its association with physical attractiveness, health, and morality (i.e., conveying desirable attributes such as self-control), thinness in affluent societies has acquired enormous symbolic value, particularly for women. It is a marker of distinction. A thinner body among those of higher SES in affluent countries may represent a host of class-based attributes, including a higher value placed on thinness and its connotations (health, self-control, and femininity); social norms that promote and encourage thinness and related behaviors (e.g., within peer groups, occupational settings, and communities); heightened awareness to health promotion messages and increased likelihood of acting on them; and greater capacity to access resources conducive to thinness.[3,21–22] That these dynamics are more pronounced in women than in men reflects myriad historical issues of patriarchy, objectification, and gender biases.[23] The gendered nature of weight bias is well-documented. The literature on the economics of beauty shows that physical unattractiveness confers an economic penalty for both men and women (i.e., lower pay for unattractive people), which if anything is stronger for men.[24,25] The economic penalty for obesity, on the other hand, appears unique to women: obesity in women is associated with lower earnings compared to nonobese women, even adjusting for a spate of other variables that should influence earnings such as ability, health, and education. This obesity penalty is believed to operate primarily through the marriage market: obese women are less likely to marry, and among those who marry, their spouses earn less than those of nonobese women.[24]

40.4 FRAMEWORKS FOR UNDERSTANDING SOCIAL INEQUALITIES IN HEALTH

Coupled with Bourdieu's theory, which accommodates gender differences and nuance by indicator of SES, four additional frameworks can help to shed light on the SES–obesity relationship. These four frameworks—behavioral, material, psychosocial, and neo-material—were drawn from the social determinants of health literature, where they have been used to understand social inequalities in health more generally.[26,27*]

40.4.1 Behavioral Framework

Beginning at the most proximate level, the behavioral framework[26,27] explains socioeconomic inequalities in health (obesity) as a function of health behaviors, particularly those with a plausible biological link to the health outcome of interest (examples for obesity are diet, physical activity, and smoking). Although such behaviors do show an association with SES[28,29] and, to a modest extent, with obesity,[30] this framework is widely viewed within the social determinants of health literature to be insufficient. The main critique is that this framework tends to downplay the fact that behaviors do not occur in a vacuum: they are heavily constrained by the circumstances of one's daily life. Furthermore, a few studies that have assessed the role of behaviors as mediators of the SES–obesity association have shown that diet, physical activity, and smoking partially, but not fully, explained the SES–obesity association in men and women,[31–33] indicating that other factors must be at play.

40.4.2 Material Framework

The material framework[26,34] addresses the critique of the behavioral framework by explicitly focusing on circumstances of daily life (e.g., quality of housing and food, working conditions, and availability of resources with which to access amenities) as key determinants of social inequalities in health (obesity). In this framework, inequalities in material resources may lead to inequalities in obesity through behaviors; for example, limited income may impede access to nutritious foods,[35] and one's neighborhood of residence may be more or less amenable to physical activity because of its safety or layout.[36] Material insecurity (e.g., income insecurity, job insecurity, work stress, and housing insecurity) is a significant source of psychosocial stress, and both animal and human research supports an association between stress and weight gain.[37] This framework would permit interpretation of gender differences in the SES–obesity relationship in terms of gender differences in economic circumstances, such as lower occupational and economic payoff for women than for men of comparable educational attainment or achievement,[38] or in terms of sex or gender differences in implications of material circumstances for weight gain.

40.4.3 Psychosocial Framework

While the material framework is pertinent to understanding social inequalities in obesity, one limitation is that, by emphasizing the economic aspect of class, it downplays other (e.g., social, cultural, and symbolic) aspects. The psychosocial framework[26,27,39] thus complements the material framework. The psychosocial framework is grounded in the observation that the SES–obesity relationship is graded or linear in nature, which is taken to mean that it is one's position in the hierarchy relative to others that is of primary importance in understanding social inequalities in health. Relative position, and knowledge of it, leads to upward and downward comparison with others, which can evoke feelings of shame, worthlessness, and envy, and these feelings can translate, through psychobiological pathways, into poor health (obesity). Research

* These frameworks are not mutually exclusive (more than one may be in operation) or exhaustive (e.g., discussion of genetic and physiological factors is omitted; while not impertinent, and not independent of social factors, these factors alone do not suffice to explain our subject).

demonstrating a link between stress and weight gain[37] is also pertinent here. Considering the highly visible nature of obesity and body weight, and the negative connotations that obesity has acquired, especially for women, it is highly plausible that comparative processes occur (i.e., upward comparison with higher SES women, who also tend to be thinner) and could have implications for the existence and perpetuation of social inequalities in obesity.

Weight-related social norms within class groups may also play a role. In two studies focused on neighborhood-level correlates of women's body dissatisfaction (feelings of dissatisfaction with one's body weight or shape), McLaren et al.[40,41] found that women living in higher SES neighborhoods (based on average neighborhood income and controlling for individual-level income) were more likely to report body dissatisfaction than women of the same BMI level living in lower SES neighborhoods. This effect was explained by the normative (average) BMI in the neighborhoods; in other words, women in rich neighborhoods were more likely to report body dissatisfaction because women in their neighborhoods were thinner. Such proximal comparison targets (other women in one's neighborhood) may establish a norm for what is acceptable, and to the extent that women living in higher SES neighborhoods are exposed, aspire to, and are successful in attaining a thinner norm, the socioeconomic patterning of obesity in women will be perpetuated.

40.4.4 Neo-Material Framework

Finally, the neo-material framework[26,42,43] extends the other frameworks (particularly the material framework) by explicitly incorporating the political, economic, and social forces that shape how a society's inequalities come about. This framework emerged, in part, in response to a critique that the other frameworks are "de-politicized,"[26] meaning that they treat the broader forces as a static background rather than as dynamically constructed, of fundamental importance in understanding population health, and amenable to change. At least two studies exist that may be characterized as taking a neo-material approach to understanding obesity and its socioeconomic patterning. Offer and colleagues[44] began their analysis with the observation that a small cluster of affluent countries, all English-speaking and all characterized by market-liberal welfare regimes, seemed to have the highest prevalence of obesity in the world. They aimed to confirm this observation and to test two possible explanations: (1) a "food shock" hypothesis, whereby high obesity prevalence reflects rapid and substantive deployment and penetration of nonnutritious, highly palatable, and easily accessible foods; and (2) a "welfare regime" hypothesis, whereby market-liberal reforms create insecurity and inequality (i.e., job, income, and housing insecurity and status insecurity through income inequality), which in turn create stress, which in turn leads to weight gain through psychobiological and behavioral mechanisms noted earlier (Sections 40.4.1–40.4.3).

Using data from 96 surveys in 11 countries, Offer et al.[44] first confirmed a main effect of market liberalism: market-liberal countries (United States, Canada, United Kingdom, and Australia) had a higher obesity prevalence than non-market-liberal countries (Finland, France, Germany, Italy, Norway, Spain, Sweden). There was support for the food shock hypothesis operating more powerfully in the market-liberal countries, in which market freedom has led to the lowest relative price of foods (particularly fast foods), as well as to opportunity for relatively unrestricted marketing. However, the strongest support was obtained for the welfare regime hypothesis. "Insecurity" (based on security from unemployment, illness, single-parent poverty, and poverty in old age) was found to drive the model, and this effect remained even when the United States (an outlier on both insecurity and obesity) was excluded. When stratified by welfare regime type, insecurity was found to operate only in market-liberal countries, thus providing a plausible pathway (insecurity → stress → weight gain) by which market-liberal countries show the highest obesity prevalence.

In further exploring the constituent elements of the insecurity concept, Offer et al.[44] found that "security from illness" (represented by the share of private expenditure on health care in personal disposable income) was the driving component. "Inequality" (represented by intensity of poverty and the Gini coefficient) did not show the expected association with obesity in multivariate models, which contrasts with some studies that have demonstrated a positive association between inequality and obesity across affluent countries (i.e., higher inequality and higher obesity prevalence).[13,45] However, a study by Su and colleagues[46] among 31 OECD countries found that the positive association between inequality and obesity was entirely driven by two countries that were outliers on both inequality and obesity: the United States and Mexico. Perhaps insecurity, created and perpetuated by dynamics of market-liberal regimes, is the more important explanatory attribute.

The apparent importance of insecurity was further examined by Wisman and Capehart,[37] who explored the "creative destruction" of capitalism as a plausible driver of the obesity epidemic. They hypothesized that the rising obesity prevalence reflects increased insecurity and stress stemming from capitalism, within an environment characterized by food abundance, and that the social gradient of obesity reflects a social gradient of insecurity and stress. Creative destruction is the process that characterizes capitalism as a dynamic system, one that, as described by Schumpeter and inspired by Marx, "incessantly revolutionizes the economic structure from within … destroying the old one … creating a new one" (p. 83).[47] While this process is responsible for capitalism's immense wealth-creating capacity (e.g., rising average incomes, new products, and technologies), it is also responsible for increasing economic and social insecurity: job and income insecurity, workplace stress, rising income inequality and resulting status insecurity, rising prison population, class-segregated neighborhoods, and declining social capital.

Human and animal research support a link between stress and weight gain.[37] The time period of increasing obesity prevalence in affluent liberal democracies has generally coincided with increasing insecurity in these environments, with the slight exception of the 1960s through the 1980s, during which

obesity prevalence stabilized yet creative destruction was "more robust than ever."[37] Wisman and Capehart attributed this anomaly to a holdover of social and economic optimism from the post-World War II period, which was characterized by a healthy economy and security-promoting public policies. With the 1973–75 and 1981–83 recessions, the historical struggle for material security returned, and capitalism's influence on obesity, through insecurity, picked up steam. Wisman and Capehart[37] provocatively argued that, if their analysis is correct, then the obesity epidemic "is symptomatic of a social mistake" and that "alongside ecological destruction, obesity may be one of the canaries dying in the mine" (p. 968) of capitalism.

It is important to emphasize that identifying capitalism as the fundamental driver of rising obesity prevalence is somewhat of an oversimplification. First, as recognized by Offer and colleagues,[44] capitalism is not a singular, uniform phenomenon; there are variants of capitalism that have varying implications for insecurity and population health. Stanford,[48] for example, distinguished between four types of capitalism: Anglo-Saxon (United States, United Kingdom, Canada, and Australia); Continental (France, Germany, and Italy); Asian (Japan, Korea, and China); and Nordic (Sweden and Denmark). These types differ in terms of, for example, the extent of economic regulation by government, taxes as a share of gross domestic product, the magnitude and importance of the financial sector, and the approach to managing income distribution. Variation in these dimensions contributes to variation in income inequality and material insecurity, which has been observed to have implications for at least some aspects of population health in at least some societies.[27,49–51] Furthermore, even to the extent that reasonably homogenous subtypes of welfare regimes can be identified, the implications for population health may be more closely related to specific policy instruments (e.g., the generosity of various types of public expenditures and their degree of coverage) than to the regime type per se.[52] It also bears mention that noncapitalist regimes (e.g., former Soviet Union, Cuba, and other Eastern European countries) do not necessarily provide a viable solution: these regimes, though socialist in orientation, may in fact be quite inegalitarian, with a small political elite and a large "equal," though poor, majority.[53]

Despite these qualifications, several authors have highlighted a trend, particularly since the 1970s, toward increasing neoliberalism, characterized by deregulation, economic liberalization, and an enhanced role of the private sector, in both capitalist and former capitalist countries.[48,54,55] This trend signifies the importance of analyses such as those by Offer et al.[44] and Wisman and Capehart[37] in understanding the determinants of obesity in populations worldwide. The obesity research literature as a whole contains a wealth of information on determinants operating at a level proximate to the individual; yet analysis rooted in a neo-material framework is essential if we wish to understand the social and economic determinants of obesity, which ultimately represent the biggest leverage point on this public health issue.

40.5 SUMMARY

This chapter showcases the extensive research literature illustrating that obesity is patterned by socioeconomic factors within and between countries worldwide. The patterns may be summarized as follows:

- There is a consistent inverse SES–obesity association among women in affluent countries; the association for men in these countries is mixed; and these patterns appear to have been largely stable over the past half-century. For children in affluent countries, an inverse relationship appears to have emerged more recently, and gender differences are not prominent.
- Globally, the SES–obesity relationship tends to be predominantly inverse in affluent countries, predominantly positive in poorer countries, and intermediate in middle-development countries; these patterns are more prominent for women than men.
- The indicator of SES matters: in affluent countries, the predominantly inverse association is most prominent when education or occupation is the indicator of SES used, while income or material factors are most important in the predominantly positive association seen in the developing world.

The nuance observed in the SES–obesity relationship worldwide reflects multiple aspects of class or status, for which Bourdieu's *habitus* provides a helpful interpretive framework. Interpretation is further assisted by application of four frameworks that have been used to understand social inequalities in health more generally; these frameworks enable understanding of the SES–obesity relationship in individuals and populations in terms of processes ranging from individual health behaviors (behavioral), to living and working conditions (material), to upward and downward social comparison (psychosocial), and to the dynamics of capitalism (neo-material). Collectively, chapter material points strongly to a view of obesity as a phenomenon with significant social and economic dimensions, the understanding of which may importantly inform intervention efforts.

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41 Influence of Culture on Obesity

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CONTENTS

41.1 INTRODUCTION

Few would question that the current obesity epidemic represents a complex public health problem that requires understanding of its multiple determinants. Although evidence suggests that obesity rates have stabilized among some U.S. populations, disparities among racial/ethnic and socioeconomically disadvantaged populations persist.[1,2] Genetic predisposition is estimated to explain 45%–75% of obesity,[3–6] it is the interaction of genes with the enabling environment that presents opportunities for intervention. For example, cultural influences may contribute to the higher than average risk of obesity among children and youth of U.S. ethnic minority populations.[7]

Culture can be defined as the behaviors, beliefs, and characteristics of a particular social, ethnic, or age group. For social and ethnic groups, these behaviors are typically learned in childhood and are often the beliefs and values that represent unconscious factors in the motivation of individual behaviors.[8] Culture can shape values and norms about dietary intake, physical activity, and body weight itself, which in turn can influence body weight and weight change of individuals through societal modernization, migration, and acculturation. This chapter explores how culture influences key behaviors that, in turn, influence overweight and obesity. Given the vast variation of cultures across countries, the work summarized here will focus only on the United States, where rates of obesity are among the highest globally.

The socio-ecologic model serves as useful theoretical framework in considering how culture may influence obesity risk behaviors at different levels—within the family, community, and larger society. Although culture is commonly placed in the outer spheres of this model, where cultural norms and values regarding body shape, for example, are societal,[9] there may be marked discordance between family contexts and community/societal contexts for specific subpopulations, including immigrants. For example, families that immigrate to the United States may have differential cultural experiences within the same family depending on their age at immigration; children may hold certain cultural values within the family context, but discard these more traditional cultural values when faced with social norms outside of the home. Section 41.2 gives a review of the literature on weight change associated with migration and acculturation. Section 41.3 describes what is known about attitudes and behaviors related to body size and how parental feeding styles and practices may be influenced by these cultural norms. Section 41.4 explores our understanding of cultural influences on diet, physical activity, and sedentary behavior. Section 41.5 provides a framework for future work on culture and obesity.

41.2 MIGRATION AND ACCULTURATION

Regardless of country of origin, upon arrival, immigrant adults have healthier dietary and physical activity patterns than their U.S.-born counterparts; these relative advantages dissipate over time,[10] and overweight and obesity increase.[11–16] The weight gain experienced by immigrants likely reflects a combination of financial, linguistic, and social stressors encountered during the acculturation process.[17] Immigrant weight gain may also be influenced by the "obesogenic" environment of the United States, characterized by the availability of energy-dense, highly palatable, inexpensive foods and limited opportunities for physical activity.[11–14,18,19]

The phenomenon of acculturation has been an area of research since 1918.[20] It has been approached from several disciplinary perspectives, including psychology, anthropology, economics, and sociology with myriad theories and numerous definitions. In the 1930s, the discipline of anthropology offered this definition: "Acculturation comprehends those phenomena which result when groups of individuals having different cultures come into continuous first-hand contact, with subsequent changes in the original culture patterns of either or both groups."[21] In the 1960s, Milton Gordon, a sociologist, defined acculturation as process of accommodation with eventual and irreversible assimilation into a dominant group.[22] More recently, John Berry, a psychologist, has defined acculturation as the process of cultural and

psychological change that results following meeting between cultures.[23] The framework associated with this latter definition reflects the awareness that acculturating individuals and groups bring cultural and psychological qualities with them to the new society and that the new society also has its own array of those qualities. To fully understand the acculturation process, one must consider the cultural values, norms, and attitudes between the two cultural communities. Importantly, no cultural group remains unchanged following cultural contact; it is a two-way interaction.[23]

Despite widespread awareness that acculturation reflects a bidirectional process of change, research and theory have focused primarily on the adjustments and adaptations made by minorities, immigrants, refugees, and indigenous peoples, and so on, in response to their contact with the dominant majority. As a complex construct, acculturation cannot be measured directly. Studies of acculturation and obesity in these populations have used proxy measures as indicators of acculturation. These proxy measures typically include immigration status, length of residence, language, and place of birth. Oza-Frank et al. synthesized the current literature as of 2010 on the relationship between immigrant duration of residence in the United States and body weight. Among the 15 articles that met inclusion criteria, 14 reported a significant, positive relationship between body mass index (BMI) and duration of residence in the United States (all p-values $< .10$). Two studies reported a threshold effect of weight gain after 10 years of U.S. residence, and another study found that BMI peaks 21 years after arrival to the United States for men and after 15 years for women.[24] Although the association of duration of residence in a Western culture, especially the United States, is associated with obesity is well established, little empirical evidence has been published to support the widespread assumption that the association is a manifestation of acculturation. Because diet and physical activity directly influence body weight through caloric imbalance, some studies have sought to characterize how these behaviors change with immigration.

As immigrants acculturate to the United States, they may modify their dietary and physical activity behaviors as they adapt to or borrow traits from this new culture.[25] In particular, increased length of exposure to the U.S. environment (e.g., time in country, first vs. second generation) is associated with greater self-reported dietary change,[11,14] such as decreases in the consumption of traditional foods, decreases in fiber intake, and increases in total fat, sugar, and calories.[26–29] Changes in activity patterns are also documented, with apparent positive associations between length of residence in the United States and leisure time physical activity.[12,13,19,30,31] In contrast, nonleisure time physical activity (occupational, transportation-related, and household-related) appears to be negatively associated with being more acculturated (e.g., English language proficiency, generation in the United States, time in country, or age at arrival).[18,32–34] It is worth noting that global shifts are occurring as well: with a transition from a world in which the higher-income countries were dominated by patterns of nutrition-related noncommunicable diseases (while less well-resourced countries were dominated by infectious disease and receding famine) to one in which the entire world is increasingly characterized by high availability of energy-dense foods, less work-related physical activity, and increased sedentary behavior.[35] The acculturation process will surely be affected by these global changes.

41.3 ATTITUDES AND BEHAVIORS RELATED TO BODY SIZE AND THE INFLUENCE ON PARENTAL FEEDING STYLES AND PRACTICES

As compared to white women, ethnic minority women and adolescents have, on average, a greater acceptance of overweight and report higher rates of body-image satisfaction, independent of body weight.[36,37] Among the most studied populations in this regard are Mexicans, Mexican-Americans, and African-Americans. For example, data suggest that Mexican-American men and women are less likely to perceive themselves as overweight as compared to white men and women.[38] Interestingly, Guendelman et al. assessed actual and perceived weight in nationally representative cohorts of adults in Mexico ($n = 9527$) and the United States ($n = 855$) using data from the National Health and Nutrition Examination Survey (waves 2001–2006) and the 2006 Mexican National Health and Nutrition Survey and found that overweight and obese Mexican-American women were more likely than overweight and obese Mexican women to label themselves as overweight and obese. This difference was significant, even after controlling for sociodemographic and weight-related variables.[39] They also found that those women who had been told by a health provider that they were overweight or obese were much more likely to perceive themselves as such. However, it is noteworthy that significantly fewer women in Mexico than in the United States recalled having been screened for obesity by their health-care provider, suggesting that the different cultural norms about body size may operate at multiple levels.

A study completed among the Hmong group, who share a heavy ideal body image, found that the majority of 9- to 18-year-old children studied were dissatisfied with their bodies and tended to endorse American ideals of beauty and attractiveness rather than the heavier, traditional Hmong body ideal supported by their parents.[40] The cultural belief that being heavier is healthier reflects experiences embedded in the history of racial and ethnic minorities whereby threats of undernutrition and food scarcity in previous generations influenced feeding and eating.[41] As more immigrant groups populate the United States, it is possible that these more traditional ideals will become less prominent or differ between children and their parents.

Body image attitudes that may be tolerant for obesity development have also been clearly documented in African-Americans.[42–46] These attitudes are particularly problematic in the context of the U.S. food environment, where high-calorie foods and beverages are abundant, low in cost, and heavily marketed. In addition, excess obesity among women

in ethnic minority populations creates a sociocultural milieu in which obesity is normative.[7] Ayala and colleagues found that a strong identification with Mexican culture was a significant predictor of body dissatisfaction during the earlier stages of childhood,[47] whereas among adolescents, individuals who identified more strongly with body ideals portrayed in the popular media were more likely to experience body dissatisfaction.

Given these cultural norms in the context of the family unit, parents frequently fail to perceive that their children are overweight;[48–50] this is especially true for minority children.[51–56] Such misperceptions may occur early in a child's life. A qualitative study that held focus groups with African-American, Hispanic, and white low-income mothers ($n = 101$) of 2- to 5-year-olds to gain insight into these issues found that mothers were concerned about their children being underweight rather than overweight. When asked to respond to a series of drawings of children on a continuum of body sizes, mothers selected the most extreme schematic drawing as their threshold to identify overweight. This suggests that mothers perceived overweight as normal-weight status.[57]

Such misperceptions are consistent with other findings as well.[42,58] For example, in a study of 622 mothers of children 23–60 months of age participating in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), mothers, especially those with less education, did not view their overweight children as being overweight.[58] Additionally, the mothers in this study did not indicate awareness of an upper limit of acceptable infant weight. Furthermore, they believed it was better for infants to be heavier and that heavier and faster growing infants were healthier and better cared for. In this study, mothers also voiced concern that infants would not be getting enough to eat without the provision of cereal and other solid foods earlier than recommended by health professionals. A study that evaluated interviews conducted with African-American mothers and grandmothers of infants who were participating in WIC found that it was the cultural norm to feed cereal in the infants' bottles as early as 1–2 weeks of age and to feed other semisolid food within the first month. Grandmothers had substantial influence on the decisions regarding what infants were fed.[59] Other investigators have found similar results both with respect to early introduction of solid foods and with respect to grandmother influence.[60,61] Hispanic parents may be more likely to hold on to cultural beliefs that their children need to be heavier for them to be healthy.[62]

41.4 CULTURAL CONTEXT OF FOOD, PHYSICAL ACTIVITY, AND SEDENTARY BEHAVIOR

The key behaviors that give rise to positive energy balance, and ultimately to obesity, provide a context for expression of ethnic ideals, identities, and roles in everyday life in families, schools, workplaces, and communities. Part of every culture reveals traditional uses and meanings for food that may help create social interactions and define pleasure and punishments. There are also traditions around how food relates to health and which foods are protective and which are harmful.[63] Culture influences eating patterns and differs among populations, classes, and groups.[64] These influences are formed by interactions with the physical, economic, and sociopolitic environments.[7] Although there is a large anthropologic and sociologic literature on the relationship between foods and culture throughout history,[65] in this section, we only review research studies, most of which have been qualitative investigations, relating to food and physical activity in relation to culture and obesity.

The consumption of food is such a central human activity that it appears to take on meaning important to cultural identity. A 2012 qualitative study examined food choices of 20 low-income African-American women and found that meanings may be ascribed to foods in a variety of ways. For example, some women emphasized the role of childhood memories associated with certain foods in their preferences for familiar foods.[66] This association has been described as food selection of past memories.[67] Using participant observations in New York and Puerto Rico and in-depth interviews of adolescent girls, Bowen and Devine identified four dominant food choice types: everybody cooks, tradition keeper, seeker, and on my own. The everybody cooks and tradition keeper subjects were more likely to have diets with more traditional foods.[68] Devine et al. found that African-Americans frequently expressed their ethnic identity through food choice, particularly at family gatherings and around holiday celebrations.[69] Also, among African-American populations in the southeastern United States, consumption of food high in fat is a part of cultural practice.[70] Compared with young white females, African-American females appeared to consume more calories from fat and reported that social influences have a greater impact on their dietary practices.[71] It should also be acknowledged that food choice can also reflect other social and environmental characteristics, such as food access[72] and discrimination.[73]

Culturally determined attitudes may also influence physical activity and inactivity levels. In the area of physical activity, culture influences time-use priorities. Interest in sports or traditions of being active may be rooted in certain cultural beliefs. Cross-sectional accelerometry data from the 2003–2004 and 2005–2006 National Health and Nutrition Examination Survey obtained from 3106 youth aged 6–19 years identified a complex interaction between age, BMI, and ethnicity in relation to time spent in moderate to vigorous physical activity. Overall, the authors found that obese youth spent 16 fewer minutes per day in moderate to vigorous physical activity than normal-weight youth. However, non-Hispanic white males spent 3–4 fewer minutes per day in vigorous physical activity than Mexican-American and non-Hispanic black males but had lower obesity rates, and obese 12- to 15-year-old Mexican-Americans recorded similar minutes in moderate to vigorous physical activity per day as normal-weight Mexican-Americans. The authors surmised that these complex relationships reflect cultural as well as biological factors.[74] Wolf et al. suggest that in Hispanic and Asian cultures, strenuous physical activity may not be considered attractive for girls, or it may be displaced by an emphasis

on academic achievement for school-aged children.[75] Other studies suggest that for African-American women, who tend to have body image ideals of being heavier, these attitudes may directly interfere with physical activity. Women also have reported avoiding physical activity because of hesitance to go out in public with sweaty, messy hair.[76,77] Studies of African-American women identify "putting the needs of others before one's own" as a cultural norm that serves as a barrier to physical activity.[78] Korean immigrant women consider physical activity from a more holistic perspective, in other words, only one of many elements in the individual's attempt to stay in overall balance.[79] An additional factor may be the translation of some of the terminology used in asking questions—the term "leisure-time" activity, when translated into Spanish, may preclude responses that include strenuous activity of any kind.[31]

Views of sedentary behavior are similarly influenced by cultural contexts and values. In some contexts, television viewing is a symbol of economic sufficiency, and thereby may predispose to sedentary behavior. In a 2010 review, Hoyos Cillero et al. found that ethnicity was consistently associated with screen time (TV viewing, computer use/video games/electronic games playing, and nonspecific media time).[80] For example, a qualitative study completed among 20 low-income Latina mothers in the Northeast found that television watching was seen as integral to family life, including watching TV during meals, using TV as a babysitter, and as a tool to learn English.[81] The authors also found that, consistent with other studies,[82,83] weather was one of the most important barriers for engaging children in physical activity. One study completed among Hispanics found that parental activity levels helped explain preschool-aged child activity levels, except for vigorous activity, which children tend to do on their own, without parental participation.[84]

41.5 CULTURALLY APPROPRIATE INTERVENTIONS AND PROGRAMS: NEXT STEPS

The clear cultural influences described in this review must be considered when thinking about obesity and tailored interventions.[85] Although some culturally tailored obesity interventions have been conducted, much work remains. For example, a 2011 review on childhood obesity interventions targeting Hispanic children found that of the nine interventions identified, only four had significant findings and only one assessed measures such as acculturation. Based on their review, the authors highlighted the need for culturally appropriate and sensitive materials and approaches.[86] A 2010 meta-analysis of interventions to treat or prevent obesity among adolescent minorities found that both parental involvement and culturally based adaptations showed promise in reduction of weight among obese children but concluded that more research needed to be done in this area.[87] Consistent with this guidance, a 2012 scientific statement from the American Heart Association emphasized the role of parents and adult caregivers as "agents of change" for their obese children and identified the lack of culturally tailored interventions as a crucial research gap.[88] In addition to focused interventions, social marketing campaigns should encompass culturally appropriate messages.

As future interventions are developed, approaches that address the cultural aspects that influence obesity are essential. As highlighted in the 2012 Institute of Medicine Report *Accelerating Progress in Obesity Prevention,* "the recognition of social, cultural and environmental factors as influencing obesity has motivated a shift to community-level strategies for health promotion, with the understanding that change at this level will encourage and sustain individual-level behavior change."[89] Thus, interventions that are designed and evaluated with input from a community and that reinforce the strengths and assets of the community have a higher likelihood of incorporating cultural influences and of sustainability.

Approaches to engage community members in the research process have been used across disciplines, from anthropology to public health, and now are being used to address obesity.[90,91] Community-based participatory research, for example, is anchored by the understanding that people in communities possess problem-solving skills and expertise about the issues they face and thus are invaluable partners (rather than subjects) in research efforts.[92] While researchers typically possess skills pertaining to program design, methodology, evaluation, and grant-writing, community members have the greatest knowledge of the specific cultural values, beliefs, and attitudes to address the strategies that the community will embrace as well as barriers and competing issues that may derail implementation.[93]

Live Well is an example of a community-based participatory project in which input from the community informed the development of a culturally appropriate intervention for recent immigrant mothers from Brazil, Latin America, and Haiti. At the beginning of the project, both community partners and academic researchers came together to cocreate the curriculum.[94] Academic researchers drew on their expertise from behavioral theory and community partners introduced a popular education approach. Popular education, heavily influenced by Brazilian educator Paulo Freire, aims to empower people who feel socially and politically marginalized to take control of their own learning and to effect social change. The intervention curriculum provided sessions that reflected the participants' experiences. Classes emphasized dialogue and interaction rather than passive receipt of information delivered by an instructor. Utilizing this participatory process created an intervention that was culturally relevant to these immigrant populations. This was particularly important given the distinct but commonly experienced barriers and challenges that these three groups faced. For example, participants in all three groups reported that both diet and physical activity changed substantially when they immigrated to the United States. They believed that there is less time for food preparation in the United States and that work is more physically demanding. They reported higher levels of stress, less control of their time, and less social support in the United States.[95]

Individual behaviors related to obesity are responsive to the contexts in which they are practiced.[96,97] Therefore, when selecting components for obesity prevention interventions, the relevant social, economic, policy, and media influences must be considered. Given the complex nature of obesity and the recognition of the force of both cultural and environmental influences, future interventions will benefit from inclusion of participatory approaches as well as cultural factors that are dynamic and occur in the environmental contexts in which they are embedded and in which they interact.[7]

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42 Bias, Discrimination, and Obesity

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CONTENTS

42.1 INTRODUCTION

Obese individuals are highly stigmatized in our society, with bias and discrimination being common outcomes.[1–3] The prevalence of weight discrimination has increased by 66% in the past decade[4] and is now comparable to and in some cases exceeds racial discrimination.[5] Given the prevalence of overweight and obesity in the American population, the number of children and adults potentially faced with stigmatization is immense. The consequences of being denied jobs, disadvantaged in education, marginalized by health-care professionals, or victimized by peers because of one's weight can have a profound impact on quality of life. Obese individuals can suffer terribly from both direct discrimination and less overt behaviors (e.g., teasing and social exclusion) that arise from weight-related stigma.

Despite a long-standing awareness of the problem of weight discrimination dating back at least 30 years,[6,7] this topic has only recently begun to receive focused attention in the obesity field. The accumulated work over the past decade provides clear evidence of weight bias in areas of health care, employment, education, and even close interpersonal relationships, thus painting a picture of obese persons as acceptable targets of stigma in multiple domains of living.[1–3] The purpose of this chapter is to summarize existing literature, examine the emotional and physical health consequences of bias, and highlight existing stigma-reduction strategies, with attention on research needs in this important area of study.

42.2 WEIGHT BIAS IN HEALTH-CARE SETTINGS

Obese individuals are vulnerable to weight bias from multiple providers in health-care settings. Negative attitudes and stereotypes toward obese patients have been reported among physicians, nurses, dietitians, psychologists, and medical students.[3,8–14] Even health professionals who specialize in obesity are not immune to negative attitudes.[13] Self-report studies by health professionals have documented perceptions that obese patients are noncompliant, unsuccessful, unpleasant, unintelligent, overindulgent, weak willed, and lazy.[1] Attributions about the causes of obesity may reinforce negative attitudes, as several studies have demonstrated that health-care professionals hold assumptions that obesity can be prevented by self-control,[14] patient noncompliance explains failure at weight loss,[9] and obesity is caused by emotional problems.[15]

Experimental research has also assessed weight bias among health professionals. Study participants are typically randomly assigned to read case descriptions of hypothetical patients varying in weight categories, followed by questions requesting their professional judgments about the patients. For example, in one study psychologists were randomly assigned to one of two conditions in which they evaluated identical descriptions of either an obese or a nonobese patient. Psychologists more frequently assigned negative attributes, more severe psychological symptoms, and more pathology to obese clients than to other clients.[11] In another study, medical students were presented with cases in which patients were depicted as average weight or obese and students perceived the obese patients to be less likely to comply with diet and lifestyle recommendations than average-weight patients.[16]

Obese patients report frequent weight bias from providers. In a self-report study, we assessed 2449 overweight and obese adult women's experiences with weight bias.[17] We provided participants with a list of 22 different individuals (such as peers, family members, coworkers, employers, strangers, and health-care providers) and asked them how often each individual had stigmatized them because of weight. Participants reported doctors to be the second-most frequent source of bias that they confronted (behind family members).

Sixty-nine percent reported that they had experienced weight bias by a doctor on one occasion, and 52% reported that this had happened multiple times. Other health-care professionals were also frequent sources of bias: 46% of women reported weight bias by nurses, 37% by dietitians, and 21% by mental health professionals.[17]

Negative attitudes by providers raise concerns about the quality of health care that obese patients receive. A number of studies have documented that obese people delay seeking preventive health services such as pelvic exams, mammograms, and other cancer screenings.[18,19] In addition, a positive relationship between body mass index (BMI) and appointment cancellations has been shown.[20] These findings are not a result of low access to care but instead point directly to bias.[21] When a sample of 498 obese women were asked about the reasons for canceling, delaying, and avoiding health services, they attributed these decisions to disrespectful treatment and negative attitudes from providers, unsolicited advice to lose weight, embarrassment of being weighed, and medical equipment that was too small to be functional for their body size. The percentage of patients who reported these barriers to heath care increased with BMI.[21] More recent research similarly found that 24% of parents would avoid future medical appointments for their overweight child if they felt a doctor had stigmatized their child because of his or her weight.[22]

42.3 WEIGHT BIAS IN EMPLOYMENT SETTINGS

Both laboratory and field studies have shown widespread weight bias in all aspects of the employment process.[23–25] Research addressing employer attitudes and hiring decisions suggests that overweight people face prejudice even prior to initial job interviews. Studies have manipulated perceptions of employee weight with written vignettes, videos, or photographs and then asked individuals to evaluate a fictional applicant's qualifications. Overweight employees were less likely to be called in for an interview, were evaluated more negatively, and were rated as less likely to be hired than average-weight employees, despite identical qualifications.[26,27]

A recent meta-analysis of 59 studies indicated that weight bias had a stronger negative effect for hiring than for any subsequent performance outcomes.[23] Although this bias has been demonstrated within a variety of employment positions, some studies have suggested that overweight applicants are especially denigrated in sales positions and are perceived to be unfit for jobs involving face-to-face interactions.[24,28,29] Population-based studies have supported the findings of this experimental research, indicating that obese individuals are less likely to be employed than thinner individuals. For example, a Canadian study of more than 75,000 adults found that obesity was associated with lower workforce participation independent of associated comorbidity and sociodemographic variables.[30]

Once an overweight person is employed, weight bias can continue from coworkers and employers. Compared to their thinner colleagues, overweight individuals may be assigned tasks that are less challenging and require less responsibility[24] and may face harsher discipline when they make mistakes.[31] Overweight employees are viewed as sloppy, lazy, slow, less competent, less attractive, poor role models, lacking in self-discipline, disagreeable, and emotionally unstable.[25,26,32] In our study of 2449 overweight and obese adult women, 54% of participants reported experiencing weight bias from coworkers and 38% stated that this had occurred multiple times. In addition, 43% of the respondents reported weight bias from employers, with 26% reporting this form of bias on multiple occasions.[17]

Negative attitudes may be a primary reason for the inequities faced by overweight employees in wages, promotions, and termination, as suggested by studies showing lower promotion prospects for obese individuals than for average-weight employees with identical qualifications.[33] Obese men are underrepresented in professional positions compared to average-weight men,[34] and overweight men and women are more likely to have low-paying jobs compared to their thinner peers.[34] There is also evidence of lower wages for obese women doing the same work performed by average-weight counterparts.[35] Given that women experience wage penalties at lower levels of excess weight than men,[35] the threshold for weight discrimination in the workplace may be lower for women than men.

Legal case documentation reveals a growing number of cases in which obese employees have been fired, suspended, or demoted because of their weight.[36,37] Many terminated employees held jobs in which body weight was unrelated to job responsibilities (computer analyst, office manager, lecturer, etc.) and received excellent job performance ratings. In a number of cases, overweight employees were discharged based on weight criteria that were instated after they were hired.

There are no federal laws that prohibit weight discrimination in employment settings, and only one state (Michigan) prohibits discrimination based on weight. Although some cases of weight discrimination have been tried under the Americans with Disabilities Act, this approach has generally been unsuccessful as obesity itself is not considered a legal disability unless it can be proved to have an underlying, physiological cause.[37] Thus, victims of weight-based employment discrimination have few options if they wish to seek redress in court.[36] These obstacles will likely remain until weight is included as a protected category of antidiscrimination statutes.

Finally, obese employees may face financial penalties because of their weight. Employers have begun to offer monetary incentives for employees whose weight is within a healthy range, as well as financial penalties for those whose weight falls outside the range, with as many as one-third of employers surveyed in 2010 planning to offer such a program.[37,38] Other employers offer "wellness incentives" through which healthy (i.e., thin and nonsmoking) employees are rewarded with lower insurance premiums.[37] Regardless of the format, such programs lead to higher premiums for obese individuals based on a condition rather than a modifiable health behavior.

Despite these challenges, recent research demonstrated substantial public support among Americans for proposed

laws prohibiting weight discrimination in the workplace, with 81% of women and 65% of men in favor of such laws.[39] Thus, as public support increases, we may see increased consideration of legislative protection for obese persons.

42.4 WEIGHT BIAS IN THE MEDIA

A particularly pervasive source of weight bias is the mass media. Stigmatizing portrayals of obese individuals are common in television shows, movies, advertisements, news media, and children's cartoons.[3] Overweight characters are underrepresented in both youth and adult entertainment media, where heavier television and film characters are often targets of derogatory humor and ridicule and are depicted as engaging in stereotypical behaviors. An analysis of prime-time television shows aired during the 1999–2000 season found that overweight or obese characters were less likely to be seen as interacting with romantic partners and overweight male characters were less likely to be seen interacting with friends and more likely than their thin counterparts to be depicted as eating.[40] A similar pattern has been observed in youth-targeted media.[3] For example, an analysis of 1221 children's television cartoons found that negative characteristics such as being unattractive, antisocial, and aggressive were significantly more likely to be found in overweight compared to thin and average-weight characters. Thinner characters were more likely to be depicted as having several positive character traits and to be portrayed as "good guys."[41]

The news media is another source of stigmatizing portrayals of obesity. Research has found that news sources, which are central to the public's understanding of obesity, tend to emphasize individual-level causes and solutions for obesity, disproportionately framing the issue in terms of personal responsibility. This emphasis ignores other important aspects of the complex etiology of obesity and may foster blame.[3] Additionally, both printed news articles[42] and the images[43] that accompany them often contain stigmatizing and stereotypical portrayals of obese individuals. For example, an analysis of 1925 articles appearing in four Swedish newspapers found that obesity was often likened to a "plague" or a "natural disaster," while obese individuals were presented as ugly, stupid, and lazy, among other stigmatized traits.[42] In addition, recent content analyses found that more than two-thirds of images and videos of obese persons accompanying news reports about obesity portrayed obese children and adults in a stigmatizing manner.[44,45]

Media exposure has been found to increase expressions of weight bias. Studies in children have demonstrated that television viewing predicts negative weight stereotyping and that media consumption is associated with stigmatizing attitudes toward obese youth.[3] This effect is likely a result of negative media portrayals of obesity. Indeed, in a recent study, adult participants ($N = 188$) who read a neutral news story about the prevalence of obesity accompanied by a stereotypical (e.g., eating unhealthy food) image of an obese individual[43] expressed stronger antifat attitudes than participants who read the same story accompanied by a "flattering" (e.g., exercising) image. Given the high level of media consumption in the United States, weight bias in the mass media must be addressed in efforts to reduce stigma.

42.5 VULNERABILITY OF YOUTH TO WEIGHT BIAS

Self-report, prospective, and experimental studies have examined various forms of weight bias toward overweight and obese youth.[46] Most of this research has examined biased attitudes, stereotypes, and peer victimization and has demonstrated that weight bias is a common experience for obese children, with antifat attitudes being established early in childhood. Biased attitudes toward overweight peers have been demonstrated in preschool children as young as age 3, and by age 4 children have been shown to attribute excess body weight as the reason for their negative attitudes.[47] Research with preschoolers found that 3-year-olds ascribed to overweight peers the negative characteristics of being mean, stupid, loud, ugly, lazy, sad, and lacking in friends.[48] Stigmatizing attitudes appear to increase throughout childhood,[47,49] and by elementary school children believe that overweight peers are ugly, selfish, lazy, and stupid and that they lie, get teased, and have few friends.[49] In qualitative research among adolescents, overweight high school students reported being stereotyped by peers as being lazy, unclean, eating too much, unable to perform certain physical activities (e.g., dancing), not having feelings, and unable to "get a boyfriend."[50]

Such attitudes set the stage for peer rejection and teasing, which are commonly experienced by overweight youth. In a recent study of adolescents aged 13–19 years ($N = 1555$), participants perceived being overweight as the most common reason that peers are bullied at school, over other factors such as sexual orientation and race.[51] Similarly, in a study of 4746 middle and high school students, 30% of girls and 24% of boys reported weight-based teasing from peers. For students at or above the 95th BMI percentile, rates of victimization increased to 63% for girls and 58% for boys.[52] A prospective study of 8210 children documented that 36% of obese boys and 34% of obese girls reported being victims of weight-based teasing and various forms of bullying.[53]

A study of 10- to 14-year-olds ($N = 156$) demonstrated weight-based teasing to be more severe, frequent, and upsetting among overweight children compared to normal-weight children.[54] Children who report the most teasing have been shown to feel less safe in school and express more weight concerns, loneliness, lower confidence in physical appearance, and higher preferences for isolating activities, independent of sex and weight.[54] Additionally, one study found that the likelihood of overweight students skipping school or reporting that weight-based teasing harmed their grades increased by 5% per reported teasing incident.[55]

In addition to peer victimization, obese children are also vulnerable to bias from educators. In a study examining attitudes toward obesity among 115 middle and high school teachers, one-fifth of respondents reported beliefs that obese persons are untidy, less likely to succeed, more emotional, and

more likely to have family problems than thinner persons.[56] More than 50% believed that obesity is often caused by a form of compensation for lack of love or attention, and 43% strongly agreed that "most people feel uncomfortable when they associate with obese people." Similarly, in a study of 227 elementary school principals more than 50% cited lack of self-control and psychological problems as primary contributors to obesity.[57]

Other work has found that physical education teachers hold biased beliefs about overweight youths' physical condition, athletic ability, self-esteem, and confidence about their bodies[58] and that they report overweight students to have poorer social, reasoning, physical, and cooperation skills than normal-weight students.[59] Participants also reported lower expectations for overweight students across a range of performance areas. These findings support a 2007 study showing strong implicit weight bias among 180 university students training to become physical educators; they expressed more negative attitudes than did a matched sample of psychology students and other health professionals.[60] Participants also showed more negative explicit beliefs that obese individuals lack willpower, and those who were near completion expressed stronger weight bias than those who were beginning their training.

Educational discrimination appears to continue at the college level. There have been cases of obese students being dismissed from college on the basis of weight despite good academic performance.[61] Research has also found that obese students received lower grades compared to normal-weight students in middle school, community college, and university, despite there being no difference in intelligence and academic test scores between these groups, even after controlling for demographic variables, intelligence, personality, and well-being.[62]

Finally, children may even experience weight-related victimization from their own family members.[63] In a study of 4746 adolescents, 29% of girls and 16% of boys reported weight-related teasing from a family member.[64] Such victimization continues into adulthood, and in our sample of overweight women as many as 72% reported having experienced weight-related teasing from a family member.[17] In addition to teasing, overweight girls are less likely to receive financial support from their parents, such as assistance in paying for college[65] and buying a car,[66] compared to their slimmer peers.

42.6 CONSEQUENCES OF WEIGHT BIAS

Given the pervasiveness of antifat attitudes, it is important to consider the consequences of being exposed to such stigmatization. A range of adverse outcomes are associated with weight bias for overweight and obese individuals, affecting emotional well-being, social relationships, and physical health.

Weight bias has clear and powerful implications for emotional well-being. Weight-based teasing and victimization are related to poorer body image, lower self-esteem, social isolation, and higher risk of depression and anxiety.[3,54,63,67] Obese youth who experience weight-based victimization from peers have been shown to be two to three times more likely to engage in suicidal thoughts and behaviors. Eisenberg and colleagues[64] found that 51% of girls who were targets of weight-based teasing from peers and family members had thought about committing suicide, compared to 25% of those who had not been teased. Among boys, 13% who were teased by family members about their weight reported attempting suicide compared to 4% who were not teased.[64] Similarly, in a study of a nationally representative sample of more than 9000 obese adults perceived weight discrimination was strongly associated with current diagnoses of mood disorders and substance abuse.[67]

Interpersonal relationships are also negatively affected by weight bias.[68] Obese children are liked less and rejected more often by peers than average-weight students. A large-scale study assessed adolescents ($N = 90{,}118$) from the National Longitudinal Study of Adolescent Health and reported that overweight adolescents were more likely to be socially isolated and less likely to be nominated by their peers as friends than average-weight students.[69] Other work with adolescents ($N = 9943$) found that obese students spent less time with friends than their thinner peers, after controlling for variables such as grade level, race, and socioeconomic status.[70] Among adults, weight has been negatively associated with frequency of dating[71] and experimental research has shown that in interpersonal conversations men rate overweight women more negatively than thinner women.[72,73]

Weight bias may also reinforce unhealthy behaviors that contribute to obesity. For example, overweight youth who are teased about their weight are more likely to engage in unhealthy weight control and binge-eating behaviors compared to overweight youth who are not targets of weight-based teasing.[52] Prospective research has demonstrated that weight-based teasing predicted binge eating at 5 years of follow-up among both male and female adolescents, even after controlling for other factors.[74]

Many studies among adults also have illustrated a relationship between experiences of weight bias and binge eating and other unhealthy eating behaviors.[3] In a study of 93 treatment-seeking adults stigmatizing experiences significantly predicted binge eating,[75] and in another study of 2449 overweight and obese women 79% of participants reported that they had coped with weight bias by eating more food and 75% reported that they refused to keep dieting in response to bias.[17] Similarly, recent experimental research found that overweight women who were exposed to a weight-stigmatizing video consumed more than three times as many calories post manipulation as overweight women who had viewed a neutral video.[76]

There is also evidence to suggest that obese individuals may avoid physical activity because of weight bias. Overweight youth who are victimized by their peers are less likely to participate in physical activity and physical education classes.[77] Adults who experience weight bias have less desire to exercise and, as a result, engage in decreased levels

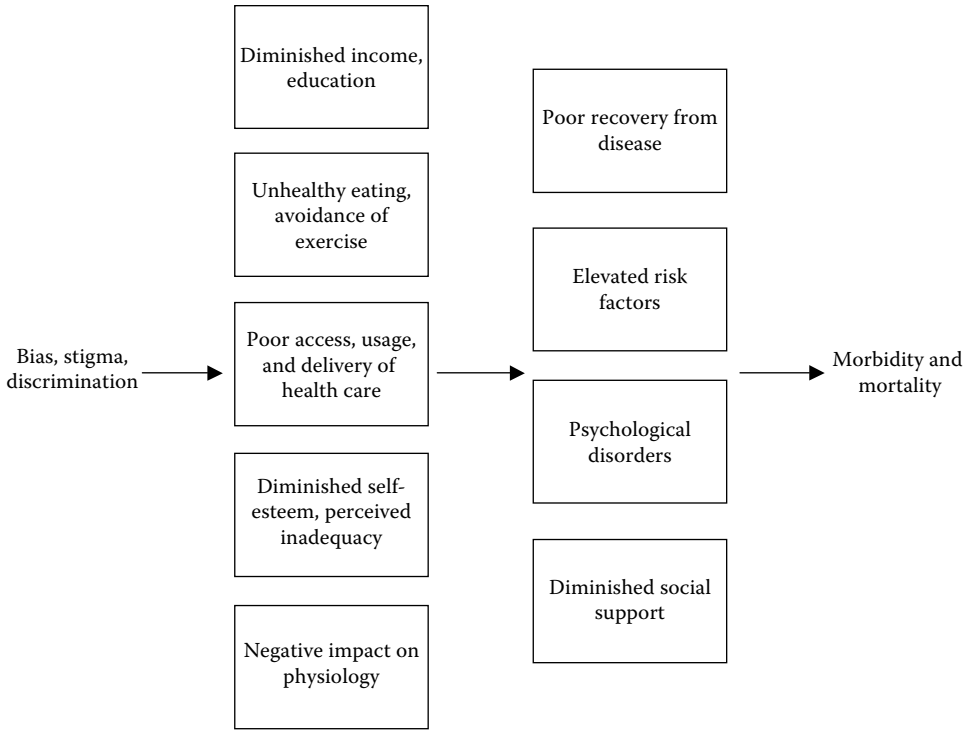

FIGURE 42.1 Conceptual scheme of potential links between weight bias and health outcomes. (From Brownell et al., *Weight Bias: Nature, Consequences, and Remedies*, Guilford Press, New York, 2005. Copyright Guilford Press. Reprinted with permission of Guilford Press.)

of strenuous and moderate exercise.[78,79] It may be that overweight individuals feel a heightened vulnerability to negative attitudes or teasing in public settings where exercise occurs and therefore make attempts to avoid potentially embarrassing or stigmatizing situations. More work is needed to determine the impact of weight bias on participation in physical activities.

It is also possible that weight bias may affect important physiological health outcomes. A growing literature has demonstrated a relationship between racial discrimination and negative physiological effects, such as elevated cardiovascular reactivity and blood pressure.[80,81] Such effects appear to exist for other forms of discrimination as well. For example, one study found that adolescents who reported unfair treatment because of their physical appearance (including body weight) had elevated ambulatory blood pressure compared to those who did not report unfair treatment, even after accounting for typical determinants of blood pressure, including BMI.[82] The negative health consequences of obesity may stem from the stress of experiencing weight stigma, as well as adiposity itself,[83] with some preliminary evidence demonstrating negative physiological effects of weight bias. A recent study found that experiences with weight-related stigma exacerbated the effects of waist-to-hip ratio on nondiabetic glycemic control,[84] a risk factor for cardiovascular disease. Furthermore, experiences with discrimination may contribute to obesity itself, as additional research has found correlations between perceived interpersonal discrimination and abdominal adiposity.[85]

The health consequences of weight bias have received very little attention but warrant additional research given the potential for stigma to worsen health outcomes among individuals whose weight already poses increased health risks. Figure 42.1 outlines possible links between weight bias and important health outcomes. Investigating and documenting these relationships are extremely important in efforts to understand and reduce the medical impact of weight bias.

42.7 IMPLICATIONS FOR PUBLIC HEALTH

The detrimental consequences of weight bias have been well documented, yet their implications for public health have been largely ignored. Obese individuals continue to be blamed for their weight with personal responsibility frequently being emphasized over more complex etiological explanations, which have been shown to be associated with more positive attitudes toward obese individuals.[86] Stigma is often viewed as a useful tool to motivate weight loss, driven by the perception that the shame resulting from weight bias may provide an incentive for obese individuals to lose weight, despite research showing that such stigma may actually increase unhealthy eating behaviors and refusal to diet and reduce the intent to exercise.[52,79]

In addition to threatening the physical and psychological health of obese individuals and further exacerbating health disparities, stigma toward obese individuals may also inhibit the implementation of successful interventions

to prevent and treat obesity. Despite the vast number of people affected by obesity, as well as the national attention being directed toward this issue, obesity interventions are not being funded on par with interventions for other, less stigmatized conditions, and available campaigns often focus on individual responsibility and/or are unhelpful and stigmatizing.[86] Weight stigma poses a threat to public health independent of the physical health consequences of obesity and must be addressed as part of efforts to address obesity.

42.8 IMPROVING ATTITUDES: THE STATUS OF STIGMA REDUCTION

Despite abundant research showing weight bias toward children and adults, little empirical work has tested strategies to reduce stigma and improve attitudes. Attributions about the causes of obesity have been the target of several experimental studies testing strategies to reduce weight bias. For example, research with students in grades 3–6 ($N = 184$) found that children attributed less blame to an obese child whose weight was attributed to external (e.g., medical) causes compared to a child whose obesity was attributed to personally controllable factors.[87] However, causal information had little effect on overall attitudes. In another study, elementary school children ($N = 99$) were less likely to blame an obese peer for being heavy if provided with information suggesting the child had little responsibility for his or her obesity, although this did not change their liking of the peer.[88] In a similar experiment in 74 children (grades 4–6), information about the uncontrollability of body size did not change negative weight-based stereotypes.[89] Experimental work in adolescents has shown similar findings.[90] Perceptions about the causes of obesity may be more modifiable than weight-based attitudes or stereotypes among youth.

With adults, experimental work has yielded mixed findings in attempts to improve attitudes by targeting attributions of causality. One study found that emphasizing external, noncontrollable causes for obesity (e.g., biological and genetic factors) had little impact on improving negative attitudes or behaviors in adults,[91] whereas three other experimental studies provided participants with information about biological, genetic, and noncontrollable reasons for obesity and found reductions in negative attitudes.[92–94]

Several other approaches have been tested with adults. Experimental studies have attempted to improve attitudes by inducing empathy toward obese individuals, including having participants read stories about weight discrimination or watch videos of obese women. These interventions were unsuccessful in changing negative attitudes compared to control groups.[91,95] A more recent study in which 40 dietetic and health promotion students were asked to follow a calorie-restricted diet for 1 week led to an improvement in antifat bias and increased respect for individuals struggling with weight loss.[96]

Hague and White[97] tested a web-based educational intervention among 258 student teachers and schoolteachers, which improved attitudes compared to a nonintervention control, suggesting that Internet-based interventions may reduce bias. Additionally, experimental work has tested a "social consensus" framework of attitude change, which highlights the importance of social norms and suggests that stigmatizing attitudes are a function of one's perceptions of other people's stereotypical beliefs. In two experiments, university students' ($N = 60$ and $N = 55$) attitudes toward obese persons were measured prior to and following manipulated feedback depicting the attitudes of other students as being more positive toward obese individuals than the participants' own.[93] Participants who received such feedback reduced their negative weight-based stereotypes, increased positive attitudes toward obese persons, and attributed obesity less to personal control. Participants' attitudes were more likely to improve if this feedback came from an in-group source (e.g., students who belonged to their university) versus an out-group source (e.g., students from a different college). In a third experiment with 200 university students, receiving social consensus feedback was equally or more effective in improving attitudes toward obese people compared to other conditions providing information about the uncontrollable causes of obesity and supposed scientific evidence about the characteristic traits of obese individuals (both of which also improved attitudes).

These experiments indicate that learning about the unbiased attitudes of others can be effective in improving attitudes toward obese people. However, in a later study of university students ($N = 64$), participants exposed to a social consensus intervention did not differ from a control group with respect to antifat attitudes.[98] This same study also introduced a cognitive dissonance intervention. Participants in this condition were given fake feedback on a measure of personal values and an antifat attitudes scale and were told that their biases were discrepant with their core values (i.e., that they scored high on kindness and equality but displayed strong stigma toward obese individuals). Participants exposed to this intervention had significantly less negative attitudes toward obese individuals compared to the control group.[98]

Taken together, insufficient research has examined methods of reducing weight bias.[99] It is important to conduct additional comparisons of existing methods and to test whether attitude change is sustained over time and translates into less biased behaviors toward obese individuals.

42.9 FUTURE DIRECTIONS FOR RESEARCH

Although there has been substantial research on the topic of weight bias, important questions remain unanswered. More work is needed to improve on previous methodologies, to address additional research questions, to determine the nature and extent of consequences of weight bias, and to test interventions to reduce bias. Table 42.1 outlines the areas of research that we believe are necessary directions for these efforts.

TABLE 42.1
Areas of Research Needed to Advance the Study of Weight Bias

Domain	Research Needs
General methodological issues	• Include behavioral measures to assess bias, and compare how these correlate with measures of self-reported attitudes. • Increase the use of randomized experimental designs, more diverse samples, and ecologically valid settings. • Develop measurement items that are relevant and sensitive to potential cultural differences in antifat attitudes and experiences of weight stigmatization. • Improve and expand the scope of existing measures assessing experiences with weight stigma to include a range of types and sources of discrimination.
Weight bias in health settings	• Assess how bias by health providers influences health-care outcomes and behaviors (e.g., health-care utilization and medication adherence). • Compare weight bias across different specialty groups of providers. • Examine the impact of different forms of weight bias in health settings (e.g., lack of appropriate equipment vs. negative provider attitudes) on obese patients. • Assess weight bias across different groups of mental-health-care providers. • Assess whether improvements in provider attitudes lead to increased utilization of health care and higher quality of care for obese patients.
Weight bias in employment settings	• Increase research attention on hiring, promotion, and benefits discrimination against obese employees. • Examine which occupations are most vulnerable to weight bias. • Evaluate the impact of BMI financial incentives and penalties on overweight and obese individuals. • Compare prevalence rates of weight discrimination in employment settings to discrimination based on gender, age, or race. • Develop and evaluate the effects of workplace curricula and training to address weight bias.
Weight bias among youth	• Identify the nature and severity of stigma toward youth by educators, parents, and family members. • Assess whether reductions in weight stigma improve social, emotional, and academic outcomes among obese youth. • Assess endorsement of stigma across variables of ethnicity, gender, age, and weight among youth. • Examine multiple impacts of different forms of weight bias (e.g., verbal teasing, physical aggression, social exclusion, and cyber bullying) on obese youth. • Develop and test curricula to reduce weight-based bullying in schools.
Consequences of weight bias	• Develop new assessment methods to assess the severity and impact (in addition to the nature and frequency) of weight discrimination. • Examine further the ways in which weight bias influences lifestyle behaviors (e.g., binge eating and exercise avoidance). • Assess how weight bias influences other physiological health outcomes (e.g., cardiovascular health). • Examine how internalization of stigma affects health outcomes among overweight youth and adults. • Assess stigma reduction as a tool for health improvement/weight loss.
Prevention/intervention	• Assess whether obesity prevention efforts (e.g., public health campaigns) promote or decrease stigma. • Identify theoretical components to guide stigma-reduction strategies. • Develop and test effects of stigma-reduction strategies on antifat attitudes. • Test experimental comparisons of different methods to reduce weight bias. • Identify the most effective modes of delivery for stigma-reduction messages. • Assess whether interventions lead to sustained attitude changes over time. • Assess whether interventions lead to changes in behavior and attitudes. • Examine coping strategies used by obese persons to combat aversive stigma experiences.

42.10 CONCLUSION

The medical consequences of obesity are of immediate concern, but we cannot ignore the negative psychological, social, and physical outcomes that obese people face as a result of bias, stigma, and discrimination. These adverse experiences are pervasive, are rarely challenged in our society, and have a detrimental impact on quality of life (see Volume 1, Chapter 58). Given the number of people affected; the inherent unfairness of prejudice; and the consequences of discrimination in key areas of living such as employment, education, and health care, much more needs to be done.

Researchers, policy makers, and health professionals in the obesity field can and must play a central role in these efforts. Although there has been increasing research attention on topics of bias and discrimination, many gaps in our knowledge remain. Without more focused work in this area to understand the nature of weight bias and the extent to which it compromises emotional and physical health, as well as to identify effective methods of improving societal attitudes, most obese individuals will be left to cope with the negative consequences of stigmatization on their own. This is especially concerning given that so many overweight and obese children are vulnerable to victimization on a daily basis without sufficient support, coping strategies, or intervention. The national obesity research agenda must include attention to weight bias so that efforts can begin to change

societal conditions that have created and perpetuated this social justice issue, which has also become a public health problem.

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43 Environmental Chemicals and Obesity

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CONTENTS

43.1 INTRODUCTION

It is widely agreed upon that the burgeoning obesity epidemic occurring throughout the world is the product of poor nutrition and lack of exercise. However, there has also been increasing interest in the concept that exposures to environmental chemicals may be contributing factors to the remarkable changes in body composition over the past 20 years. Recent studies have identified a subclass of endocrine disrupting chemicals (EDCs) that interfere with endocrine signaling, which can disrupt hormonally regulated metabolic processes, especially during early development.[1] Certain chemicals, called "obesogens," may predispose individuals to gain weight despite efforts to limit caloric intake and increase physical activity.[2] Plausible evidence also suggests that chemical exposures early in life can predispose individuals to weight gain through changes in metabolic "set points" and enhance dysfunctional eating behaviors later in life. This chapter reviews the latest research on the obesogen concept, including discussions of windows of susceptibility and the Developmental Origins of Health and Disease (DOHaD) model. We provide examples of known obesogens, and their general mechanisms of action, as well as emerging obesogens for which the mechanisms are less clear. The relevance and reality of the research reviewed here provides a solid foundation of knowledge from which health scientists may draw from and build upon to inform their research and decision making.

43.2 ENDOCRINE DISRUPTING CHEMICALS AND OBESOGENS

EDCs are synthetic chemicals that were originally designed for a specific purpose such as a pesticide, plasticizer, or solvent. Such chemicals, when absorbed into the body, have the side effect of mimicking or blocking hormones by binding to their cognate receptors and disrupting the body's normal functions.[1] EDCs can also disrupt normal hormone levels by inhibiting or stimulating the production and metabolism of hormones or changing the way hormones travel through the body, thus affecting the functions that these hormones control. Some EDCs are obesogens that specifically promote obesity by increasing the number of fat cells or the storage of fat into existing cells.[3] They can also act on fat cells indirectly by altering metabolic rate and hormonal control of appetite and satiety.[3] Nicotine, air pollution, polyhalogenated flame retardants, insecticides, fungicides, plastics, plasticizers, heavy metals, fructose, food additives, and some prescription

medications have all been linked to obesity and/or the metabolic syndrome. This could be just the tip of the iceberg since there are close to 800 chemicals with reported EDC properties[4] and only a very few of the ~80,000 chemicals in commerce have been tested for endocrine disrupting activity.

The original definition of an obesogen was founded in the observation that certain chemicals could activate peroxisome proliferator-activated receptor gamma (PPARγ), the master regulator of fat development.[5] Hence, preadipocytes treated with a PPARγ activator, such as the fungicide tributyltin (TBT), would differentiate into fat cells more efficiently than controls.[6] Animals treated with the chemical became fatter as a result, despite consuming a normal diet.[6] Since this original finding, many other chemicals have been shown to activate PPARγ, increase fat cell differentiation, and make animals or humans fatter.[7,8] Over the past decade, several other mechanisms for obesogen action have been identified. Although obesogens function locally by interfering with a specific biochemical process, they can act globally to affect the entire endocrine system. Their target tissue may not always be the adipocyte, but the liver, brain, pancreas, stomach, intestines, or endocrine glands.[3] Therefore, obesogens are not solely associated with obesity but also have a strong correlation to type 2 diabetes (T2DM) and the metabolic syndrome. Other end points of interest for obesogen research include glucose homeostasis, visceral versus subcutaneous fat, brown fat versus white fat, cardiovascular health, and measures of appetite and physical activity.

43.3 DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Early development is a highly orchestrated series of biochemical, physical, and organizational events that must be tightly coordinated to ensure proper growth. Because the developmental period is a "plastic" phase, an organism is critically sensitive to perturbations such as alterations in hormone levels that can lead to changes in gene expression and protein levels, which persist as tissues and organs develop.[9] This increased sensitivity is also a consequence of incomplete development or partial function of protective mechanisms such as DNA repair, immunity, xenobiotic metabolism, and the blood–brain barrier in the fetus or newborn compared with older individuals. The DOHaD hypothesis was proposed to explain observations that poor in utero nutrition resulted in high rates of cardiovascular disease (CVD) manifested later in life.[10] Nutrition during development also plays an important role in the obesity epidemic.[11] The DOHaD concept now includes nonnutritional early life exposures that have been shown to alter the body's physiology. Prenatal exposure to obesogenic factors can modify normal cellular and tissue development and function, especially at the level of the stem cell (discussed in section 43.4). Adverse perturbations in the metabolic system of the developing organism translate to a higher risk of metabolic and hormonal disorders later in life.[12] Thus, the DOHaD hypothesis provides a framework to assess the effect of not only early nutrition but also obesogenic chemicals on long-term health. Many disease patterns linked to poor nutrition have also been traced to maternal chemical exposure,[13] suggesting a common mechanism for chemical and nutritional stress that ultimately leads to long-term obesity.

43.4 GENERAL MECHANISMS OF OBESOGEN EXPOSURE DURING IMPORTANT DEVELOPMENTAL WINDOWS

Obesity is currently an intractable problem—nearly 90% of those who lose a significant amount of weight regain it within a year.[14] Therefore, it is important to understand prenatal or perinatal mechanisms that contribute to stagnant metabolic set points and the physical and emotional anguish associated with losing weight. Focusing on the fetus and/or neonate is of primary concern since, as noted in section 43.3, developing organisms are extremely sensitive to perturbation by chemicals with hormonelike activity. EDCs can affect fetal adipose tissue by increasing adipocyte number and size, resulting in enlarged white adipose depots.[3] Adipose tissue is generated from mesenchymal stem cells (MSCs), which are also capable of differentiating into bone, cartilage, and other tissue.[15] Obesogenic chemicals can affect the lineage allocation of MSCs (with more of these stem cells becoming committed preadipocytes), the differentiation of preadipocytes into adipocytes, and the filling of mature adipocytes with triglycerides, reviewed in the work by Janesick and Blumberg.[3]

A less recognized action of EDCs occurs in the developing brain. EDC exposure can trigger changes in the hypothalamus, the region of the brain that plays a particularly important role in feeding behaviors.[1] Improper hypothalamic programming may adjust metabolic "set points" in adolescents and adults, and these adjustments may help explain differences between the eating behavior of lean and obese individuals. Exposure to EDCs disrupts the organization and function of dopaminergic pathways throughout the brain, resulting in a wide range of behavioral effects including elevated impulsivity, anxiety, and disrupted sociality. Bisphenol A (BPA) alters both presynaptic and postsynaptic dopamine activity in brain regions associated with addiction and impulse control, suggesting that this may be a mechanism by which BPA exposure alters feeding behavior.[16] There may be parallels between chemical exposures early in life and later life onset of obsessive eating in obese individuals and other addictive behaviors. Lean individuals eat primarily to sustain fitness and tend to stop eating when they perceive they are full, even when food is bountiful. Obese people tend to eat more high-fat and high-sugar foods and continue to eat even when they are not hungry, suggesting addiction.[17] Some brain mechanisms that support drug addiction in humans are also responsible for compulsive eating behaviors and development of obesity in animals.[17] While it is not entirely clear whether the psychological and physiological characteristics of the obese are a cause, or consequence, of weight gain, it appears likely that there are common underlying changes in behavioral circuitry predisposing individuals to gain weight.

It seems likely that at least of part of the developmental programming of disease and metabolic dysfunction is the result of

alterations in the epigenetic control of gene expression during development. Epigenetic modifications, such as DNA methylation and histone methylation, acetylation, and ubiquitination regulate gene expression during development and are thus responsible for normal tissue and organ development.[18,19] During this critical time period, the epigenome cycles through a series of precisely timed methylation changes designed to ensure proper development. The appropriate timing and extraordinary accuracy of methylation in the gametes and following fertilization makes this system particularly vulnerable to interference from environmental exposures.[20] Indeed, it is now clear that the epigenetic system is responsive to environmental stimuli, such as drugs of abuse, diet, or chemical exposures.[21] Many changes to our epigenetic landscape are likely to be permanent and can be manifested in multiple generations, even if the original chemical insult is no longer found in the environment.[22]

Recent reports have identified epigenetic modifications in the CNS in response to altered diet, particularly in the prenatal or early postnatal time period, when brain development is particularly vulnerable to perturbations.[23] For example, consumption of a palatable high-fat diet increases DNA and histone methylation and decreases histone acetylation status in the promoter region of the opioid receptor mu 1 (*MOR*1) gene, which correlates with decreased mu-opioid receptor expression.[23] Thus, changes in DNA methylation patterns and chromatin remodeling in response to nutritional status in utero or during early postnatal development can affect dietary preference and metabolism.[24]

While fetal development is commonly known to be a period of increased sensitivity to chemical insult, childhood and adolescence are also marked by continued maturation of key endocrine systems, including the major metabolic organs, and are therefore susceptible to chemical exposure.[25] For example, TBT is known to be obesogenic with chronic or single-dose prenatal exposures.[6,26,27] It was recently shown that pubertal exposure to TBT yields weight gain and fatty liver.[28]

An adolescent's risk for obesity later in life is based on multifactorial inputs related to chemical exposure.[3] First, prenatal exposure to obesogens might have already increased the risk of obesity in the adolescent. Chemical exposure during the pubertal period is linked with early menarche in females and delayed sexual maturation in males. These changes in sexual maturation are risk factors for obesity later in life. Furthermore, adolescents tend to have the worst nutrition of any age group, especially with regard to sugar consumption.[29] Future studies that separate prenatal versus perinatal, in utero versus nursing, and prenatal versus pubertal obesogen exposures will be important in understanding the degree to which obesogens contribute to the obesity epidemic.

Using ^{14}C labeling it has been shown that childhood and adolescent periods are the main time of adipose hyperplastic growth.[30] In early adulthood, the total number of fat cells stabilizes; the number only increases when existing cells have reached full capacity through hypertrophic growth.[30] Although fat tissue is less plastic in the adult,[3,30] it is a fully accepted principle that adipose depots are endocrine organs[31,32] and have the ability to affect the health of the entire body, given an environmental insult. Furthermore, recent data suggest that the liver, pancreas, and brain also behave as endocrine organs during adult life and are very susceptible to EDCs.[31–36] An increasing number of studies have correlated the presence of persistent organic pollutants, including EDCs, in adult humans with indicators of obesity or metabolic disease. Phthalate exposure is linked to increased waist circumference, incidence of diabetes, and increased fat mass.[37–40] Heavy metals such as cadmium, lead, and arsenic are linked to the prevalence of diabetes in adults.[41–46] Numerous organochlorines including certain polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), trans nonachlor (TNC), dioxins, β-HCH, DDT, DDE, oxychlordane, and nonachlor are linked to increased body mass index (BMI), abdominal obesity, and insulin resistance in children, adults, and elderly (see Table 43.1).

43.5 EXAMPLES OF OBESOGENIC CHEMICALS IN ANIMAL AND HUMAN STUDIES

Table 43.1 lists the known obesogenic chemicals, the evidence for each and the mechanisms of action through which the chemicals have been demonstrated to act in at least one system. This does not necessarily mean that the indicated mechanism has been demonstrated to cause or be associated with the particular end point. Rather we wish to highlight plausible mechanisms through which the obesogens might be expected to act. This topic has been extensively reviewed in recent years.[3,7,8] Therefore, rather than exhaustively describing all potential obesogens and the evidence for their action, we will highlight a few notable classes of obesogens including those for which the evidence is particularly strong and others for which important new data have recently emerged.

43.5.1 Tributyltin and Triflumizole: Obesogens that Act through PPARγ

Only a fraction of known obesogens have a defined mechanism of action. TBT and triflumizole (TFZ) are two fungicides known to act through PPARγ, the master regulator of adipogenesis.[5] TBT is a superior activator of PPARγ and 9-cis retinoic acid receptor (RXR)[6,47,48] compared to TFZ, which only activates PPARγ.[146] However, both stimulate adipogenesis at nanomolar doses in murine 3T3-L1 preadipocytes[6,48,146,147] and in human and mouse MSCs.[27,146,148] These effects were shown to be dependent on PPARγ, since TBT- or TFZ-induced adipogenesis was inhibited by PPARγ antagonists.[27,146,148] A single prenatal exposure to TBT resulted in strikingly elevated lipid accumulation in adipose depots, liver, and testis of neonate mice and increased adipose depot mass in adult mice.[6] Similarly, chronic exposure to TFZ in utero, at a dose 400-fold below the established no-observed-adverse-effect level, increased fat depot size and programmed mouse MSCs to favor the adipogenic lineage.[146] The MSCs derived from TBT- or TFZ-exposed offspring also exhibited a decreased capacity to differentiate into bone.[27,146]

TABLE 43.1
Known Obesogenic Chemicals, Exposure, and Mechanisms of Action

Publications	Chemical	Endpoint	Exposure
		Organotins: Fungicides, House Dust, Seafood	
		Mechanisms: PPARα,β/δ,γ, RXRα, RXRγ, NURR1 Activator[6,47,48]; ER Activator[49]	
Biemann (2012)[50]	TBT	Increased adipocyte number and LA in C3H/10T1/2 cells	
Bo (2011)[158]	TBT	Hypothalamic disruption in C57/BL6 adult male mice	
Grün (2006)[6]	TBT	Increased LA in frogs, mice, 3T3-L1 cells; weight gain in mice	**PRE-GAV**
Inadera (2005)[147]	TBT	Increased LA in 3T3-L1 cells	
Janer (2007)[51]	TBT	Increased lipogenesis in the digestive gland/gonad of Ramshorn snail	
Kanayama (2005)[48]	TBT, TPT	Increased LA in 3T3-L1 cells	
Kirchner (2010)[27]	TBT	Increased LA in MSCs at the expense of bone in C57BL/6J mice	**PRE-GAV**
Li (2011)[148]	TBT	Increased LA in 3T3-L1 cells	
Penza (2011)[49]	TBT	Increased fat mass in pubertal C57BL/6J mice	
Si (2011)[52]	TBT	Decreased E2, T, and LH levels in adult Kun Ming mice	**PUB-DW**
Zuo (2011)[28]	TBT	Weight gain, insulin resistance, increased leptin, fatty liver in adult Kun Ming mice	**PUB-GAV**
		Organobromines: Flame Retardants, Poultry, Red Meat, House Dust	
		Mechanisms: General Thyroid Dysfunction; No Specific Mechanism Identified	
Allgood (2009)[188]	PBDE, PBDE + HF/HS diet	Weight gain, increased adipose mass, decreased T4, impaired glucose homeostasis in male Wistar rats	
Chao (2007)[193]	BDE-47, BDE-99, BDE-100	Low birth weight in human offspring	**BM**
Hallgren (2001)[189]	Bromkal 70-5 DE, DE-47	Decreased T4 in female Sprague–Dawley rats and C57B/l6N mice	
Herbstman (2008)[194]	BDE-100, BDE-153	Low TSH, T4, Free T4 in human neonates	**CB**
Hoppe (2007)[190]	penta-BDE	Dyslipidemia, impaired glucose homeostasis in adipocytes from Sprague–Dawley rats	
van der Ven (2006, 2008)[191,192]	HBCD	Thyroid dysfunction, increased cholesterol in female Wistar rats	
		Organochlorines: Pesticides, Herbicides, Fungicides, Food	
		Mechanisms: AhR,[53] Aromatase Inhibitor[54]; DDE is an Antiandrogen[178]; Triflumizole is a PPARγ Activator[146]; Tolylfluanid and Endrin Activate GR[204]	
Arsenescu (2008)[53]	PCB 77, TCDD	Weight gain in mice, increased LA in 3T3-L1 cells	
Calvert (1999)[186]	TCDD	Diabetes, serum glucose, free T4 in adult veterans	
Dirinck et al. (2010)[55]	β-HCH	Increased BMI, WC, fat mass, IR in human adult men and women	
Eggesbo (2009)[177]	HCB	Low birth weight in human offspring	**BM**
Elobeid (2010)[182]	OCDD, DDT, hpcdd, oxychlordane	Increased BMI, WC in adults (NHANES)	
Gladen (2000)[56]	PCBs (congeners not specified), DDE	Weight gain in females (PCB), males (DDE) at puberty	**BM, SER, CB**
Glynn (2003)[179]	PCBs 105, 118, DDE, HCB, β-HCH	Increased BMI and T2DM in human adult and elderly women	
Govarts (2012)[57]	PCB 153	Low birth weight (ENRIECO, EU OBELIX)	**CB**
Hallgren (2001)[189]	Aroclor 1254, PCB 105, Bromkal 70-5 DE and DE-47	Decreased T4 levels in Sprague–Dawley rats and C57BL/6 N mice	
Herbstman (2008)[194]	PCBs (many congeners)	Low TSH, T4, free T4 in human neonates	**CB**
Hertz-Picciotto (2005)[58]	PCBs 101, 105, 110, 118, 137, 138, 153, 156, 170, 180, and 187	Low birth weight in human male offspring	**SER**

Karmaus (2009)[59]	DDE	Weight and BMI in adult human female offspring	**SER**
Kern (2004)[185], Cranmer (2000)[187]	TCDD	Insulin resistance in adult veterans	
Lee (2006)[181]	PCB 153, HpCDD, OCDD, oxychlordane, DDE, TNC	Increased T2DM in adults (NHANES)	
Lee (2007)[180]	Oxychlordane, TNC	Insulin resistance, waist circumference in adult humans	
Lee (2011)[183]	Oxychlordane, TNC, p,p'-DDE, HCB	Increased BMI, triglycerides, and insulin resistance in adult humans	
Lee (2011)[60]	p,p'-DDE and dioxin	Increased abdominal obesity in elderly individuals	
Li (2012)[146]	Triflumizole	Lipid accumulation in prenatally exposed MSCs and in 3T3-L1 cells; weight gain	**PRE-DW**
Mendez (2011)[61]	DDE	Rapid growth and increased BMI in human infants	**SER**
Rayner (2005)[62]	Atrazine	Low birth weight in Long–Evans rats	**PRE-GAV**
Rönn (2011)[178]	PCBs 74, 99, 105 and 118, TNC, DDE, HCB	Increased fat mass in elderly individuals	
Roos (2012)[173]	PCBs 105, 118, 189, DDE, HCB, TNC	Increase VAT and SAT, VAT/SAT ratio in elderly individuals	
Sargis (2010)[204]	Tolylfluanid, endrin	Increased LA in 3T3-L1 cells	
Sargis (2012)[63]	Tolylfluanid	Insulin resistance in primary mice, rat, and human adipocytes	
Smink (2008)[176]	HCB	Overweight in human children offspring	**CB**
Valvi (2012)[64]	PCBs 28, 52, 101, 118, 138, 153, 180, DDE	Overweight in human children offspring	**CB**
Verhulst (2009)[175]	HCB, PCBs 118, 138, 153, 170, 180, DDE	Increased BMI in children	**CB**
Vitalone (2010)[65]	PCB-126	Weight gain in adult Wistar rats	**PERI-GEL**
	Organophosphates: Insecticides		
	Mechanisms: Mostly Unknown (Potential Neuroendocrine Disruptor)		
Lassiter (2008, 2010)[66,67]	Parathion ± HFD	Weight gain, metabolic dysfunction in adult Sprague–Dawley rats	**NEO-INJ**
Lassiter (2008)[68]	Chlorpyrifos	Weight gain in adult Long–Evans rats	**PERI-GAV**
Roegge (2008)[69]	Diazinon + HFD	Weight gain in adult Sprague–Dawley rats	**NEO-INJ**
Slotkin (2005)[70]	Chlorpyrifos	Increased serum triglycerides; hyper-insulinemia in adult Sprague–Dawley rats	**NEO-INJ**
	Phenols: Paints, Adhesives, Pesticides, Adhesives, Plastics, Rubbers, Cosmetics, Herbs, Flame Retardants		
	Mechanisms: ER,[64,71] GR,[204] Akt,[72] PPAR[73]; TBBPA, TCBPA, TMPBA Inhibit T3 Binding[74]		
Alonso-Magdalena (2010)[75]	BPA	Impaired glucose homeostasis in adult OF-1 mice and their offspring	**PRE-INJ**
Cagampang (2007)[76]	BPA	Increased fat mass, low birth weight, catch-up growth, MetS in MF-1 mice offspring	**PRE-INJ**
Carwile (2011)[77]	BPA	Increased obesity in adults (NHANES)	
Chamorro-García (2012)[172]	BADGE	Increased LA in 3T3-L1 cells and MSCs	
Huc (2012)[78]	BPA	Increased LA in HepG2 cells	
Lang (2008)[79]	BPA	Increased T2DM in adults (NHANES)	
Masuno (2002)[80]	BPA + insulin	Increased LA in 3T3-L1 cells	
Masuno (2005)[81]	BPA, BPB, BPE, BPF, BPS	Increased LA in 3T3-L1 cells	
Miyawaki (2007)[163]	BPA	Increased body weight, adipose tissue weight, and hyperlipidemia in adolescent CD-1 mice offspring	**PERI, POST-DW**
Miyawaki (2008)[82]	4-Tert-Octylphenol	Increased LA in C3H10T1/2 cells; inhibition of bone	
Ryan (2010)[83]	BPA, BPA + HFD	Increased body mass in young CD-1 mice	**NEO**
Sargis (2010)[204]	BPA	Increased LA in 3T3-L1 cells	
Shankar (2011)[84]	BPA	Increased T2DM in adults (NHANES)	

(*Continued*)

TABLE 43.1 (*Continued*)
Known Obesogenic Chemicals, Exposure, and Mechanisms of Action

Publications	Chemical	Endpoint	Exposure
Silver (2011)[85]	BPA	Increased T2DM in adults (NHANES)	
Somm (2009)[164]	BPA, BPA + HFD	Increased body weight and fat mass in young Sprague–Dawley rat offspring	**PERI-DW**
Wang (2010)[73]	BPA	Increased LA in Huh7-PPRE-Luc and 3T3-L1 cells	
Wang (2012)[86]	BPA	Increased IR and obesity in human adults	
Wei (2011)[87]	BPA ± HFD	MetS in adult Wistar rat offspring	**PERI-GAV**
Xu (2011)[165]	BPA	Weight gain, increased fat mass, sweet preference in adult Sprague–Dawley rat offspring	**PERI-DW**
	Heavy Metals: PVC Stabilizer, Seafood		
	Mechanisms: Cadmium binds ER and Mimics Estrogen;[207] Cadmium Also Inhibits 11β-HSD2;[88] Arsenic Affects the Biochemistry of Glucose Metabolism[89]		
Afridi (2008)[46]	Pb, Cd, and As	Increased T2DM prevalence	
Haswell-Elkins (2008)[44]	Cadmium	Increased albuminuria (associated with T2DM)	
Lai (1994)[41]	Arsenic	Increased T2DM prevalence	
Leasure (2008)[90]	Lead	Obesity in adult male C57BL/6 mice	**PRE-DW**
Rahman (1995)[91]	Arsenic	Increased T2DM prevalence	
Rahman (1998)[43]	Arsenic	Increased T2DM prevalence	
Schwartz (2003)[45]	Cadmium	Impaired glucose metabolism, increased T2DM prevalence	
Tseng (2000)[42]	Arsenic	Increased T2DM prevalence	
	Nicotine, PAH: Cigarettes, Tobacco, Smoke, Air Pollution, Charbroiled Food		
	Mechanisms: Cholinergic/Catecholaminergic[92]; Oxidative Stress Leading to Apoptosis of β-cells, Activation of Nicotinic Receptors Reduces Insulin Secretion[93,208]		
Bergmann (2003)[94]	Nicotine (inferred)	Reduced birth weight, increased BMI in human children offspring	**MS**
Bergmann (2003)[94]	Nicotine (inferred)	Increased BMI, skinfold thickness in child offspring	**MS**
Bolton (2012)[95]	Diesel exhaust, ± HFD	Weight gain, increased insulin in C57BL/6 adult mice offspring	**PRE-INH**
Bruin (2007)[93]	Nicotine	Reduced β-cell mass and impaired glucose homeostasis in adult Wistar rat offspring	**PERI-INJ**
Friedman (2012)[96]	Nicotine (cotinine)	T2DM, obesity in adults exposed to second hand smoke	
Gao (2005)[97]	Nicotine	Increased postnatal body weight, fat pad weight, PVAT in adult Wistar rat offspring	**PRE-INJ**
Grove (2001)[98]	Nicotine	Decreased NPY, reduced leptin, increased POMC in rhesus monkey neonate offspring	**PRE-OP**
Holloway (2005)[99]	Nicotine	Dyslipidemia, impaired glucose homeostasis, weight gain in adult Wistar rat offspring	**PERI-INJ**
Irigaray (2006)[100]	BaP	Weight gain, increased fat mass in C57Bl/6J male mice	
Montgomery (2002)[101]	Nicotine (inferred)	T2DM, obesity in adult offspring	**MS**
Oken (2008)[102]	Nicotine (inferred)	Increased BMI in child offspring (meta-analysis)	**MS**
Oliveira (2009)[103]	Nicotine	Weight gain, hyperleptinemia, and hypothyroidism in adult Wistar rat offspring	**NEO-OP**
Power (2002)[104]	Nicotine (inferred)	Reduced birth weight, increased BMI in adolescent and adult offspring	**MS**
Rundle (2012)[105]	PAH	Increased BMI, % body fat in human children offspring	**MS**
Somm (2008)[106]	Nicotine	Increased WAT weight, larger adipocytes in young Sprague–Dawley rat offspring; metabolic syndrome in the adult offspring	**PRE-OP**
Syme (2009)[107]	Nicotine (inferred)	Abdominal obesity in adult adolescent human offspring	**MS**
von Kries (2002)[108]	Nicotine (inferred)	Increased BMI in children human offspring	**MS**

Widerøe (2003)[109]	Nicotine (inferred)	Increased BMI, skinfold thickness in human children offspring	**MS**
Williams (1984)[110]	Nicotine	Increased fetal body fat in Sprague–Dawley rats	**PRE-DW**
Xu (2011)[111]	$PM_{2.5}$	Decreased adiponectin and leptin; insulin resistance in C57Bl/6J male mice	
	Phthalates: Plasticizer, PVC Tubing, PVC Flooring, Personal Care Products		
	Mechanisms: PPAR Activator[73,112–114]; GR Activator[204]; TR Antagonist or Increased SMRT Recruitment to TR[115,116]; DBP is ER Agonist.[115]		
Biemann (2011)[50]	DEHP	Increased adipocyte number, lipid accumulation in C3H/10T1/2 cells	
Bility (2004)[113]	MBenP, MEHA, MIHP2, MEHP, MIHP, MnOP, MINP, MIDP	Increased LA in 3T3-L1 cells	
Boas (2010)[117]	MEP, MCiOP, MBP, MBzP	Decreased T3 levels in children	
Feige (2007)[112]	MEHP	Increased LA in 3T3-L1 cells	
Hatch (2008)[38]	MEP, MBP, MBzP, MEHHP, MEOHP	Increased WC and BMI in adult males	
Hurst (2003)[114]	MEHP, MBzP, MBuP	Increased LA in 3T3-L1 cells	
James-Todd (2012)[118]	MnBP, MiBP, MBzP, MCPP, and ∑DEHP	Increased diabetes prevalence, IR in women	
Lind (2012)[40]	MMP, MiBP, MEP	Increased diabetes prevalence, IR in elderly individuals	
Lind (2012)[39]	MiBP	Increased WC, total fat mass, abdominal SAT in elderly women	
Sargis (2010)[204]	DCHP	Increased LA in 3T3-L1 cells	
Schmidt (2012)[119]	DEHP	Impaired fertility, increased body weight and larger adipocytes in C3H/N female F0 mice, F1 offspring showed increased visceral fat and body weight	**PRE-FD**
Stahlhut (2007)[37]	MBP, MBzP, MEHHP, MEOHP, MEP	Increased WC in adult males	
Wang (2010)[73]	BBP	Increased LA in Huh7-PPRE-Luc and 3T3-L1 cells	
	PFCs: Teflon and Scotchgard		
	Mechanisms: Unknown		
Halldorsson (2012)[196]	PFOA	Increased adiposity biomarkers, waist circumference, BMI	**SER**
Hines (2009)[195]	PFOA	Increased body weight, insulin, leptin in postpubertal female mice offspring	
	Medications: Antidiabetic, Atypical Antipsychotics, Synthetic Estrogens, Anti-Inflammatories		
	Mechanisms: Thiazoloadinediones Activate PPARγ[120]; Cox2 Inhibitors Inhibit Prostaglandin Synthesis[121] and Could Potentially be PPARγ, PPARα Activators[122]; Olanzapine and Clozapine Affect TGFβ, Neurotransmitters[123]; DES is a Synthetic Estrogen[205]		
Jin (2002)[124]	Clozapine, olanzapine, quetiapine, and risperidone	Increased T2DM (meta-analysis) in human adults	
Knight et al. (1987)[125]	Indocin	Increased LA in 3T3-L1 cells	
Newbold (2005)[205]	DES	Increased body weight in adult CD1 mice	**NEO-INJ**
Pratley (2006)[126]	Pioglitazone	Weight gain in human adults	
Shim (2006)[127]	Rosiglitazone	Increased HDL-C and body weight in human adults	
Vegiopoulos (2010)[121]	Cox2 inhibitors	Reduced brown fat production	
Williams (1997)[128]	Indocin	Increased LA in 3T3-L1 cells	

(*Continued*)

TABLE 43.1 (*Continued*)
Known Obesogenic Chemicals, Exposure, and Mechanisms of Action

Publications	Chemical	Endpoint	Exposure
		Sugar, Trans Fat, Phytoestrogens: Food, Food Additives, Beverage, Infant Formula	
		Mechanisms: Fructose Alters Liver Biochemistry[129–131]	
Abdel-Sayed (2008)[132]	Fructose	Impaired lipid metabolism in human adult males	
Abid (2009)[133]	Fructose	NAFLD in human adults	
Assy (2008)[134]	Fructose	NAFLD in human adults	
Dawson (1981)[135]	Excitotoxin	Increased fat mass, obesity in adult Sprague–-Dawley rats	
He (2008)[214]	Excitotoxin	Overweight in human adults	
Hermanussen (2006)[136]	Excitotoxin	Low birth weight in Wistar rats	**PRE-FD**
Le (2008)[137]	Fructose	Impaired glucose and lipid metabolism in human adult males	
Montonen (2007)[138]	Fructose	Increased T2DM in human adults	
Newbold (2005)[205]	Genistein	Increased body weight in adult CD1 mice	**NEO-INJ**
Olney (1969)[139]	Excitotoxin	Obesity in adult mice	**NEO-INJ**
Ouyang (2008)[218]	Fructose	NAFLD in human adults	
Palmer (2008)[140]	Fructose	Increased T2DM in human adult females	
Perez-Pozo (2010)[141]	Fructose	MetS in human adult men	
Stanhope (2009)[142]	Fructose	Increased visceral adiposity and IR in human adult males	
Stettler (2005)[143]	Genistein (inferred)	Overweight in human adults	**NEO-FD**
Tetri (2008)[144]	HFCS ± trans fat	NAFLD in adult C57BL/6 mice	
Yoshida (2007)[145]	Fructose	Insulin resistance	

Notes: BM, breast milk; CB, cord blood; DW, drinking water; FD, food; GAV, gavage; GEL, Transgel; INH, inhalation; INJ, injection; IR, insulin resistance; LA, lipid accumulation; MetS, metabolic syndrome; MS, maternal smoking; NEO, neonatal exposure; OP, osmotic pump; PERI, perinatal exposure; PRE, prenatal exposure; PUB, pubertal exposure; SER, maternal serum; T2DM, type 2 diabetes.

TBT continues to be a model obesogen and new research has expanded its role in contributing to obesity. Recently, it was shown that TBT can also act through mechanisms not related to adipocyte differentiation. PPARγ is expressed in the brain, and knocking down neuronal-specific PPARγ reduces food intake and weight gain on a high-fat diet.[149] TBT crosses the blood-brain barrier[150] and could potentially activate PPARγ in the brain. The TBT–PPARγ interaction in the brain has not been shown directly; however, rosiglitazone activates PPARγ in the CNS and increases c-fos expression in the arcuate nucleus.[151] c-fos expression is indicative of activated neurons, some of which express neuropeptide Y (NPY) and agouti-related protein (AgRP). NPY and AgRP promote feeding behavior[152,153] and are inhibited by leptin and insulin, but stimulated by ghrelin.[154–157] Treatment of adult mice with TBT resulted in increased c-fos expression in the arcuate nucleus[158]; however, it is unknown whether this effect is mediated by PPARγ. These results demonstrate that obesogenic chemicals need not affect adipocytes directly, but can give an animal an increased drive to eat.

Many chemicals administered during precise temporal windows during fetal development have been shown to generate phenotypes not just in the first generation, but in the second or third generation. Such phenotypes are nongenetically determined since low-dose chemical exposures do negligible damage to DNA and multiple independently exposed animals produce the same phenotypes. Transgenerational effects occur when genes are epigenetically patterned to create a permanent change in the germ line. Certain diseases or gene expression changes can be found in the F3 generation (and beyond, i.e., F4, F5, F6) as a result of chemical exposure that has affected DNA loci, which have escaped reprogramming mechanisms during gametogenesis that normally erase epigenetic marks acquired by the previous generation.[19,22,26] For example, F0 exposure to fungicides, pesticides, plastics, and air pollution is linked to ovarian diseases in the F3 generation.[159] Maternal exposure to BPA is linked to social behavioral changes in F4.[160] Data surrounding transgenerational inheritance of obesity is beginning to appear in the literature. Prenatal exposure of pregnant F0 mice to TBT led to increased adipose depot weight, larger adipocyte size, and biased cell fate in the MSC compartment to favor the adipocyte lineage in the F1, F2, and F3 generations.[26] Moreover, prenatal TBT exposure led to fatty liver in all three generations.[26] These results demonstrate that the effects of early life obesogen exposure are permanent and transgenerational, increasing the risk of future generations to develop obesity and related disorders.

43.5.2 Obesogens with Unconfirmed Mechanisms of Action

43.5.2.1 Bisphenol A

There has been a great deal of interest in BPA because of its high production volume and widespread commercial use. Numerous animal studies have shown a link between BPA exposure with increased body weight and adiposity and it is presumed, although, not yet demonstrated that these effects of BPA are mediated through one of the estrogen receptors (ERs).[161,162] BPA exposure during gestation and lactation accelerated adipogenesis or increased fat pad weights at the time of or soon after weaning.[163–165] A recent study in rats confirmed an increase in the expression of adipogenic genes in adipose tissue at the time of weaning in BPA-exposed animals.[164] Some evidence suggests that the increases in body weight are sex specific, but timing and dose may contribute to the complexity of these findings.[163,164,166] Thus far, changes in body weight have been reported in animals exposed to BPA during gestation, or gestation and lactation, and in one study BPA exposure continued through postnatal day 30 when animals were sacrificed.[167] To date, no studies have continued BPA exposure throughout life, and few have followed measurements of body weight and adiposity through adulthood and to later ages. Far more investigation is needed to understand the effects of BPA exposure on body weight and adiposity prepubertally and later in life and the mechanisms through which BPA may be acting.[162]

Since the 1990s, several dozen studies have been dedicated to determining human exposure to BPA and its impact on human metabolic systems.[44] The correlation between urinary BPA concentrations and metabolic disorders was investigated in a nationally representative cross-sectional sample of U.S. adults from the National Health and Nutrition Examination Survey (NHANES).[167,168] Among 2948 adults participating in two cycles of the NHANES (2003/2004 and 2005/2006), urinary BPA concentrations were associated with increased prevalence odds of self-reported CVD and diabetes. However, associations between BPA and CVD and diabetes were stronger in the 2003/2004 cycle, when geometric mean BPA concentrations were higher (2.5 vs. 1.8 μg/L). Positive correlations between urinary BPA and serum liver enzyme concentrations were also observed. The interpretation of these results is limited by the cross-sectional design. CVD and metabolic disorders have long latency periods, and contemporaneous urinary BPA concentrations may not reflect the relevant etiologic window for the development of cardiovascular and metabolic diseases, which is known to be years or decades earlier. In addition, time-dependent confounding (i.e., reverse causality) may be responsible for observed associations since obese individuals are at increased risk for CVD and metabolic disorders and may consume more packaged and processed foods that contain BPA. Even in the face of these caveats, animal studies show that prenatal BPA exposure may influence the development of metabolic disorders.[162] Thus, fetal exposure to BPA may be more important to the development of metabolic disorders than exposure later in life.

43.5.2.2 Bisphenol A Diglycidyl Ether

Bisphenol A diglycidyl ether (BADGE), produced by reacting BPA and epichlorhydrin, is used as an intermediate in the manufacture of epoxy resins and paints and also as a coating on food cans and food storage vessels.[169] Like BPA, BADGE migrates from container linings into foods and is routinely ingested,[170,171] raising questions concerning its

potential adverse effects on human health. BADGE induces adipogenesis and the expression of adipocyte marker genes in MSCs; however, unlike TBT or TFZ, this effect is PPARγ-independent.[172] BADGE does not activate or antagonize PPARγ at up to 10 μM, and BADGE-induced adipogenesis is not inhibited by treatment with high-affinity PPARγ antagonists GW0662 or T0070907.[172] Therefore, BADGE is unlikely to act as a ligand for the RXR-PPARγ heterodimer at doses that could be encountered, in vivo,[172] and probably acts independently, or downstream of PPARγ. Since BADGE is closely related to BPA, one might suppose that it has a similar mechanism of action. However, BADGE can induce differentiation in MSCs whereas BPA cannot,[172] which suggests that their mechanisms of action may be distinct.

43.5.2.3 Organochlorines

Although TFZ and DDE are obesogenic organochlorine chemicals for which the mechanism of action is known, most other organochlorines that are linked to obesity or adipogenicity have no known mechanism. The five broad categories of obesogenic organochlorines include PCBs, DDE, HCB, chlordane-based, and dioxin-based chemicals (see Table 43.1). PCBs were commonly produced in North America for over half a century. Upon the discovery that they negatively affect the health of humans and other animals, use of these chemicals was banned in the United States, yet they remain persistent environmental contaminants. Most associations of obesity, diabetes, and visceral obesity in humans have occurred with increased plasma levels of PCBs 74, 99, 105, 118, 138, 153, 170, 180, and 189 (see Table 43.1). There have been attempts to link congener number (degree of chlorination) with the risk of obesity[173]; however, this research is ongoing. HCB was once widely used as a fungicide, particularly on wheat seeds, and remains present in the population[174] despite being banned in 1966. Higher concentrations of HCB in cord blood,[175] maternal serum,[176] or breast milk[177] were associated with low birth weight[177] and increased BMI in children.[175,176] HCB concentrations in adult serum are also positively correlated with fat mass in elderly individuals[173,178] and diabetes.[179] Chlordane and its relatives were used as pesticides on crops and for termite control. Chlordane and its breakdown products, such as oxychlordane, trans-nonachlor, and cis-nonachlor, are linked to increased BMI, fat mass, triglycerides, and waist circumference in adults, and are also associated with insulin resistance and diabetes.[178,180–183] Dioxins such as 2,3,7,8-tetrachlorodibenzodioxin (TCDD) were notorious for their contamination of the defoliant Agent Orange and might provide a reason for why diabetes risk is higher for veterans who were in contact with Agent Orange compared to veterans who were not exposed.[184] TCDD serum levels are positively associated with insulin resistance and T2DM.[185–187]

43.5.2.4 Organobromine Flame Retardants

Polybrominated biphenyls and polybrominated diphenylethers (PBDEs) are widely used as flame retardants. Although a subset of these are now banned, the majority of the population has significant blood levels (http://www.cdc.gov/nchs/nhanes.htm) that have been associated with various adverse health outcomes including obesity and reduced thyroid function.[188–192] Prenatal or neonatal exposure to PBDEs is associated with low birth weight and thyroid function in offspring.[193,194]

43.5.2.5 Perfluorochemicals

Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), found in Teflon® and formerly Scotchgard™, are linked to the prenatal programming of obesity. Young adult mice that were exposed in utero to PFOA[195] have increased serum insulin and leptin levels. In humans, prenatal exposure to PFOA is associated with increased BMI, adiposity biomarkers, and waist circumference.[196]

43.5.2.6 Phthalates

Phthalates and phthalate metabolites have been associated with waist circumference, insulin resistance, and obesity in humans,[37,38] and an abundance of studies show that phthalates can induce adipogenesis in cell culture models, reviewed in the work by Casals-Casas et al.,[197] but until recently, there was no strong evidence from animal studies linking phthalates with obesity. Two recent studies have linked exposure to diethylhexylphthalate (DEHP) with obesity in animal models. Schmidt and colleagues showed that prenatal exposure of C3H/N female mice led to increased body weight, visceral fat, and adipocyte size in F0 females and in F1 offspring. Feige and colleagues showed that DEHP-exposed C57BL6/J mice carrying the human PPARα were susceptible to high-fat-induced obesity, whereas wild-type mice were not.[198] Apparently, the mouse PPARα protects against high-fat-diet-induced obesity, whereas its human counterpart does not. These results have important implications for interpreting negative results of chemicals that can activate PPARs on obesity.

43.6 ADDITIONAL MECHANISMS THROUGH WHICH OBESOGENS MIGHT ACT

The reader is directed toward more extensive reviews for a thorough description of potential mechanisms for obesogen action.[3,7,24,199,200] In addition to the mechanisms in the preceding discussion, the following mechanisms may also be relevant to obesity in humans.

43.6.1 Obseogenic Chemical Influences PPARγ in a Nonligand-Dependent Fashion

While ligand activation of nuclear receptors (such as TBT activation of PPARγ) has been a prominent mechanism of action for EDCs and obesogens, nuclear receptors can also be derepressed or activated through various posttranslational modifications causing active release of co-repressors in the absence of PPARγ ligands, reviewed in the works by Janesick and Blumberg,[3] Perissi et al.,[201] and van Beekum et al.[202] The presence or absence of posttranslational modifications on PPARγ could be obesogenic by causing allosteric hindrance of

corepressor release, protecting PPARγ against ubiquitination and subsequent degradation, by encouraging heterodimerization with RXR, or by preventing PPARγ from recruiting methyltransferases to its promoter. All of these mechanisms would increase the steady-state levels of PPARγ protein and target genes. Whether obesogens exist that target, one of these mechanisms remains to be seen, but we consider this possibility quite plausible.

43.6.2 Obesogenic Chemical Serves as a Ligand for a Different Receptor

Obesity is linked to a general increase of positive feedback within the hypothalamic-pituitary-adrenocortical axis, characterized by the impaired ability to clear or inactivate cortisol in adipose tissue, particularly visceral adipose tissue.[168] Glucocorticoids increase adipocyte proliferation and their differentiation from stromal cells; hence, the presence of excess glucocorticoids will undoubtedly stimulate adipogenesis locally.[203] BPA, dicyclohexyl phthalate, endrin, and tolylfluanid were all found to activate glucocorticoid receptors and increase adipogenesis in the 3T3-L1 preadipocyte model.[204] Prenatal or perinatal exposure to excess estrogen also promotes obesity in adult offspring, reviewed in the works by Rubin and Soto,[167] Newbold et al.,[205] and Vom Saal et al.[206] Cadmium binds to the ER and mimics estrogen[207] and is associated with diabetes in adults.[44,45] Other chemicals can activate receptors in the brain. For example, maternal smoking activates nicotinic acetylcholine receptor, which induces oxidative stress and pancreatic β-cell death and reduces insulin secretion in offspring.[208]

43.6.3 Chemical Interferes with an Enzyme–Substrate Interaction

EDCs can act independently of a hormone receptor. For example, an EDC could alter the synthesis of a hormone or modulate its breakdown. Dibutyltin and dithiocarbamate pesticides inhibit 11-β-hydroxysteroid dehydrogenase-2, thereby interfering with glucocorticoid breakdown and upregulating glucocorticoid levels.[209,210] TBT is a low-affinity competitive inhibitor of cytochrome P450 19 (CYP19, aka P450 aromatase), which normally converts testosterone to estradiol. TBT increases the expression of CYP19 mRNA and protein in some cell types, which will lead to higher levels of estradiol[211] while inhibiting it in others, thereby reducing estradiol levels.[212]

43.6.4 Chemical Is a Nutrient Required for Development and Survival, but Has the Capacity to Be Overconsumed and thus Adversely Affect Adipogenic Pathways, much as an EDC Does

Obesogens are most commonly viewed as industrial chemicals; however, they can also be the chemicals that we ingest purposely in our diet. Soy has been found in the diets of Asian populations for centuries; however, soy formula and soy milk are mostly phenomena in the United States. In particular, infant exposure levels are much higher in the United States compared to Asia.[213] The effects of early life exposure to soy and obesity consequences later in life have been reviewed.[200] Monosodium glutamate is associated with obesity[214] and permeates American diets.

Sugars, particularly fructose, have been increasingly linked with obesity (albeit not without controversy). The glycemic index of fructose is significantly lower than glucose. However, the majority of fructose is quickly metabolized in the liver[215] without inducing insulin secretion.[216] For this reason, low doses of fructose are thought to help regulate glucose homeostasis, reviewed in the work by Sievenpiper et al.,[217] but at the high doses ingested by most Americans, fructose has pathological consequences. Unlike glucose, which is stored as glycogen, fructose metabolites are stored as triglycerides in the liver,[218] and excess fat is secreted in the form of very-low-density lipoprotein, which is highly associated with T2DM.[219] Fructose creates de novo lipogenesis in the liver and thus is a unique obesogen by directly stimulating inappropriate storage of fat in the liver, as opposed to the adipocyte. Table 43.1 provides many examples of the correlative link between fructose and fatty liver.

43.7 PERFECT STORM FOR OBESITY

We propose that the confluence of developmental programming of metabolic set points by obesogens in association with continued obesogen exposures, overconsumption of processed foods containing added sugars and EDCs from the packaging materials, together with decreased physical activity throughout life create "The Perfect Storm" that is driving the obesity epidemic. There are now nearly 20 chemicals shown to cause long-term weight gain and metabolic dysfunction in humans or animals and there is no systematic effort yet underway to identify obesogens or to determine whether they promote weight gain and obesity in animal models or humans. Obesogen exposure during critical periods of development can disrupt normal hormone and neuronal signaling pathways that are being established, leading to an increased vulnerability during early life. It is undoubtedly true that adults have the self-preservation instinct to entertain the idea of detoxifying themselves, avoiding chemical exposure, and increasing activity. However, emerging data from animal studies suggest that the effects of prenatal or early life obesogen exposure may be permanent and be transmitted to subsequent generations. It will be important to understand how prenatal obesogen exposure elicits transgenerational effects on fat depot size, adipocyte size, adipocyte number, and fatty livers. It will be particularly interesting to elucidate how obesogen exposure alters stem cell fate and lineage allocation in the stem cell compartment to favor adipogenesis at the expense of osteogenesis. Once outside of the womb, children and adults must further contend with the ubiquitous presence of dietary and chemical obesogens, which confound their ability to fight obesity. Determining how diet interacts with prenatal and early life obesogen exposure to influence obesity will harmonize nutritional, toxicological, endocrinological, and developmental studies that

will make important contributions to our understanding of the degree to which obesogen exposure contributes to the obesity epidemic. In turn, these studies will provide important new tools for policymakers in the ongoing debate about what should be done about EDC and obesogen exposure.

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44 Economic Costs of Obesity

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CONTENTS

44.1 INTRODUCTION

In addition to its negative impact on health, obesity imposes large economic costs on many entities, including health-care systems, employers, governments, obese individuals and their families, and society as a whole. In this chapter, we briefly describe the methods used to quantify the economic costs of obesity and then summarize the major findings up to the present and their policy implications.

44.2 METHODS TO ESTIMATE THE COSTS OF OBESITY

Cost-of-illness (COI) is the method most commonly used to estimate the economic costs of obesity. With the COI method, the total economic costs of obesity are divided into three components: direct, indirect, and intangible costs. Direct costs are further divided into medical and nonmedical costs.

44.2.1 Direct Medical Costs

The *direct medical costs of obesity* include medical costs associated with treating obesity itself and the medical costs for treating those diseases for which excess body weight is a risk factor, such as type 2 diabetes and hypertension. *Medical costs of treating obesity* are the value of health-care resources use for reducing and maintaining body weight, including counseling services, outpatient visits, medications, surgical procedures, and hospital stays. *Medical costs for treating obesity-related diseases* are the value of health-care resources use that are associated with diagnosing and treating those diseases, including medical costs for hospital and physician inpatient care, emergency department and physician outpatient visits, nursing home care, hospice care, rehabilitation care, specialist and other health professional care, diagnostic tests, prescription drugs, and other medical supplies. In the calculation of direct medical costs, the entire medical cost of treating obesity is included. However, only a percentage of the total medical costs spent on treating obesity-related diseases, such as type 2 diabetes, is accounted for as part of the direct medical costs of obesity. This percentage is based on the proportion of total prevalence of these diseases accounted for by obesity as the cause. In addition, only those medical costs paid for by a health-care system are included as direct medical costs. Medical costs that health-care systems do not cover such as meal replacement for reducing or maintaining body weight are not considered as part of the direct medical costs.

Direct nonmedical costs include the costs of health education efforts intended to help people maintain a healthy lifestyle and the costs of preventing and treating obesity, but not covered by health-care systems, such as costs associated with purchasing exercise equipment for losing weight, travel to health-care providers, and the patient's time involved in the treatment. Direct nonmedical costs are normally paid by the individual. Few COI studies on obesity include this component in deriving estimates of the total direct costs of obesity.

44.2.2 Indirect And Intangible Costs

Indirect costs include the value of the time lost from employment or other productive activities due to an obese person's excess risk of mortality and morbidity. In addition, some but not all estimates include as indirect costs the value ascribed to time lost from housekeeping and other tasks and time lost by family members or friends who provide transportation and care for those being treated for obesity and its attributable diseases.

The human capital approach, defined below, is the most commonly used method for estimating the indirect costs of obesity. This approach measures the indirect costs of an illness in terms of market valuation of lost wage earnings from morbidity and mortality. The human capital approach assesses the loss in productivity for those who normally stay at home by the value of lost household services. This value is imputed as the expected costs for having services performed by service workers, such as maids or cooks, rather than by oneself. Indirect costs due to morbidity are the value of time lost, as measured by wage equivalent of time, from decreased productivity while on the job (presenteeism) and from the number of missed workdays (absenteeism) that result from obesity and its related diseases. Indirect costs due to mortality, as assessed in the human capital approach, are the value of future income lost due to obesity-related premature death. The human capital approach excludes from the indirect cost estimates the value of leisure time and volunteer work that are not reflected in earnings.

Intangible costs are those associated with the pain and suffering from obesity itself, and from those diseases for which obesity is a contributing factor. Because of the difficulty of assigning a monetary value to physical or emotional suffering, this component of the costs has not been included in the total costs of obesity.

44.2.3 Prevalence-Based versus Incidence-Based Estimates

The COI method has been used to derive two sets of estimates related to the total economic costs of obesity: one based on the prevalence of obesity and the other on the incidence. The prevalence-based (or annual costs) approach measures the direct and indirect costs that accrue during a base year due to all existing (prevalent) cases of obesity in that year. If a person died prematurely in the base year because of obesity or from a disease to which obesity contributed, the loss in future productivity is also included. The loss in future productivity is estimated as the discounted present value of future earnings expressed in the currency value in the base year.

Two main approaches, epidemiological and econometric, have been used to derive the prevalence-based direct medical costs. Using the epidemiological approach, also referred to as the attributable-risk approach, the total medical costs of obesity are estimated as the sum of direct medical costs for obesity plus those from across all diseases that are attributable to obesity. For obesity, all medical costs associated with obesity treatment are included in the costs of obesity. For diseases attributable to obesity, such as type 2 diabetes, costs were estimated by multiplying the total direct medical costs by the population-attributable fraction (PAF) for that disease. The PAF is calculated by using (1) information on the prevalence rate of obesity and (2) the unadjusted relative risk of an obese person, compared with that for a person of normal weight, of developing diseases commonly associated with obesity. For estimates of the total medical costs of each obesity-related disease, needed for using the attributable-risk approach, information is often obtained from published studies rather than being estimated directly by the authors of those studies.

The econometric approach estimates the difference in costs between a cohort of obese persons and a cohort of persons of normal body weight. Regression analysis is used to adjust the differences between the two cohorts in those factors, such as demographic characteristics (e.g., sex, age, race, geographic location) and the presence of other chronic conditions that may affect medical expenditures. The additional cost of obesity is the difference between the regression-estimated costs for persons with obesity and that for persons without obesity. Both the mean difference approach and a multistage regression approach are used to derive the additional costs, where the former compares the mean costs incurred by the two cohorts to determine the additional difference, and the latter uses a multiple-stage (usually a two-part) regression technique. The multiple-stage regression approach is most appropriate when a substantial proportion of the population has zero expenditure and a small proportion has very high costs. This approach involves estimating the probability of an individual incurring any costs and, if so, the additional cost for the health care received. Using this approach, the aggregate medical costs of obesity for a nation or region are estimated as the product of the additional cost per case of obesity and the number of obese persons in the nation or region.

The incidence-based (or lifetime costs) approach measures the present value for the lifetime costs or for costs in a certain year of all new cases of obesity that occurred during the given base year. Incidence-based costs require knowledge of the diseases to which obesity contributes, the likely course and duration of each of those diseases, survival rates, age at onset, and patterns and costs of medical care used to treat persons with those diseases, and the impact of obesity on employment. The incidence-based approach is more useful for comparing the effects of alternative interventions to prevent, treat, or manage obesity. However, incidence-based estimates are generally more difficult to obtain than prevalence-based estimates, and because of the greater complexity and data need, few cost estimates related to obesity are incidence based.

44.2.4 Study Perspective

Studies of the economic costs of obesity have been conducted from multiple perspectives: costs to health-care systems, employers, governments, obese individuals and their families, and society as a whole. Each perspective includes different costs, thus providing useful information about the costs to that particular group. For example, the health-care system

perspective is concerned with only the direct medical costs of obesity, while the government perspective focuses specifically on the share of those costs to be paid by the government. The societal perspective is the most comprehensive; the total direct medical and nonmedical costs and indirect costs for all members of that society are included.

44.2.5 Limitations of COI Estimates

The economic cost of obesity measures the amount of resources that would be saved if obesity were eliminated. While such estimates can reveal the magnitude of obesity as an economic problem, they are of limited use for informing policymakers about how to allocate limited financial resources among different interventions or programs for the prevention and control of obesity. This is because allocating resources for a high-cost illness or condition that is not necessarily responsive to treatment by current medical technology may not be an efficient use of resources. In contrast, investing in a condition that presents a low cost to society and tends to be fully amenable to low-cost prevention can lead to health gains and better use of health-care resources. Thus, knowing the economic cost alone without an understanding of the benefits (or health outcomes) gained, it is not possible to assess whether resources should be spent on treating or preventing obesity.

44.3 CURRENT ESTIMATES OF THE COSTS OF OBESITY

We reviewed literature to summarize the estimates on the costs of obesity from various perspectives. We searched in three databases (MEDLINE, Embase, and EconLit), using the key words "obesity," "overweight," "economics," and "cost," for studies that were published in English between 1990 and 2011. We searched for additional studies from the reference lists of the selected studies. We presented the cost estimates in both U.S. dollars and local currency, if the study was done in another country. We converted other currencies into U.S. dollars using the annual average exchange rate or the exchange rate on July 15 if the annual average was not available.

Throughout the chapter, we refer to a person as "obese" if his or her body mass index (BMI) was ≥30 kg/m^2, and within that broader group, as "class I obese" if his or her BMI was 30.0–34.9 kg/m^2, "class II obese" if his or her BMI was 35.0–39.9 kg/m^2, and "class III obese" if his or her BMI was ≥40 kg/m^2; the collective term "class II/III obese" was used in places for any BMI of ≥35 kg/m^2. We refer to a person with a BMI of 18.0–24.9 kg/m^2 as having "normal body weight." If the threshold values used in some studies to define obesity were different from the classification above, we used those actual BMI values as reported instead of these obesity categories. We used two different terms in describing the economic burden of obesity, "economic cost," and "financial cost." The term "financial cost" was used for instances in which income was transferred between different entities as a tax or subsidy, for example, or between an individual or an employer or a government.

44.3.1 Prevalence-Based Cost Estimates

An overwhelming majority of previous studies derived an estimate of the economic costs of obesity at given point of time such as a specific year using prevalence data. These studies assessed the economic costs of obesity from the perspective of society, health-care systems, governments, employers, and obese individuals and their families.

44.3.1.1 Economic Costs of Obesity to Societies

Total annual economic costs of obesity to society for four countries, including both direct and indirect medical costs, were estimated in six studies (Table 44.1). The estimated costs in the United States were $66.8 billion in 1990[1] and $99.2 billion in 1995,[2] in Germany, $4.76 billion (€4.24 billion) in 1998,[3] and in Switzerland, $0.87 billion (Swiss ₣1.32 billion) in 2001.[4] The estimated total economic costs of obesity in Canada were $2.77 billion (Canadian $4.34 billion) in 2001[5] and $6.36 billion (Canadian $7.1 billion) in 2006.[6] However, the two Canadian studies were not strictly comparable because of different comorbidities or cost categories included. After adjusting the number of comorbidities, years

TABLE 44.1
Annual Economic Costs of Obesity in Different Countries

Source	Country and Year of Estimation	Total Costs[a] (Billions)	Total Indirect Costs (Billions)	Total Indirect Costs as % of the Total
Wolf and Coldtz, 1994[1]	United States, 1990	$68.80	$23.00	33.0
Wolf and Coldtz, 1998[2]	United States, 1995	$99.20	$47.60	48.0
Sander and Bergemann, 2003[3]	Germany, 1998	$4.76 (€4.24)	$2.48 (€2.21)	52.0
Schmid et al., 2005[4]	Switzerland, 2001	$0.78 (CH ₣1.32)	$0.38 (CH ₣0.66)	50.0
Katzmarzyk and Janssen, 2004[5]	Canada, 2001	$2.77 (CA $4.34)	$1.77 (CA $2.74)	63.2
Anis et al., 2010[6]	Canada, 2006	$6.36 (CA $7.1)	$2.82 (CA $3.2)	45.1

Note: $, dollars; €, euros; CH, Swiss; ₣, francs; CA Canadian. The results on direct medical costs from these studies and several others are reported in Table 44.2. All studies were based on a prevalence-based approach.

[a] Include both direct medical and indirect costs.

of expenditures, and prevalence rate, the direct medical costs in 2006 remained higher than that in 2001.[6] The estimate in the 2006[6] study would have been even larger if the study had included the indirect costs due to missing work days and premature mortality as the 2001 study did.[5]

Several factors may have contributed to the variation in the cost estimates of obesity across countries. In addition to the year of estimation, variations in population size, prevalence of obesity, and per capita health-care expenditures may have been the main factors. For instance, in 2009, there were 298 million people who lived in the United States, compared with 33 million in Canada, 82 million in Germany, and 7 million in Switzerland (http://stats.oecd.org/index.aspx? queryid = 254; accessed on May 11, 2012). Prevalence of obesity also varied, 33.8% in the United States, 24.2% in Canada, 14.7% in Germany, and 8.1% in Switzerland (http://www.oecd.org/dataoecd/1/61/49716427.pdf; accessed on May 11, 2012). As another factor in the difference, per capita health-care expenditures in 2009 were $7980 in the United States, $4363 in Canada, $4212 in Germany, and $5144 in Switzerland (http://stats.oecd.org/index.aspx? DataSetCode = SHA; accessed on May 11, 2012). Differences in the total number of diseases and which specific diseases (i.e., those for which obesity is considered to be a risk factor) included in the analyses might also have contributed to the different estimates.

The direct medical costs of obesity to a society were reported in numerous studies. We have summarized the results of those studies in the following section, "Economic Costs to Health-care Systems." The estimates of total annual indirect medical costs of obesity are presented in Table 44.1. The estimates ranged from $0.38 billion (Swiss ₣0.66 billion) in Switzerland in 1991,[4] and $2.48 billion (€2.2 billion) in Germany in 1998,[3] to $47.6 billion in the United States in 1996.[2] The estimated indirect costs for Canada ranged from $1.77 billion (Canadian $2.74 billion) in 2001[5] to $2.82 billion (Canadian $3.2 billion) in 2006.[6] On average, about half of the total economic costs of obesity were accounted for by the indirect costs of obesity, ranging from 45% to 63% in Canada, 33% to 48% in the United States, 50% in Switzerland, and 52% in Germany (Table 44.1). The same explanations for differences in estimates of total economic costs across countries can also be applied to the indirect costs of obesity.

44.3.1.2 Economic Costs to Health-Care Systems

Economic costs to health-care systems were assessed at both the aggregate level, for a nation or region, and at the individual patient level. Economic costs of obesity to health-care systems are often labeled "the direct medical costs of obesity." Conversely, as all or most of those costs are paid by health-care systems, direct medical costs are often referred to as "the costs to health-care systems."

44.3.1.2.1 Aggregate Direct Medical Costs for a Nation or Region

The annual direct medical costs attributable to obesity among adult populations have been estimated for various countries[1,4,6–15]; the results are summarized in Table 44.2. To make the results comparable across studies, we included only those studies that reported findings as either the total cost estimate or as the percentage of the total health-care expenditures attributable to obesity. The studies could cover subgroups of the population, such as children or older people only, or geographical areas smaller than the nation, such as states or provinces. The predominant method used to estimate the direct medical costs of obesity has been the epidemiological approach. However, a few recent studies in the United States have used the econometric approach.[9–11]

The estimated direct medical costs of obesity in the United States ranged from as low as $46 billion in 1990 to as high as $147 billion in 2008. As a percentage of total national medical expenditures, they increased from 5.3% in 1998 to 9.1% in 2008.[9–11] Over time, on a per capita basis, the medical costs of obesity in the United States have also increased from $1145 in 1986 to $1429 in 2006 (in 2008 U.S. dollars).[11] Compared with the United States, the estimated costs in other countries were much lower in magnitude and as a percentage of total national health-care expenditures (Table 44.2). The magnitude of total medical expenditures due to obesity in a country is largely determined by the country's population size, the prevalence of obesity, and per capita health-care expenditure. Medical costs as a percent of national health-care expenditure are also affected by the level of the national health-care expenditure and varying priorities for spending on different diseases or health programs. Differences in the year of estimation, criteria used to define obesity, the number and types of obesity-related diseases included, and estimation methods used have also contributed to the differences in estimates, both within countries and between countries.

The number and specific types of diseases included in the analysis varied across the studies. Among studies using an epidemiological approach, the number of obesity-associated diseases included ranged from 4 to 18 (Table 44.2). As a result, the proportion of the total direct medical costs contributed by spending on each disease differed greatly across the studies. For example, in the United States in 1995 approximately 52% of the direct medical costs of obesity were from type 2 diabetes, 23% from coronary heart disease, 11% from hypertension, 6% from gallbladder disease, 5% from osteoarthritis, and 2% from other diseases.[8] In contrast, in Canada in 2006, the largest proportion was from coronary artery disease (26%), followed by type 2 diabetes (20%), hypertension (18%), stroke (8%), and congestive heart failure (7%).[6] In China in 2003, hypertension contributed the largest proportion (55%) of the direct medical costs of obesity, followed by stroke (21%), diabetes (13%), and coronary heart disease (12%).[14]

44.3.1.2.2 Individual-Level Direct Medical Costs

An obese person has higher total medical care costs than a person of normal body weight.[9,11,16–21] For example, in the United States, the estimated additional per capita medical costs for an obese person were $732 (37% higher costs than for a person of normal body weight) in 1998[9] to $1429 (42% higher) in 2008.[11] Among persons with private health insurance, the estimated additional costs were $1244 (56% higher

TABLE 44.2
Annual Direct Medical Costs (in Billions) of Obesity in Different Countries

Source	Country, Year of Estimation	Obesity Criteria	Diseases Included/Controlled for	Absolute Amount[a]	% of Total Health-Care Expenditure
Wolf and Colditz, 1994[1]	United States, 1990	BMI ≥29.0	Type 2 diabetes, hypertension, gallbladder disease, endometrial cancer, colon cancer, breast cancer, coronary heart disease, musculoskeletal disease	$45.8	6.8
Colditz, 1999[8]	United States, 1995	BMI ≥30.0	Type 2 diabetes, hypertension, gallbladder disease, endometrial cancer, colon cancer, breast cancer, coronary heart disease, osteoarthritis	$70.0	7.0
Finkelstein et al., 2003[b,9]	United States, 1998	BMI ≥30.0	None	$47.5	5.3
Finkelstein et al., 2004[b,10]	United States, 2003	BMI ≥30.0	None	$75.1	5.7
Finkelstein et al., 2009[b,11]	United States, 2008	BMI ≥30.0	None	1998: $74.20 2006: $147	1998: 6.5% 2006: 9.1%
Segal et al., 1994[12]	Australia, 1989	BMI ≥30.0	Type 2 diabetes, hypertension, gallbladder disease, colon cancer, breast cancer, coronary heart disease	$0.3 (AU $0.39)	2.0
Birmingham et al., 1999[7]	Canada, 1997	BMI ≥27.0	Type 2 diabetes, hypertension, stroke, coronary heart disease, hyperlipidemias, pulmonary embolism, gallbladder disease, postmenopausal breast cancer, endometrial cancer, colorectal cancer	$1.30 (CA $1.80)	2.4
Anis et al., 2010[6]	Canada, 2006	BMI ≥30.0 WC: Men: ≥102 Women: ≥88	Type 2 diabetes, cancer (eight conditions), cardiovascular diseases (five conditions), asthma, gallbladder disease, osteoarthritis, chronic back pain	$3.5	2.6
Zhao et al., 2008[14]	China, 2003	BMI ≥28.0	Hypertension, diabetes, coronary heart disease, strokes	$1.1 (CN ¥8.07)	1.4
Levy et al., 1995[15]	France, 1992	BMI ≥27.0	Hypertension dyslipidemias, gallbladder disease, endometrial cancer, colon cancer, breast cancer, osteoarthritis, myocardial infarction, gout, genitourinary cancer	$2.4 (FR ₣11.9)	2.0
Swinburn et al., 1997[13]	New Zealand, 1991	BMI ≥30.0	Type 2 diabetes, hypertension, hyperlipidemias, coronary heart disease, gallbladder disease, colon cancer, breast cancer	$0.08 (NZ $0.135)	2.5
Schmid et al., 2005[4]	Switzerland, 2001	BMI ≥30.0	Hypertension, hypercholesterolemia, type 2 diabetes, coronary heart disease, ischemic stroke, cancer (15 types), gall bladder diseases, osteoarthritis (hip and knee), depression, sleep apnea, thrombosis, gout, poly ovary syndrome, miscarriage	$0.86 (CH ₣1.27)	2.8

Note: $, dollars; AU, Australian; CA, Canadian; CN, Chinese; ¥, yuan; FR, French; ₣, francs; NZ, New Zealand; CH, Swiss. BMI is expressed in kilogram per square meter, and waist circumference (WC) is expressed in centimeter.

[a] Where the costs are not reported in U.S.$ only, the equivalent in U.S.$ is given in addition to the domestic currency (www.federalreserve.gov/releases; accessed April 3, 2012).

[b] Econometric study. All other studies are prevalence based.

costs than for a person of normal body weight) in 2002.[21] In other countries, additional medical costs due to obesity were generally lower compared with those in the United States, except in a percentage term for a study in Australia. Colagiuri et al.,[18] using data from the Australian diabetes, obesity, and lifestyle obesity follow-up study, estimated that, in 2005, annual mean direct medical costs among obese adults aged ≥25 years were $633 (Australian $830) (48%) higher than for persons of normal body weight. In France in 1992, by comparison, the estimated per capita additional costs among obese adults (aged ≥18 years) were $220 (French ₣ 911) (12% higher costs than for persons of normal body weight),[19] and in Osaka, Japan, in 1995, additional costs among obese adults aged 40–79 years were $688 (22% higher).[20]

The additional medical costs of obesity increased with the severity level of obesity.[22–27] For example, using the 2000 U.S. Medical Expenditure Panel Survey (MEPS), a nationally representative survey, Arterburn et al.[23] estimated that persons with class I, class II, and class III obesity had, respectively, $560 (23%), $1087 (45%), and $1975 (81%) higher per capita

annual medical costs than persons of normal body weight. Similarly, based on the pooled analysis of responses from 3 years (1996, 1998, and 2000) of the nationally representative Health and Retirement Survey of 54–69 years old Americans, the additional per capita costs estimated for persons with class I, II, and III obesity in 2002, relative to persons of normal body weight, were $974 (25% higher costs), $2043 (50% higher), and $4174 (100% higher), respectively.[22]

The additional medical costs associated with obesity also varied by gender and age. Obese women appear to experience higher additional health-care costs than obese men.[28–30] For instance, Bell et al.,[28] using the 2000–2005 MEPS data, estimated that obese women incurred $1665 (52%) and men incurred $1089 (49%) higher medical costs (in 2005 dollars) than their counterparts of normal body weight. However, the age-specific pattern of additional medical costs due to obesity is not consistent across studies.[26,30–32] For example, using data from a large health maintenance organization in northern California, Quesenberry et al.[26] estimated that, in 1994, the additional medical costs for combined outpatient and inpatient health care for persons with class II or III obesity, relative to persons of normal body weight in the same age group, were $970 (48% higher costs than for persons with normal body weight in the same age range) for those aged 20–39 years, $1752 (72% higher) for those aged 40–59 years, $3086 (38% higher) for those aged 60–74 years, and $4460 (53% higher) for those aged ≥75 years. In comparison, Hu et al.[30] estimated that, in Taiwan, the additional annual medical costs associated with obesity increased with age: $39 (15% higher costs than for persons of normal body weight in the same age range) for those aged 18–34 years, $206 (63% higher) for those aged 35–49 years, and $542 (83% higher) for those aged 50–60 years. For persons aged >60 years, however, additional costs then decreased to $277 (22% higher).

Higher medical costs for persons who are obese result from higher costs in all three types of health services: outpatient, inpatient, and prescription medications.[11,26,28,30,31,33,34] Finkelstein et al.,[11] estimated that, in 2008, compared with persons of normal body weight, those who were obese incurred $444 (27%) more in inpatient costs, $420 (46%) more in outpatient costs, and $568 (80%) more in prescription drug costs. The additional costs of both inpatient and outpatient care increased with the severity level of obesity. In another study, Quesenberry et al.[26] estimated that persons with class I obesity incurred 21% more in outpatient costs and 33% more in inpatient costs compared to persons with BMIs of 20–24.9 kg/m^2. The corresponding percentages for persons with class II or III obesity were higher, at 37% (inpatient) and 70% (outpatient), respectively.

44.3.1.3 Financial Costs to Governments

Obesity costs governments in various forms, including through subsidies for disability pensions and compensation, mobility allowances, sickness allowances, unemployment benefits, publicly financed health-care and medical care programs, and through reductions in tax revenues. Colagiuri et al.,[18] considering both BMI and waist circumference criteria to define obesity, estimated that in Australia in 2005, the government paid an additional $17.4 billion (Australian $22.8 billion) for persons who were obese. The average per capita annual payment to persons who were obese was $1349 ($3357 vs. $2008), a 67% more than for those of normal body weight. Swedish data showed that middle-aged obese men were 2.8 times as likely to receive disability pensions than men with BMIs of 20.0–24.9 kg/m^2.[35] Similarly, among women aged 30–59, those with BMIs of 28–68 kg/m^2 were 2.0–2.8 times as likely to receive disability pensions than women in the general population.[36]

In the United States in 1996–1998, Medicare, a government-financed insurance program for the elderly, and Medicaid, a government-financed insurance program for the poor, paid $1486 (37%) and $868 (39%) more per capita, respectively, for persons who were obese than for those of normal body weight.[9] In 2008, of the estimated $147 billion in additional medical costs in the United States due to obesity, 23% were financed by Medicare and 19% by Medicaid.[11] Obesity also reduced tax revenue as a consequence of negative labor market outcomes. Using data from New Mexico, Frezza et al.[37] estimated the revenue impact of obese people who underwent laparoscopic gastric bypass and laparoscopic banding during September 2003–September 2005. They estimated that the loss of state and local tax revenues collected due to obesity over this period was more than $48 million.

44.3.1.4 Financial Costs to Employers

The financial costs of obesity to employers are due to added health-care expenditures, lost productivity, and disability. Wang et al.,[38] using medical claims data from 1996 to 1997 for 178,000 General Motor employees, estimated that the additional median medical costs for employees with class I, class II, and class III obesity were, respectively, $576 (26% higher than for employees of normal body weight), $957 (43% higher), and $1528 (69% higher). In another study that used the same database but focused on 23,490 active employees, Wang et al.[33] estimated additional annual medical costs for obese employees in 2002 to be $490 (22% higher than for employees of normal body weight). Similarly, in a large firm in Chicago, employees with BMIs of ≥27.8 kg/m^2 for men and ≥27.3 kg/m^2 for women incurred $2326 ($6822 vs. $4496) (52%) higher health-care costs in 1996 compared with nonobese employees.[39] The higher costs reflect both a greater number of health claims for obese employees and a higher average cost per claim.

Obese employees miss more work days and are more likely to be disabled than nonobese employees.[24,29,39] For example, Burton et al.[39] reported that obese employees used, on average, more than twice as many sick leave days as their nonobese counterparts (8.45 vs. 3.73 days/year). Finkelstein et al.[29] reported that class II or III obese men and women employees missed 2 and 5 more days of work per year, respectively, than their counterparts of normal body weight.

Loss in productivity due to obesity from reduced performance while at work (presenteeism) is substantial.[40–42] Finkelstein et al.[41] and Ricci and Chee[42] estimated that, of the

estimated productivity loss due to both absenteeism and presenteeism, presenteeism accounted for about two-thirds: $7.8 billion (of $11.7 billion total) in 2002 and $30 billion (of $42.8 billion total) in 2006.

Two studies have estimated the total financial burden on employers—medical and nonmedical costs combined—from obesity.[29,31] The costs to U.S. businesses in 1994 due to obesity (BMI $\geq$ 25 kg/m^2) were estimated to be $12.7 billion, including $7.7 billion in health insurance expenditures, $2.4 billion in paid sick leave, $1.8 billion in life insurance, and $800 million in disability insurance.[31] Combining medical expenditures and absenteeism costs, additional per capita total costs in 2004 ranged from $462 to $2027 for male obese employees and from $1372 to $2485 for female obese employees, depending on the severity level of obesity.[29] Costs were highly skewed across the BMI categories. For example, persons with class III obesity represented 3% of the employee population, but accounted for 21% of total costs.

Obese individuals also have a higher risk of workplace illnesses and injuries, such as musculoskeletal problems, hence accounting for a higher proportion of claims for workers' compensation. Following 34,858 full-time-equivalent employees from Duke University from 1997 to 2004, Ostbye et al.[43] estimated that, compared with employees of normal body weight, obese employees had a higher average number of workers' compensation claims and medical claims and resulting financial losses increased exponentially along with a rise in the severity level of the obesity.

44.3.1.5 Financial Costs to Individuals and Their Families

The costs of obesity to individuals and their families can be measured in both monetary and nonmonetary terms. Nonmonetary costs to obese people include a shorter life expectancy[44–47] and lower health-related quality of life.[48] Based on data from the Framingham Heart Study with follow-up from 1948 to 1990, Peeters et al.[46] estimated that a 40-year-old nonsmoking male or female would lose, on average, 5.8 and 7.1 years of life, respectively, because of obesity. Another study in the United States that estimated the mean number of years of life lost for nonsmoking persons with class II/III obesity at ages 18, 40, and 60 ranged from 3 to 9 years, depending on age at baseline, sex, and race/ethnicity.[44]

Compared to persons of normal body weight, obese persons tend to have a lower quality of life and fewer quality-adjusted life years. Using health-utility scores, in which "1" represents full health and "0" represents death, as a quality-of-life measure a one-unit increase in BMI was associated with an average decrease of 0.0024 in health-utility score for men and 0.0034 for women in an Australian population.[49] Using 2003 and 2006 Health Survey of England data, Stafford et al.[50] showed that obesity contributed a mean loss of 0.045 in health-utility score. A similar health-utility loss was also reported in the United States, based on 1993–2008 data from the Behavioral Risk Factor Surveillance System (BRFSS).[51] Using the same 1993–2008 BRFSS data, Jia and Lubetkin[52] estimated a 127% increase in the quality-of-life lost accounted for by obesity, as measured by health-utilty scores, from 0.020 in 1993 to 0.046 in 2008. This loss in health-related quality-of-life scores increased with the severity of obesity. For example, Jia and Lubetkin[53] estimated that, compared to persons of normal body weight, persons with class I and class II/III obesity had 0.031 and 0.075 lower health-utility scores, respectively. A decrease due to obesity in quality-adjusted life expectancy (QALE), a measure of life years with full health, was estimated to be an average of 5.5 years among men in Australia.[49] The loss in QALE was estimated to be greater for women than men: 7.2 years to 4.4 years in the United States,[54] and 6 years to 3 years in Denmark.[55]

The monetary costs to individuals and their families attributable to obesity include higher out-of-pocket medical costs, extra expenses for weight management, and loss in income. Finkelstein et al.[9] estimated that, of the total medical costs ($47.5 billion) attributed to obesity in 1998, 14.5% was from out-of-pocket expenses borne by individuals. The additional average per capita out-of-pocket costs incurred per year by obese individuals were $125 (26.1% higher expenses than for persons of normal body weight). Blanck et al.[56] estimated that 17.2 million Americans used nonprescription weight loss products during 1996–1998. The expense that consumers incurred on weight loss products and programs in 2000 was estimated to be $34.7 billion.[57]

Obese persons are more likely to be unemployed or work in low paying jobs and are likely to earn less than persons of normal body weight. Such negative impact is more prominent among women than men.[58–60] As one example, using data from a 2000–2001 national survey from Finland, Johansson et al.[58] estimated that obese women in the labor force had a 10% lower rate and obese men had a 4% lower rate of employment compared with their counterparts of normal body weight. Sarlio-Lahteenkorva and Lahelma[60] reported that obese women were 2.5 times as likely than women of normal body weight to experience long-term unemployment. Obese women were also more likely to be excluded from high-paying managerial, professional, and technical occupations and to be relegated to relatively low-paying occupations.[59]

Women and men who are obese, on average, earn less than their counterparts of normal body weight. Bhattacharya and Bundorf[61] estimated that, in the United States, obese women earned $1.66/hour less and men $1.21/hour less than their nonobese counterparts. For those obese women who worked for firms in which they received employer-sponsored health insurance, their lost earnings were even larger, $2.64/hour. The negative impact of obesity on earnings was higher for women than for men: obese women earned 6.1% less than women of normal body weight, and obese men earned 3.4% less than men of normal body weight.[62]

44.3.2 Incidence-Based Cost Estimates

A few incidence-based cost estimates were available,[47,63–69] and all of them estimated direct medical costs at the individual level. Whether an obese person incurs higher lifetime medical costs than a person of normal body weight is unclear.

Persons who are obese tend to have higher average "annual" medical costs due to the costs of treatments for obesity and its related diseases, but perhaps accrue lower "lifetime" medical costs due to shortened life expectancy.

All incidence-based studies using U.S. data reported higher average lifetime medical costs for an obese individual than for an individual of normal body weight.[47,63–68] Allison et al.[63] estimated that 4.3% of total lifetime direct medical costs among U.S. adults aged 20 to 85 years was attributable to obesity. Thompson et al.[67] estimated that, in 1996, relative to those for persons with a BMI of 22.5 kg/m^2, the average additional lifetime costs of treating five obesity-related diseases (hypertension, hypercholesterolemia, type 2 diabetes, coronary heart disease, and stroke) ranged from $8,600 to $11,200 for persons with a BMI of 32.5 kg/m^2 and ranged from $14,500 to $17,100 for persons with a BMI of 37.5 kg/m^2, depending on age at onset and sex.

Using data from incidence-based studies, lifetime medical costs attributable to obesity also varied by age group. The highest additional lifetime medical costs were for the 45–54 age group among men and the 55–64 age group among women.[67] Cai et al.,[64] based on data from the follow-up of an age 35–55 cohort from 1971 through 2000, estimated that the additional lifetime costs to Medicare for an obese person aged 45 years in 1971, who survived to age 65, was $45,634 (i.e., 39% higher costs) than for a man of normal body weight in the same age cohort. Another study in the United States estimated that, for a person aged 70 years who was obese, the lifetime medical costs were $39,740 or 20.8% higher than for a person of the same age with a BMI of 20–24.9 kg/m^2.[66]

Also, using data from incidence-based studies, the lifetime additional medical costs for obese individuals appear to vary by gender, but the patterns of variation are not clear. Yang and Hall[47] estimated that the lifetime medical costs of treating comorbidities attributable to obesity (cardiovascular and cerebrovascular diseases, respiratory system diseases, cancer [excluding skin cancer], and diabetes) at age 65 years among obese women were $32,224 (17% higher) and, among obese men, $21,227 (12% higher) compared with their counterparts of normal body weight in the United States in 2001. Similarly, Cai et al.[64] estimated that the additional medical costs of obesity were $764 ($46,693 vs. $45,929), slightly higher for woman than men compared with their counterparts of normal body weight, but the cost ratio was greater for men than for women (1.47 vs. 1.37). Furthermore, two studies showed that the pattern of additional costs due to obesity by gender varied also by race/ethnicity, age group, and severity of obesity.[65,68]

Only one study reported lower lifetime medical costs for obese individuals compared to individuals of normal body weight. Van Baal et al.[69] followed a simulated hypothetical cohort from age 20 years until death in the Netherlands and found that the lifetime costs for persons in the obese cohort were lower than those of normal body weight: $283,025 vs. $318,120 (€250,000 vs. €281,000). The longer life expectancy among the cohort of persons of normal body weight (64.4 vs. 59.9 years) contributed to the higher lifetime medical costs.

44.4 CONCLUSIONS AND FUTURE DIRECTIONS

The method most commonly used to estimate the economic costs of obesity, both prevalence based and incidence based, has been the COI method. Both the epidemiological fraction approach and econometric approach have been used to estimate the direct medical costs of obesity. Earlier studies tended to use the epidemiological fraction approach, while more recent studies, especially in the United States, have tended to use the econometric approach.

Several conclusions can be drawn from previous studies:

- First, the economic burden imposed by obesity was substantial in all countries for which the costs were studied. The estimated costs were much higher in the United States than other countries—up to 9.1% of total health-care expenditures in the United States, compared to up to 3% in other countries. At the individual level, medical costs associated with obesity were 37% to 42% higher than for persons of normal body weight in the United States and 12% to 48% higher in other countries. Considering the increase in prevalence of obesity, the future economic burden of obesity is expected to increase. The large and continually increasing economic burden to society implies that obesity should be a public health priority, especially in developed countries. More resources need to be invested to find effective measures for preventing and treating obesity and thus to reduce the economic burden of obesity.
- Second, the financial burden to the public sector due to obesity, especially on government-financed health-care programs, is substantial. For instance, in 1996–1998, the Medicare and Medicaid programs in the United States made about 40% more per capita in medical care payments for persons who were obese than for persons of normal body weight.[9] The government also receives less tax revenue because of obesity. The extra economic burden of obesity on the government might be used to justify measures to reduce obesity.
- Third, compared to individuals of normal body weight, an obese individual not only pays more out-of-pocket costs for medical care and loses more income but also experiences a lower life expectancy and lower quality of life. Obesity could lead to a loss of as many as 7 years of life with full health in the United States.[54] Both the general public and individuals who are obese or at risk of being obese would benefit from being educated about this economic and health burden and from getting motivated to take personal actions to move toward and reach a normal body weight.
- Finally, the study showed that employers also faced a larger financial burden because of higher medical costs and employee benefits paid and because of

loss in employee productivity in the workplace. The estimated per capita annual costs due to obesity for employers were large—ranging from $462 to $2017 for an obese male employee and from $1372 to $2485 for an obese female employee.[29] Employers, therefore, might examine the feasibility of offering worksite health programs, financial incentives, or both to promote healthy behaviors among employees.

Several issues need to be addressed in future research. First, numbers and types of obesity-related diseases included in assessing the economic costs of obesity varied widely across the studies. Excluding costs from some diseases for which obesity is a risk factor would lead to an underestimation of the costs due to obesity, including costs from diseases in which obesity plays an insignificant role would lead to an overestimation of obesity costs. The variation in the number and types of diseases included also makes comparisons across studies difficult. Thompson and Wolf[70] reported that there was strong evidence for and consensus on only six medical conditions (coronary heart disease, type 2 diabetes, hypertension, gallbladder disease, endometrial cancer, and osteoarthritis of the knee) for which obesity is a risk factor. Knowledge about obesity-associated diseases is evolving with our understanding of obesity. The number and type of diseases included in future studies on the economic costs of obesity need to be standardized, based on the best available scientific evidence at the time, to increase comparability across studies. Second, few previous studies included all components of the economic costs associated with obesity. None of the previous economic cost studies considered all cost components (absenteeism, presenteeism, long-term disability, and premature mortality) associated with loss in productivity in assessing the indirect cost of obesity. The costs incurred by caregivers have not been included in any of the previous studies. This lack of complete data has led to studies underestimating the "true" economic burden of obesity. Studies are needed to fill in this information gap.

Third, while BMI was the criteria most commonly used to define obesity, the criteria used to define obesity by BMI ranged differed by study and country. A few studies also defined obesity based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes and waist circumference. This inconsistency again may have contributed to differences in cost estimates and has made comparisons across studies difficult. Criteria to define and classify obesity need to be standardized in future cost studies. Fourth, studies on the costs of obesity mainly concentrated on the direct medical cost component. While a handful of studies estimated the economic costs of obesity to society, such estimates using recent data are lacking. Similarly, studies on the indirect costs of obesity, including from premature mortality, lost productivity, and disability using recent data are also limited. More studies are needed to estimate the economic costs of obesity to society in the United States and other counties. Fifth, most economic studies focused on deriving prevalence-based estimates of the costs of obesity (i.e., based on the economic burden from the number of obesity cases at a given time). Only a few studies were designed to derive an incidence-based cost estimate (i.e., based on lifetime costs of new obesity cases). While prevalence estimates are useful for documenting the economic burden of obesity, such estimates are less useful for evaluating intervention options related to preventing and controlling obesity. Current incidence-based cost studies vary in terms of age cohorts and remaining life expectancy. In addition, the current incidence-based studies may well underestimate the "true" economic burden of obesity.[70] Incidence-based estimates using more recent data and focusing on a range of age cohorts are needed.

In summary, besides its negative health consequences, obesity also presents contemporary society with a large and serious economic problem. Obesity imposes large and growing economic costs on many sectors of society. A substantial amount of economic costs to health-care systems, employers, governments, individuals, and the nation could be avoided if we succeeded in lowering the prevalence of obesity. Unfortunately, current trends in the incidence and prevalence and in the severity of obesity across demographic groups are not encouraging.[17,71,72] A recent study projected that, by 2030, the United States and United Kingdom would experience, respectively, 65 million and 11 million additional obese adults and $48–60 billion and £1.9–2.0 billion in additional medical costs to treat the associated diseases.[73] This continuing increase in the economic burden of obesity, in the home, in the workplace, and in society as a whole calls for more concerted efforts to identify effective interventions to prevent and control obesity.

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Part V

Consequences of Obesity

45 Obesity and Mortality Rates

Gary Whitlock and Rachel R. Huxley

CONTENTS

45.1 INTRODUCTION

Adiposity levels have risen in many countries during recent decades,[1–3] and these increases have had estimable effects[4–7] on particular national mortality rates. The aim of this chapter is to describe the likely effects of recent adiposity levels on cause-specific mortality rates in five selected countries: two in North America (United States and Canada), two in Europe (England and Wales—which are actually two countries but considered here as one—and France), and one in Asia (Japan). The countries were selected because of their large populations (collectively about 600 million) and because of the ready availability of reliable data for them.[8,9] There are about 30 other countries to which this approach could be applied equally well, although that would be beyond the scope of a single chapter. For most of the world's 160 or so other countries, the underlying information necessary for such estimates has simply never been collected.[9–11]

The following calculations are mostly for mortality in the age range of 40–79 years, since death at a later age is, for those who reach it, inevitable, but many deaths in this range are not. Most of the avoidable person-years of life lost because of obesity are in this age range: each avertable death after the age of 80 causes relatively few years of life to be lost, and obesity causes few deaths before the age of 40.

The calculations in this chapter all relate to body mass index (BMI)[12–14] because there is a much greater volume of published information on BMI than on any other measure of adiposity, although some other adiposity measures give better information about body composition and distribution of body fat.[15–18] Although all five selected countries have applicable data on relative risks for BMI in relation to cause-specific mortality, on national BMI levels, and on national cause-specific mortality rates, the following calculations are merely approximate and are intended to be indicative of broad patterns only. Caution is needed because of intrinsic limitations of the methodology used (see footnotes to Tables 45.1 and 45.2), because no allowance is made for the play of chance (e.g., in the estimation of relative risks) and because the underlying relative risks were calculated for populations in which most obese individuals had reached this state not by childhood or adolescence but rather by early or late middle age (which may underestimate the effects of lifelong obesity[4,27,28]). In addition, this chapter makes no attempt to quantify the enormous burden of nonfatal illness and disability caused by obesity;[29] the chapter is concerned solely with estimated effects on mortality rates.

The association of a risk factor with mortality blends (1) the underlying association with disease incidence (i.e., first occurrence among people who did not previously have the disease) and (2) the association with subsequent prognosis (i.e., survival among those with established disease). For a few diseases, a higher BMI is associated with higher disease incidence but, surprisingly, a better prognosis.[30–33] However, prognostic follow-up studies can be seriously affected by epidemiological biases (e.g., reverse causation[4] and the index-event bias[34]), and there is little certainty that associations in such studies reflect biological reality. The etiological relevance of obesity to cause-specific mortality is therefore considered here only from the findings of large prospective epidemiological studies in which all or most people were generally healthy at the start of follow-up. The likely impact of obesity on mortality rates is assessed in this chapter in four sections (Sections 45.2 through 45.5): vascular, neoplastic, other cause-specific, and all-cause mortality rates.

Gary Whitlock died of a rare type of cancer, parotid carcinoma, on October 18, 2013 in Oxford. His exhaustive, informative, and uniquely entertaining work detailing trends in national mortality rates can be found at www.mortality-trends.org. The website will continue until March 2022—when, like its maker, it will expire.

45.2 VASCULAR MORTALITY RATES

The first and most important category of diseases whose mortality rates can be affected by obesity is vascular disease, which encompasses coronary heart disease (CHD), stroke, and various other diseases of blood vessels. The preeminent relevance of vascular disease to obesity arises from the high background mortality rate for CHD and stroke in most middle-aged and elderly populations and from the particularly strong associations that these two diseases have with obesity.

45.2.1 Coronary Heart Disease

A substantial body of evidence from prospective studies of generally healthy people shows that higher BMI is associated with higher subsequent CHD incidence[35–37] and mortality.[4,5,35,36] Moreover, this association continues down even to low levels of BMI: in Western populations[4] there is no clear BMI threshold below which greater leanness is not still associated with lower CHD mortality, and in Asian populations[36–38] the positive association continues down at least to a BMI of 20 kg/m^2. In the Prospective Studies Collaboration,[4] which shared data on nearly 1 million people from about 60, mostly Western, studies, higher BMI was associated with higher CHD mortality throughout the full BMI range, and above 25 kg/m^2 each 10 kg/m^2 higher BMI was associated with about a doubling in CHD mortality (slightly more than a doubling in middle age, and slightly less in old age). The strength of this association (i.e., the relative increase in risk per unit of BMI or, equivalently, the steepness of a plot of logarithm of risk against BMI) appears to be broadly similar in women and men,[4] and there is little evidence that it differs importantly between Western[4,5] and East Asian[36,39] populations.

Taking this approximate doubling in CHD mortality for each 10 kg/m^2 higher BMI, it can be estimated that in 2007 the CHD mortality rates for U.S. men aged 40–79 years would have been about 170 per 100,000 men who were "lean" (a term denoting, in this chapter only, a BMI of ~22.5 kg/m^2) and about 330 per 100,000 men who were "moderately obese" (a BMI of ~32.5 kg/m^2): the actual CHD mortality rate across all BMI levels at this age was 259 per 100,000 men (Table 45.1). For U.S. women, the CHD mortality rate at

TABLE 45.1
Estimated CHD Mortality at Different BMI Levels in Selected Countries

		At Ages 40–79 Years in 2007[a]										
		Mean BMI[b] (kg/m^2)	Prevalence (%) of BMI (kg/m^2) Range[b]		CHD Mortality Rate (Annual Deaths per 100,000), Overall[c] and at Particular BMI (kg/m^2) Levels[d]				CHD Deaths, Overall[e] and Number Attributable to Particular BMI (kg/m^2) Ranges[f]			
			25–29	≥30	Overall	22.5	27.5	32.5	Overall	≥25	25–29	≥30
Male	United States	28.7	42	36	259	170	240	330	101,436	26,100	7,200	18,900
	Canada	28.4	46	31	277	190	260	360	12,012	2,900	900	2,000
	England & Wales	28.0	47	28	306	210	300	410	25,831	5,900	2,000	3,900
	France	26.1	41	16	121	100	130	180	11,714	1,900	800	1,100
	Japan	23.8	29	3	98	90	130	170	25,148	1,700	1,200	500
Female	United States	28.7	32	36	122	80	110	160	52,888	12,700	2,800	9,900
	Canada	27.8	34	29	113	80	110	150	5,189	1,100	300	800
	England & Wales	27.5	36	29	121	90	120	170	10,995	2,400	700	1,700
	France	25.1	24	18	35	30	40	60	3,852	600	200	400
	Japan	22.9	20	3	38	40	50	70	10,675	600	400	200

[a] BMI and mortality data are estimates or actual data for 2007, except that Canada's mortality information is for 2004 (the CHD mortality rate in Canada could, based on trends in 2001–2004, have been nearly 20% lower in 2007 than in 2004 for both sexes, in which case there would also have been nearly 20% fewer attributable CHD deaths).

[b] Sources of BMI data: the 2007–2008[19] and 2009–2010[20] National Nutrition Health and Examination surveys (NHANESs) for the United States, the 2007 Health Survey for England,[2] the 2007–2009 Canadian Health Measures Survey,[21] the 2006–2007 ENNS (French Nutrition and Health Survey),[22] and the 2007 National Health and Nutrition Survey in Japan.[23]

[c] Overall actual CHD mortality rate calculated directly from World Health Organization mortality data[8] and United Nations Population Division data[24]: rate standardized for age by taking the mean of the age-specific rates for each 5-year age band from 40–44 to 75–79 years.[25]

[d] CHD mortality rate at each BMI level estimated by assuming that the mortality rate at the population's mean BMI equals that population's actual overall mortality rate and that each 5 kg/m^2 higher BMI within the range of 22.5–32.5 kg/m^2 is associated with 39% higher CHD mortality.[4] Rate rounded to the nearest 10 deaths per 100,000 person-years.

[e] Overall actual number of CHD deaths as recorded in World Health Organization mortality data (see also footnotes a and c).

[f] Number of CHD deaths attributable to BMI of 25–29 kg/m^2 calculated as $p(RR - 1)/(p[RR - 1] + 1)$, where p is the sex-specific proportion of the population in this BMI range and RR is the CHD mortality rate at 27.5 kg/m^2 relative to that at 25 kg/m^2 (assumed here[4] to be 1.18). Number attributable to BMI ≥ 30 kg/m^2 calculated in the same way, but with p as the sex-specific prevalence of BMI ≥ 30 kg/m^2 and RR as the relative CHD mortality at a BMI of 32.5 kg/m^2 versus 25 kg/m^2 (assumed[4] to be 1.64). Number of deaths attributable to BMI ≥ 25 kg/m^2 calculated as the sum of the preceding two attributable numbers. All estimates of attributable deaths are rounded to the nearest 100 deaths but in reality should be considered even more approximate than that.[26]

ages 40–79 years would have been about half as high as for men at each BMI level: 80 per 100,000 lean women, and 160 per 100,000 moderately obese women. The estimated CHD mortality rates at different BMI levels for all five countries are shown in Table 45.1.

In such prospective studies, the association between BMI and CHD mortality can be accounted for largely or wholly by the associations of BMI with usual blood pressure levels, usual blood cholesterol concentrations, and diabetes.[4,5] Furthermore, numerous randomized trials of weight-loss interventions have demonstrated causal associations of adiposity with blood pressure, cholesterol fractions, and measures of insulin resistance,[40] which, in turn, are causally related to CHD incidence.[41–45] These observations, reinforced by copious other evidence,[46,47] firmly establish that greater adiposity—of which higher BMI is an indicator—is causally related to CHD mortality.

However, although excess adiposity is a real and important cause of CHD it is not in its own right an overwhelmingly powerful cause, and its effects are much less than the sum of the effects of all other causes. At least three lines of evidence show that this must be the case: first, in most Western countries, CHD mortality in middle age and old age fell steeply during the 1980s, 1990s, and 2000s even as average BMI levels rose. In England and Wales, for instance, CHD mortality at ages 40–79 years fell by 60% for men and 64% for women in the brief 14-year period between 1993 and 2007 (from 757 per 100,000 males to 306, and from 332 per 100,000 females to 121) (Table 45.1),[8,48] whereas the average BMI in this age range rose over the same period by about 1.4 kg/m^2 in males and 1.0 kg/m^2 in females.[2]

Second, the age-specific CHD mortality rates for some obese groups are much lower than those for some "normal" BMI groups. In Table 45.1, for example, estimated CHD mortality in each country was lower for moderately obese women than for lean men; in addition, it was lower among moderately obese Japanese and French men (170–180 per 100,000) than among lean men in Canada or England and Wales (190–210 per 100,000). Factors other than obesity must account for these differences.

Third, although a doubling in CHD mortality for each 10 kg/m^2 higher BMI is a considerable causal effect, it could be, and demonstrably has been,[49,50] more than offset by reductions in other potent risk factors[2,51–55] and by the increasingly widespread use of treatments that greatly reduce CHD mortality.[41,42,56] For instance, heavy smoking is also associated with a doubling in CHD mortality[57,58]; but in recent decades, the prevalence of smoking has declined enormously in many countries.[2,54,55] Furthermore, even though increased adipose tissue raises blood pressure and (up to a BMI of about 30 kg/m^2) low-density lipoprotein (LDL)-cholesterol levels,[4,40] the average adult blood pressure and LDL-cholesterol levels have been falling in many Western countries[51,59] even as average BMI levels have been rising.[1–3,60] The combined effects of other major determinants of blood pressure and lipid levels—such as medication and modification of lifestyle—have outweighed[49,50] the effects of increased obesity on these strong intermediate factors.

Although age-specific CHD mortality rates have been falling in many countries, adiposity has generally been increasing and may consequently be accounting for an increasing proportion of CHD deaths. For the United States, about one-quarter of male and female CHD deaths in 2007 was attributable to a BMI in excess of 25 kg/m^2; for Canada and for England and Wales, just under one-quarter; for France, nearly one-sixth; and for Japan, a little more than one-twentieth (Table 45.1). For the United States, these estimates correspond to about 26,000 male and 13,000 female CHD deaths at ages 40–79 years in 2007, that is, to at least 100 avoidable CHD deaths attributable to excess adiposity each day. About three-quarters of these deaths occurred among people with a BMI of 30 kg/m^2 or more and the remaining quarter among people with a BMI of 25–29 kg/m^2. (As there is no known lower threshold in the relationship between BMI and CHD, at least in Western populations,[4] some CHD deaths are attributable to excess adiposity even below a BMI of 25 kg/m^2, but no attempt is made here to estimate these numbers.) In Japan, by contrast, the total number of attributable CHD deaths across both sexes was just 2000–3000, that is, some 95% less than the deaths in the United States, despite Japan having precisely 50% as many people aged 40–79 years in 2007. This low number of attributable CHD deaths in Japan stems partly from the country's low background CHD mortality rate and partly from its population being relatively lean (Table 45.1). Also in contrast with the United States, most CHD deaths attributable to raised BMI in Japan occurred among those with a BMI of just 25–29 kg/m^2; only half as many occurred among people with a BMI of 30 kg/m^2 or more.

45.2.2 Stroke

Stroke is probably a constellation of underlying specific diseases, but it usually manifests as one of just two main pathological subtypes: ischemic stroke and hemorrhagic stroke. Ischemic stroke resembles CHD pathogenically and epidemiologically[14,61] and is associated positively with BMI across a wide range of BMI levels in both East Asian[36,62,63] and Western[64,65] populations (the evidence in the Prospective Studies Collaboration,[4] however, was more equivocal). Hemorrhagic stroke may have a somewhat different pathogenesis, and the evidence for its association with BMI in lean and moderately overweight people is only weak;[14,63–65] however, there is some evidence that a BMI more than 30 kg/m^2 is associated with increased risk.[36,62]

Reliable national mortality rates for the main pathological subtypes are not available, but for many countries good data on total stroke mortality have been collected for decades.[8] In the Prospective Studies Collaboration, there was little evidence that BMI was associated with total stroke mortality in the range of 15–25 kg/m^2 (despite lower BMI being associated with lower blood pressure down to at least 17 kg/m^2); but above

that range, each 10 kg/m^2 higher BMI was, as for CHD, associated with about a doubling in the mortality rate (somewhat more than a doubling in middle age and somewhat less in old age).[4] As with CHD, and for generally similar reasons,[40–42,66] this positive association with stroke above 25 kg/m^2 can be considered largely causal.

In most parts of the world CHD is a more common cause of premature death than stroke, but in most of East Asia the opposite is true. For example, in 2007 the overall stroke mortality rate at ages 40–79 years for Japanese males (Table 45.2) was about one-third higher than the corresponding CHD rate (Table 45.1) and for Japanese females the stroke rate was nearly two-thirds higher. (In North America, by contrast, the mortality rates at this age were two to four times higher for CHD than for stroke.) As a consequence, in Japan nearly 1000 more stroke deaths than CHD deaths were attributable to a BMI above 25 kg/m^2. In a similar vein, recently published evidence for China showed that for every one CHD death in this country attributable to raised BMI there are four such stroke deaths.[42] However, for all the five countries in Table 45.2 (i.e., not just Japan), the numbers of stroke deaths attributable to a BMI above 25 kg/m^2 are considerable; in the United States, for example, the estimated number of such deaths was 13,000 in 2007 (compared with 39,000 CHD deaths). Moreover, nearly half of these 13,000 deaths were among females (whereas only one-third of the attributable CHD deaths were) and, indeed, the estimated stroke mortality rate for moderately obese women in the United States (80 per 100,000) was almost as high as that for moderately obese men (90 per 100,000) (Table 45.2).

As with CHD, obesity is a major, but not an overwhelmingly important, cause of stroke, for stroke mortality rates have been in uninterrupted decline since at least the 1960s in all five countries (e.g., the rates for both sexes at ages 40–79 years in the United States[8,48] declined by about 80% between 1960 and 2007, from 347 per 100,000 men to 73 and from 278 per 100,000 women to 59) even as the mean BMI in early and late middle age rose in these populations (e.g., by 3.0 to 3.5 kg/m^2 between 1960 and 2007 in

TABLE 45.2
Estimated Stroke Mortality at Different BMI Levels in Selected Countries

			At Ages 40–79 Years in 2007[a]									
		Mean BMI[b] (kg/m^2)	Prevalence (%) of BMI (kg/m^2) Range[b]		Stroke Mortality Rate (Annual Deaths per 100,000), Overall[c] and at Particular BMI (kg/m^2) Levels[d]				Stroke Deaths, Overall[e] and Number Attributable to Particular BMI (kg/m^2) Ranges[f]			
			25–29	≥30	Overall	22.5	27.5	32.5	Overall	≥25	25–29	≥30
Male	United States	28.7	42	36	73	50	70	90	27,462	7,000	1,900	5,100
	Canada	28.4	46	31	71	50	70	90	2,767	700	200	500
	England & Wales	28.0	47	28	93	60	90	130	7,274	1,700	600	1,100
	France	26.1	41	16	67	50	70	100	6,127	1,000	400	600
	Japan	23.8	29	3	130	120	170	230	32,235	2,200	1,600	600
Female	United States	28.7	32	36	59	40	50	80	25,805	6,200	1,400	4,800
	Canada	27.8	34	29	51	40	50	70	2,341	500	100	400
	England & Wales	27.5	36	29	75	50	80	100	6,797	1,500	400	1,100
	France	25.1	24	18	38	30	40	60	4,293	600	200	400
	Japan	22.9	20	3	62	60	80	120	17,709	900	600	300

[a] BMI and mortality data are estimates or actual data for 2007, except that Canada's mortality information is for 2004 (the stroke mortality rate in Canada could, based on trends in 2001–2004, have been about 15% lower in 2007 than in 2004 for both sexes, in which case there would also have been about 15% fewer attributable stroke deaths).

[b] Sources of BMI data: the 2007–2008[19] and 2009–2010[20] NHANESs for the United States, the 2007 Health Survey for England,[2] the 2007–2009 Canadian Health Measures Survey,[21] the 2006–2007 ENNS,[22] and the 2007 National Health and Nutrition Survey in Japan.[23]

[c] Overall actual stroke mortality rate calculated directly from World Health Organization mortality data[8] and United Nations Population Division data[24]: rate standardized for age by taking the mean of the age-specific rates for each 5-year age band from 40–44 to 75–79 years.[25]

[d] Stroke mortality rate at each BMI level estimated by assuming that the mortality rate at the population's mean BMI equals that population's actual overall mortality rate and that each 5 kg/m^2 higher BMI within the range of 22.5–32.5 kg/m^2 is associated with 39% higher stroke mortality.[4] Rate rounded to the nearest 10 deaths per 100,000 person-years.

[e] Overall actual number of stroke deaths as recorded in World Health Organization mortality data (see also footnotes a and c).

[f] Number of stroke deaths attributable to a BMI of 25–29 kg/m^2 calculated as $p(RR - 1)/(p[RR - 1] + 1)$, where p is the sex-specific proportion of the population in this BMI range and RR is the stroke mortality rate at 27.5 kg/m^2 relative to that at 25 kg/m^2 (assumed here[4] to be 1.18). Number attributable to BMI ≥ 30 kg/m^2 calculated in the same way, but with p as the sex-specific prevalence of BMI ≥ 30 kg/m^2 and RR as the relative stroke mortality at BMI of 32.5 kg/m^2 versus 25 kg/m^2 (assumed[4] to be 1.64). Number of deaths attributable to BMI ≥ 25 kg/m^2 calculated as the sum of the preceding two attributable numbers. All estimates of attributable deaths are rounded to the nearest 100 deaths but in reality should be considered even more approximate than that.[26]

the United States[1,20]). Moreover, whatever accounts for the high background stroke mortality rate in Japan probably also accounts for the estimated stroke mortality rate in lean Japanese men (120 per 100,000) being substantially higher than that for moderately obese men in the United States and Canada (90 per 100,000) (Table 45.2). Although obesity affects stroke mortality, it is just one among several important causal factors.

45.2.3 Other Vascular Diseases

Aside from CHD and stroke, there are several less common vascular causes of death that are also associated positively with BMI, including aortic aneurysm,[4] hypertensive diseases,[4] atrial fibrillation,[67] and heart failure.[4,68] In the Prospective Studies Collaboration, the relative increase in mortality for the aggregate of all these other vascular diseases was similar to that for CHD and stroke, and the absolute death rates (which would mainly reflect the mortality patterns prevailing at the time in Western countries[48]) were comparable to those for stroke.[4] It could be cautiously inferred, therefore, that the number of other vascular deaths attributable to raised BMI in Western countries might generally be similar to that seen in these countries for stroke.

45.3 NEOPLASTIC MORTALITY RATES

The second large category of diseases whose mortality rates can be affected by obesity is cancer.[4,6,7,69,70] Indeed, in 2007 the number of deaths from all cancers combined (e.g., at ages 40–79 years, 390,000 in the United States and 220,000 in Japan) was larger than the sum of all vascular deaths (350,000 in the United States and 120,000 in Japan). This was not the case in the 1990s and earlier, however, when vascular mortality greatly predominated; since at least the 1970s, though, vascular mortality declined spectacularly in all the selected countries, whereas neoplastic mortality experienced more moderate declines (Figure 45.1).[48] The number of neoplastic deaths attributable to raised BMI is nonetheless much smaller than the number of attributable vascular deaths. The principal reason for this is that the vascular category is dominated by just two very common causes of death that are both strongly related to obesity (CHD and stroke), whereas the neoplastic category consists largely of a dozen or so quite common types of cancer, some of which appear to be unrelated to obesity (e.g., lung and stomach) and only a few of which appear to be related to obesity at least as strongly as these vascular diseases are (e.g., endometrium and liver). The net result is that whereas a 10 kg/m^2 higher BMI among people with a BMI of at least 25 kg/m^2 was associated with

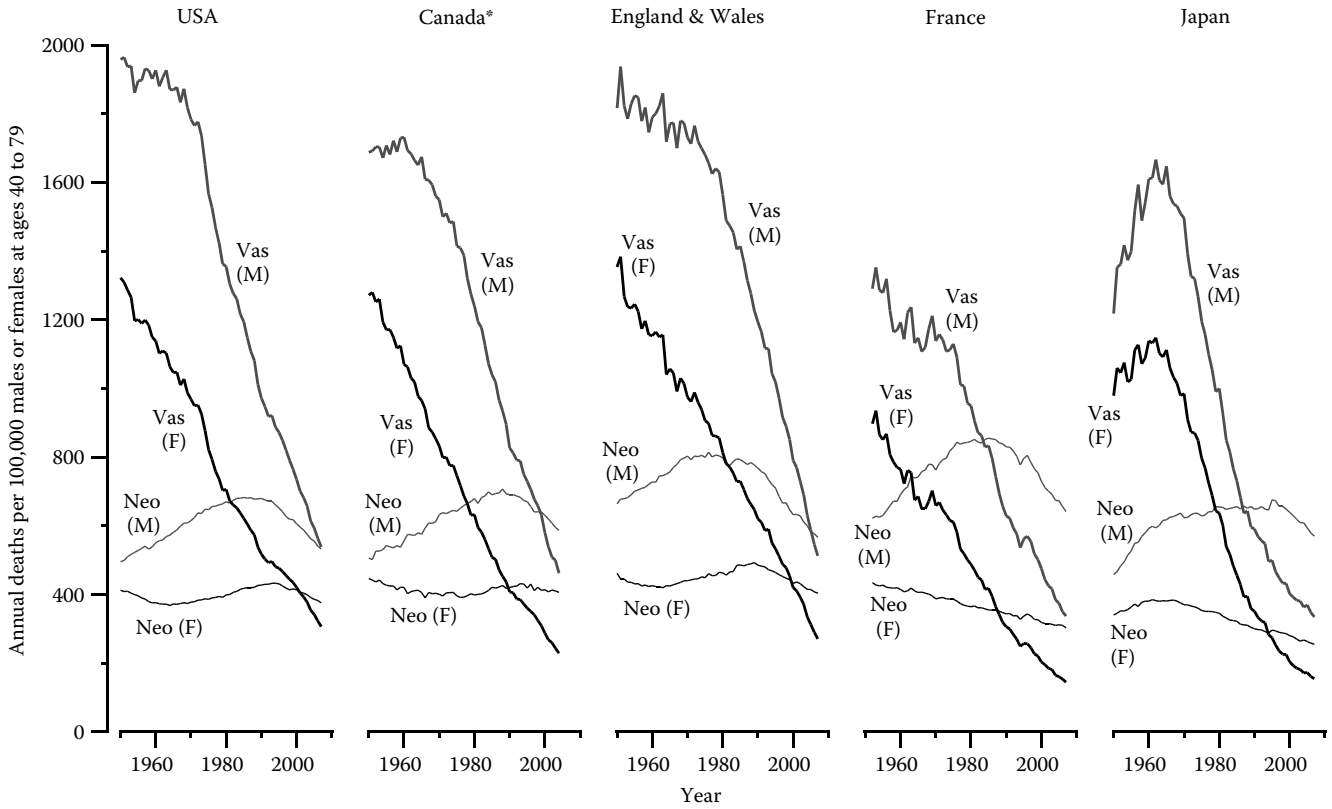

FIGURE 45.1 Vascular and neoplastic mortality rates at ages 40–79 years between 1950 and 2007: mortality rates are standardized for age by taking the mean of the age-specific rates for each 5-year age group from 40–44 to 75–79 years. Mortality data were obtained from the World Health Organization,[8] and population data were obtained from the United Nations Population Division.[24] Vas = vascular mortality, defined as I00–I99 in the tenth edition of the International Classification of Diseases (ICD-10) and as corresponding codes in earlier ICDs; Neo = neoplastic mortality, defined as C00–D48.9 in ICD-10 and as corresponding earlier codes; M = male; F = female. All rates are plotted against the same vertical axis. *Mortality data for Canada available only up to 2004.

a doubling in vascular mortality in the Prospective Studies Collaboration, it was, in each sex, associated with an increase in overall neoplastic mortality of at most a fifth.[4] Assuming this relative increase in mortality is generalizable to the five selected countries, fewer than 1 in 10 neoplastic deaths at ages 40–79 years during 2007 were attributable to a BMI over 25 kg/m^2: about 7%–8% for the United States, 7% for England and Wales, 6%–7% for Canada, 4%–5% for France, and just 2% for Japan.

Although a modest relative increase, one-fifth greater neoplastic mortality for a 10 kg/m^2 higher BMI nonetheless translates into substantial absolute excess mortality rates since the total background neoplastic mortality rates are so high. This relative risk implies, for example, that the overall neoplastic mortality rates in 2007 in the United States were about 470 per 100,000 lean men but 570 per 100,000 moderately obese men and, similarly, about 330 per 100,000 lean women but 400 per 100,000 moderately obese women. Although these excess neoplastic mortality rates associated with obesity are considerable, they are still much less than the excess mortality rates seen for vascular disease (Figure 45.2). Altogether, there would, by this calculation, have been about 29,000 neoplastic deaths in the United States during 2007 attributable to a BMI of 25 kg/m^2 or more compared with 39,000 for CHD, 13,000 for stroke, and possibly another 13,000 for other vascular diseases, making a possible total for all vascular diseases of about 65,000 deaths.

The evidence that the association between obesity and neoplastic mortality is causal is less complete than it is for CHD or stroke because the proposed causal mechanisms are more complex,[71] are less easily demonstrable by randomized trials,[40] and may well vary by type of cancer.[14,70,71] The evidence for causation is now probably strongest for endometrial cancer, postmenopausal breast cancer, colorectal cancer (in men, at least), kidney cancer, liver cancer, and adenocarcinoma of the esophagus.[4,6,7,70] There is also suggestive evidence of a relationship with obesity for cancers of the pancreas[72,73] and prostate,[73] as well as for cancers at a few other[14,70,73] sites.

Endometrial cancer mortality is particularly strongly associated with BMI: across the full BMI spectrum, each 10 kg/m^2 higher BMI has been associated with a doubling or more in this mortality.[4,6,7] However, endometrial cancer accounts for just 2%–4% of female cancer deaths at ages 40–79 years in the five selected countries, and an estimated U.S. mortality rate in 2007, for example, of 14 per 100,000 moderately obese women is only modestly higher in absolute terms than the estimated rate of 7 per 100,000 lean women. This would have equated to about 1200 endometrial cancer deaths in that year attributable to having a BMI over 25 kg/m^2; the corresponding numbers for the other countries are much smaller, ranging from about 100 to 200. By contrast, although the association between BMI and postmenopausal breast cancer is substantially weaker[4,6,7] (perhaps a 30%–40% increase in risk per 10 kg/m^2), this disease is generally a much more common cause of death. In 2007, at ages 50–79 years (i.e., 50 rather than 40, to allow informally for menopause) there would have been about 50 deaths per 100,000 lean women in the United States, compared with about 70 deaths per 100,000 moderately obese women, and there would have been an excess of 5000–6000 postmenopausal breast cancer

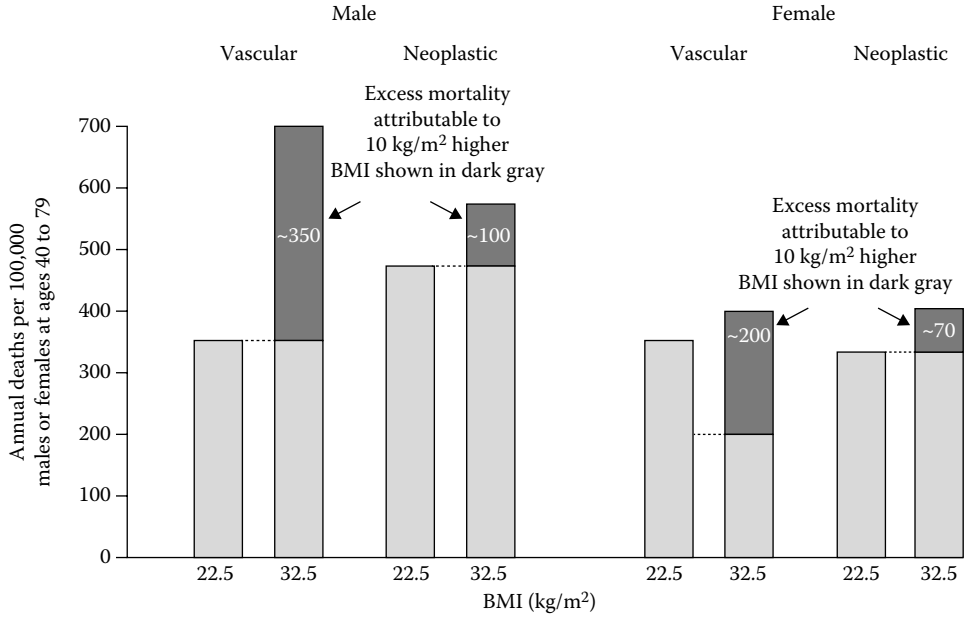

FIGURE 45.2 Estimated excess vascular and neoplastic mortality rates associated with moderate obesity in the United States, ages 40–79 years, in 2007: data sources, end point definitions, and age adjustments are as in Figure 45.1. The mortality rate at each body mass index (BMI) level is calculated by assuming that the mortality rate at the population's mean BMI equals that population's actual overall mortality rate and that each 5 kg/m^2 higher BMI within the range of 22.5–32.5 kg/m^2 is associated with 41% higher vascular and 10% higher neoplastic mortality.[4] The white numbers inside the dark gray rectangles show the annual excess deaths per 100,000 men or women with a BMI of 32.5 kg/m^2.

deaths attributable to a BMI over 25 kg/m^2—that is, four to five times the excess for endometrial cancer, despite the narrower age range.

The relative risk for liver cancer in relation to BMI may be about as extreme as that for endometrial cancer, but that for kidney cancer appears to be slightly weaker.[4,6,7] In many Western countries, all three of these site-specific cancers are similarly common causes of death in women; so among women the absolute excess mortality from liver cancer attributable to raised BMI is probably similar to that for endometrial cancer, whereas that for kidney cancer may be somewhat less. For men, kidney and liver cancer mortality rates in Western countries are about twice as high as those for women at any given age, so the burden attributable to obesity is commensurately larger. However, these inferences about liver cancer might not be applicable to Japan, where the disease generally has a different pathological basis.

Colorectal cancer is consistently related more strongly to adiposity in men than in women.[4,6,7,69,74] The observed relative risks—which again may be of uncertain generalizability to Japan—imply that 9% (France) to 14% (United States) of male colorectal cancer deaths at ages 40–79 years are attributable to having a BMI over 25 kg/m^2, being equal in 2007 to about 2700 deaths in the United States, 600 in England and Wales, 500 in France, and 300 in Canada.

45.4 OTHER CAUSE-SPECIFIC MORTALITY RATES

Some hepatic and renal diseases can also be caused by obesity and are discussed in this section together with their frequent etiological precursor, diabetes. Innumerable other diseases,[14,75] as well as some circumstances of injury (e.g., suicide[76,77] and motor vehicle crash[78]), may also be associated with BMI, but whether these associations are largely causal remains to be elucidated.

Obesity is associated with the chronic accumulation of triglyceride in the liver, which even in the absence of alcohol consumption can develop into nonalcoholic fatty liver disease and cirrhosis.[79–81] In general population studies, a higher BMI is strongly associated with cirrhosis mortality,[4,82] even among lifelong nondrinkers, so several thousand cirrhosis deaths occurring each year in the United States, for example, can now be attributed to having a BMI over 25 kg/m^2. Furthermore, the absolute number of cirrhosis deaths attributable in the United Kingdom to raised BMI would be substantial (at least 1000 a year), and it may be increasing rapidly not only because obesity itself is increasing but also because the background cirrhosis mortality rate is rising sharply.[48,83] For even if this steep increase in cirrhosis deaths has been driven chiefly by growing alcohol consumption,[83] obesity might have hastened the increase not only by its own direct hepatotoxic effects but also by exacerbating some of the noxious hepatic effects of alcohol.

Lipid deposition in the liver is closely intertwined with the development of insulin resistance and type 2 diabetes.[84–86] However, national estimates of excess mortality attributable to obesity-induced diabetes are hard to derive because of widely varying practices for coding diabetes on death certificates. In some countries diabetes is listed only rarely as the underlying cause of death, whereas in others this is done commonly. Moreover, in most countries very many deaths in which obesity-induced diabetes played a mechanistic role would have CHD or stroke recorded on the death certificate as the underlying cause.[87]

The aggregate of mortality attributed to all nonneoplastic renal diseases—including glomerular diseases, tubulointerstitial nephritis, and acute and chronic renal failure—is strongly positively associated with BMI.[4,88] The chief causal mechanisms underlying this association are likely to be the diabetes and raised blood pressure caused by excess adipose tissue.[4,40,89,90] The association with BMI appears to be at least as strong as that for vascular diseases, and a third or so of renal deaths in typical Western countries might now be attributable to a BMI of 25 kg/m^2 or more. This would be a substantial burden of attributable deaths: in 2007, at least 7000 men and 5000 women of ages 40–79 for the United States and at least several hundred men and several hundred women for each of the other countries.

45.5 ALL-CAUSE MORTALITY RATES

The association between BMI and all-cause mortality[4,39,91–95] is simply the sum of the associations of BMI with mortality from specific diseases and types of injury. For some specific end points, such as CHD, the association with BMI is positive (i.e., higher mortality at higher BMI); for a few, such as chronic obstructive pulmonary disease, it is negative (higher mortality at lower BMI); for many, such as hemorrhagic stroke, it appears to be U or J shaped (higher mortality at both high and low BMI); and for many more, no doubt, there is no association at all. The contribution of the association for each specific end point depends not only on the association's shape but also on its strength and on how common the disease is as a cause of death in the particular population: diseases that are more strongly associated and more common exert greater influence on the shape and steepness of the all-cause mortality curve. The net result of all these influences in most Western[4,91–93] and East Asian[39,94,95] populations is a U-shaped association between BMI and all-cause mortality, with the lowest mortality often at a BMI of around 24 kg/m^2.

In the relatively small number of studies that have reported a much higher optimum BMI for overall mortality,[96–99] there were, typically, methodological flaws—such as not simultaneously[91,100] allowing for the confounding effects of smoking and prior disease—which may have led to the overestimation of mortality at lower BMI levels. Moreover, even in those studies that have taken stringent steps to control for smoking and prior disease, it is probably not possible to entirely eliminate residual confounding by these factors; the *real* optimum BMI in Western and East Asian populations might consequently be lower than the 24 kg/m^2 or so commonly observed, but it seems unlikely to be much higher.

In the Prospective Studies Collaboration the apparent optimum BMI for all-cause mortality was 23 to 24 kg/m^2, and above this level 10 kg/m^2 higher BMI was associated on average with about 60% higher overall mortality.[4] If this relative increase in mortality is applied to U.S. mortality rates for ages 40–79 years in 2007—bearing cautiously in mind that this assumes the mix of causes of death in the Prospective Studies Collaboration was reasonably representative of that same mix quite recently in the United States—this would suggest annual all-cause mortality rates of about 12 per 1000 lean men, compared with about 20 per 1000 moderately obese men, and about 8 per 1000 lean women, compared with about 13 per 1000 moderately obese women. If the 2007 age- and sex-specific mortality rates were to continue indefinitely, a 40-year-old moderately obese U.S. man would have a 56% chance of dying of any cause before the age of 80, compared with the average chance of 49% for all 40-year-old U.S. men, and a 40-year-old moderately obese U.S. woman would have a 41% chance of dying before the age of 80, versus the average chance of 36% for all 40-year-old U.S. women. These estimated absolute risks of premature death are illustrated in Figure 45.3, together with corresponding absolute risks for the other countries.

As a result of the differing mortality rates at different BMI levels, a BMI of 30–35 kg/m^2 is associated in Western countries with a reduction in life expectancy of about 3 years and a BMI of 40–50 kg/m^2 is associated with a reduction of about 10 years[4] (about the same as the reduction caused by lifelong smoking[58]). Moreover, in particularly obese Western countries (e.g., the United States), about one-fifth of all deaths at ages 40–79 years may now be attributed to having a BMI over 25 kg/m^2; in relatively lean Western countries (e.g., France) it may be about one-tenth, and in Japan it may be less than half that again, or just under one-twentieth.

45.6 CONCLUSIONS

Excess adiposity is an important cause of premature mortality in North America, Europe, and East Asia and is probably so in many other less well-studied parts of the world, especially in populations with very high levels of obesity, such as Latin America, the Middle East, and Pacific Island nations. Moderate obesity typically curtails life expectancy by a few years, chiefly because of its effects on vascular diseases, most especially on CHD in the West and on stroke in East Asia. Most of the observed relationship between BMI and CHD can be accounted for by the associations of BMI with blood pressure, blood lipids, and diabetes. However, obesity is just one of several important determinants of vascular mortality, and population declines in mean levels of vascular risk factors and improvements in treatment have caused national mortality rates for CHD and stroke to fall fast even as levels of obesity have gradually risen. In addition to its effects on vascular disease, obesity also shortens life expectancy in part because of its effects on a few specific neoplastic diseases (most notably postmenopausal breast cancer and, in men, colorectal cancer), cirrhosis, and renal diseases. Calculations of the mortality burden attributable to excess adiposity, such as those presented in this chapter, depend not only

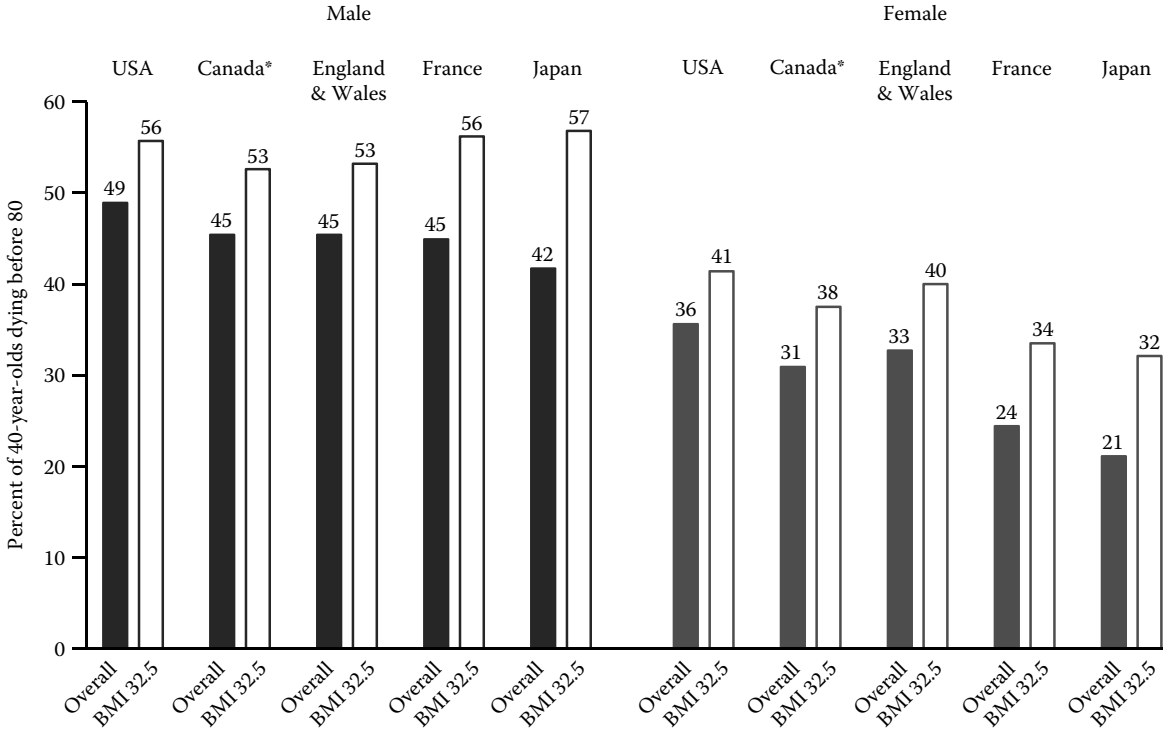

FIGURE 45.3 Approximate risk of a 40-year-old dying before the age of 80 years, at year 2007 mortality rates: probability of a 40-year-old person dying before the age of 80 years was calculated as $1 - e^{-40R/100,000}$, where R is the age-standardized all-cause mortality rate per 100,000 at ages 40–79 years in 2007.[25] Data sources and age adjustments are as in Figure 45.1. *Mortality data for Canada available only up to 2004.

on the availability of applicable relative risks for BMI (or other adiposity measures) in the national population in question but also on reliable national estimates of the population distribution of the adiposity measures and on national mortality rates for specific diseases and injuries. Although there is now enough information from many Western and East Asian countries to make these calculations, most of the rest of the world remains in a partial or total data vacuum.[9–11]

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46 Obesity and Heart Disease

Peter W.F. Wilson

CONTENTS

46.1 INITIAL AND RECURRENT CARDIOVASCULAR DISEASE EVENTS

Greater adiposity is highly associated with increased risk for almost all forms of cardiovascular disease (CVD). The lowest risk for heart disease in adults is associated with a body mass index (BMI) of approximately 22 kg/m^2. Below this level, there is generally greater CVD risk in persons because of chronic underlying diseases, heavy cigarette smoking, or malnutrition. Above this cutoff, there is a positive association between BMI and risk for CVD morbidity and mortality.[1] Table 46.1 shows the summary results from a meta-analysis that included >300,000 adults and used a BMI $\leq$ 25 kg/m^2 as the referent group. They reported a 32% increase in CVD risk for persons with BMI = 25.0–29.9 kg/m^2 (relative risk of 1.32) and an 81% greater risk among persons with BMI > 30 kg/m^2 (relative risk of 1.81).[2] These risk estimates included adjustment for a basic variable list of age, sex, smoking, and physical activity. The overall relative risk estimates diminished modestly when a full variable adjustment was undertaken that included the basic variables plus blood pressure and cholesterol level.

Long-term risk of CVD has been associated with greater adiposity in men and women, and effects are seen in diabetic and nondiabetic individuals. Results from >30 years of follow-up from the Framingham study showed a positive association with CVD risk, according to BMI level. For example, 47% of nondiabetic women with a BMI > 30 kg/m^2 developed CVD during follow-up in this analysis, as shown in Figure 46.1.[3]

Increased BMI has been associated with a greater risk for both ischemic stroke and hemorrhagic stroke, and the association has been observed more convincingly in men than in women.[4–7] Experts have reported that it is difficult to consistently show that greater BMI increases the risk of stroke in European, North American, and Asian population groups.[8] Additionally, for persons who survive a stroke the data show that persons with elevated BMI experience improved survival.[9]

The effect of excess adiposity on risk for recurrent CVD or CVD death is not consistent. In fact, obese individuals with CVD may experience fewer CVD events in the future in comparison with normal-weight survivors of previous CVD events. This phenomenon has been labeled the "obesity paradox" and has been observed in persons with cardiac failure, a history of heart disease and hypertension, and non-ST elevation on the electrocardiogram myocardial infarction events.[10,11] Survivors of CVD events may be seriously ill, may be taking multiple medications, or may have participated in weight loss programs that can affect the risk for recurrent CVD.[11] Recurrent CVD has been highly associated with lower BMI. Individuals with low BMI are often older, and their lean body mass may be declining, which makes it difficult to identify the risks associated with adiposity.[12]

46.2 OBESITY AND TRADITIONAL CARDIOVASCULAR RISK FACTORS

Adults who are overweight or obese generally bear a heavy CVD risk factor burden, and examples of some of these factors are displayed in Table 46.2. Elevated blood pressure or frank hypertension, diabetes mellitus, elevated triglycerides, elevated low-density-lipoprotein (LDL)-cholesterol, and low high-density-lipoprotein (HDL)-cholesterol are more prevalent at high levels of BMI. Experts believe that better control of blood pressure is obtained in diabetic and probably in obese patients with angiotensin blockade using an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker. Agents such as thiazide diuretics and β-blockers have been associated with hyperglycemia.[13,14]

TABLE 46.1
Overweight, Obesity, and Coronary Heart Disease Summary Estimates of Relative Risk[a]: Meta-Analysis of 21 Cohorts Including More than 300,000 Persons

BMI Level	Adjustments	Relative Risk Estimate (95% Confidence Interval)
Overweight	Basic[b]	1.32 (1.24–1.40)
(BMI = 25–30)	Full[c]	1.17 (1.11–1.23)
Obese	Basic[b]	1.81 (1.56–2.10)
(BMI ≥ 30)	Full[c]	1.49 (1.32–1.67)

Source: Bogers RP et al. *Arch. Intern. Med.*, 167, 1720–8, 2007.

[a] The referent group consists of persons with normal BMI (≤25 kg/m²).

[b] Basic variable list (age, sex, smoking, and physical activity).

[c] Full variable list (age, sex, smoking, physical activity, blood pressure, and cholesterol).

Considerable effort to prevent CVD has focused on treatment of lipids with statins. The Cholesterol Treatment Trialists meta-analysis has shown that lipid lowering is effective in the prevention of major vascular events across all strata of BMI that were investigated, as shown in Table 46.3. The test for heterogeneity was not significant, indicating similar effects at all levels of BMI, and the relative risk associated with a 1 mmol/L reduction in LDL-cholesterol was approximately 78%.[15]

Many investigations have focused analyses on the metabolic syndrome and risk for CVD events over the past decade. The syndrome comprises five metabolic traits (increased waist girth [>90 cm in women; >100 cm in men; and smaller circumferences in other regions of the world, especially Asia], impaired fasting glucose, elevated blood pressure, increased triglycerides, and low HDL-cholesterol).[16–18] For example, in the Framingham Offspring Study each of the metabolic syndrome traits was associated with a greater risk of developing coronary heart disease (CHD) in both sexes. The relative risk

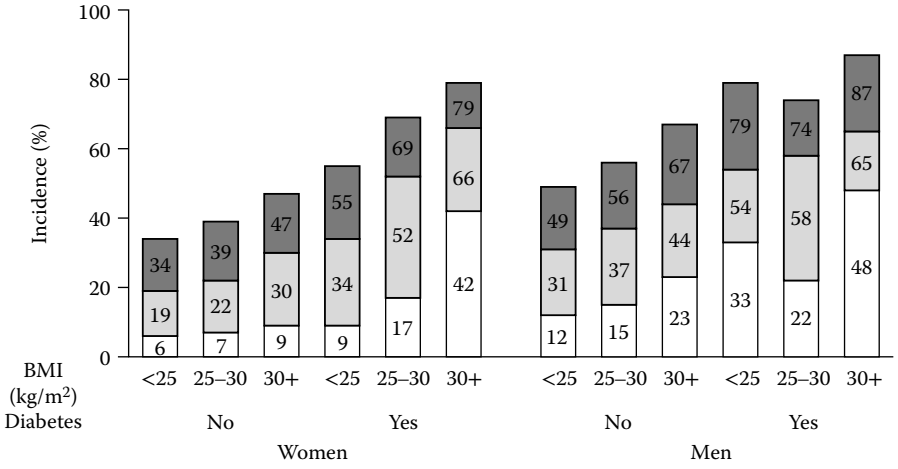

FIGURE 46.1 Adiposity level, sex, and diabetes status are strong contributors to the development of cardiovascular disease over 10 years, 20 years, and 30 years of follow-up for Framingham men and women. (Adapted from Fox et al., *Diabetes Care*, 31, 1582–4, 2008.)

TABLE 46.2
Prevalence and Means for Risk Factors According to BMI Level, from the Framingham Offspring Study

		BMI Level (kg/m²)					
Men		<21	≥21 to <23	≥23 to <25	≥25 to <27.5	≥27.5 to <30	≥30.0
	Hypertension (%)	7.4	12.5	14.9	23.3	26.9	38.8
	Diabetes mellitus (%)	0	2.8	3.7	4.6	4.0	6.3
	Triglycerides (>2.26 mmol/L)	0	6.9	8.0	14.4	20.9	27.1
	Elevated LDL-C > 4.14 mmol/L)	7.4	11.1	18.6	24.5	26.9	25.0
	Low HDL-C (<0.91 mmol/L)	7.4	8.3	9.0	13.8	19.0	24.2
Women							
	Hypertension (%)	8.0	16.3	20.8	27.3	22.7	41.8
	Diabetes mellitus (%)	0.0	0.0	1.0	1.0	3.4	6.7
	Triglycerides (>2.26 mmol/L)	0.0	1.9	3.9	9.3	15.9	14.9
	Elevated LDL-C (>4.14 mmol/L)	8.6	15.2	15.5	28.4	28.6	28.9
	Low HDL-C (<0.91 mmol/L)	0.6	1.1	0.5	2.6	2.5	7.7

Source: Lamon-Fava et al., *Arterioscler. Thromb. Vasc. Biol.*, 16, 1509–15, 1996.

Note: All trends are across the BMI level $P < 0.001$; HDL-C = HDL-cholesterol; LDL-C = LDL-cholesterol.

TABLE 46.3
BMI and Risk for Major Vascular Events with Statin Therapy from the Cholesterol Treatment Trialists Meta-Analysis

BMI Level (kg/m²)	Relative Risk Per 1 mmol/L Reduction in LDL-C	Heterogeneity Trend Test
<25	0.79 (0.74–0.84)	Chi square = 0.01
≥25 to <30	0.78 (0.74–0.82)	(p = .8)
≥30	0.78 (0.73–0.84)	
Total	0.78 (0.78–0.80)	

Source: Baigent et al., Lancet, 376, 1670–81, 2010.

for CHD associated with increased waist girth was 1.9 (95% confidence interval: 1.4–2.5).[16]

Canadian investigators demonstrated that individuals with elevated triglycerides and with increased waist circumference experienced a greater risk for CHD outcomes. In their investigation, women with a waist circumference >85 cm and triglycerides >1.5 mmol/L experienced a greatly increased risk of CHD in comparison with other prediction methods such as the number of metabolic syndrome traits or a Framingham risk score.[19]

46.3 FAT DISTRIBUTION AND CARDIOVASCULAR DISEASE

In the 1970s and 1980s, investigators first identified increased CVD risk in persons with greater abdominal adiposity.[20,21] Abdominal imaging with computerized tomography subsequently showed that a greater CVD risk was linked to visceral abdominal fat rather than subcutaneous fat in the abdomen.[22–25] Increased fat deposition in unusual areas may be associated with a greater risk for CVD. For instance, persons with HIV-AIDS may develop increased fat deposits between the scapulae and may experience a greater risk for CVD events.[26] It is difficult to sort out the role of excessive fat deposition in these cases, and affected individuals frequently have abnormal plasma lipids, underlying immunologic abnormalities, or elevated concentrations of inflammatory cytokines.[26] Investigators have reported that a greater amount of epicardial fat is associated with an increased risk for CVD. These findings are from observational studies that included computerized tomography imaging of the chest. It is thought that the fat around the heart is metabolically active. The pathophysiological mechanisms related to epicardial fat and increased CVD risk have not been well described.[27–29]

46.4 PATHOPHYSIOLOGICAL MECHANISMS

46.4.1 Insulin Resistance

Greater insulin resistance is associated with heightened CVD risk.[30–32] Clinical investigators have often used simple metabolic measures like the homeostasis model to assess insulin resistance (HOMA-IR), which is calculated by multiplying fasting glucose by fasting insulin and dividing by a constant.[33] Insulin resistance assessed by this approach is correlated with the gold standard euglycemic–hyperinsulinemic clamp,[33–35] and HOMA-IR is a practical approach to assess insulin resistance in the clinical setting. Persons with insulin resistance typically harbor traits associated with the metabolic syndrome.

Many investigators have considered clustering of metabolic syndrome traits as an indicator of insulin resistance, and reports have shown greater risk for CVD events in association with a greater burden of metabolic syndrome traits.[16] HOMA-IR, as well as other surrogates of insulin resistance, helps to identify persons at high risk for the development of first CHD events.[32,36,37] Steady state plasma glucose levels and the ratio of triglycerides to HDL-cholesterol have also been proposed as measures of insulin resistance that are associated with greater adiposity and CVD risk.[37]

Severe coronary atherosclerosis is associated with insulin resistance,[38] and quantitative coronary angiography in subjects who were suspected to have clinical coronary artery disease is illustrative. Finnish investigators compared angiographic findings to a reference group of nondiabetic persons without insulin resistance, and they found severer distal coronary artery disease lesions in diabetic patients and nondiabetic individuals with insulin resistance than in those without insulin resistance.[39] Intravascular ultrasound was used in these investigations, and remodeling was considered to be present if there was a >5% difference in lumen diameter paired to a proximal coronary artery reference segment.[40] Remodeling of coronary vessels has also been associated with insulin resistance, and it has been thought that insulin may affect vascular wall smooth muscle cell proliferation and augment coronary artery disease risk synergistically with the renin–angiotensin system.

Insulin resistance has been shown to be associated with severer coronary artery disease in cross-sectional studies and with a higher risk for CVD outcomes in nondiabetic persons. For example, insulin resistance was reported to be highly associated with diffuse coronary artery stenosis in a Korean study that evaluated persons with angina pectoris.[41] An analysis of HOMA-IR data and death certificate mortality information among National Health and Nutrition Examination Survey (NHANES) participants followed up to 12 years showed that HOMA-IR was associated with greater mortality among nondiabetic individuals, and significant findings were confined to persons with a normal BMI.[42] Additionally, higher levels of insulin resistance have been shown to be predictive of greater risk for recurrent angina in persons who have undergone percutaneous coronary intervention with a drug eluting stent.[43]

Advanced plaque progression occurs in persons with insulin resistance and in those with diabetes mellitus. Apoptosis of endothelial cells, vascular smooth muscle cells, and death of macrophages are all believed to be important mechanisms that enhance the vulnerability of atherosclerotic

plaques. Elevated levels of saturated fatty acids may lead to a decreased ingestion of apoptotic cells by macrophages, a process that contributes to plaque necrosis, as reviewed by Bornfeldt.[38] Insulin resistance is believed to enhance several pathophysiological processes, including oxidation, stress on the endoplasmic reticulum, and inflammation. A variety of plasma biomarkers have been used to study these phenomena, including C-reactive protein, oxidized lipids, greater LDL particle number, cytokines, interleukins, and tumor necrosis factor-α (TNF-α), as shown in Figure 46.2.[44–46] Increased concentrations of fat in visceral adipose tissue, subcutaneous tissue, and pericardial tissue may all be important contributors to insulin resistance and exert differential effects on metabolism and cardiovascular risk, as recently reviewed by Dandona and colleagues.[44]

It has been difficult to identify successful treatment strategies that reduce insulin resistance and concomitantly reduce the risk for CVD events. Most oral hypoglycemic agents do not have major effects on insulin resistance. Thiazolidinediones have been shown to reduce insulin resistance and, in some cases, reduce atherosclerotic disease, but they have been associated with an increased risk of cardiac failure and their overall CVD risk–benefit ratio has not been favorable.[47] Newer therapeutic strategies that might affect glycemia, insulin resistance, and inflammation are being evaluated and include novel agents such as interleukin-1 β-neutralizing antibody and the newer hypoglycemic treatments such as glucagon-like peptide inhibitors and DPP-IV inhibitors.[38]

The American Heart Association and the American Diabetes Association have published joint scientific statements that urge comprehensive risk assessment, lifestyle management, and assiduous attention to risk factor control.[48] The focus has generally been on primary prevention, but an increasingly large number of insulin-resistant and diabetic patients have prevalent CVD, which elevates the risk for subsequent CVD events.[49] Determining the level of insulin resistance helps to characterize persons with moderate to severe abnormalities of glucose, insulin, and fat metabolism. Such assessments have generally been reserved for clinical research and provide clues to improve the identification of persons at high CVD risk over the near term and the longer term.

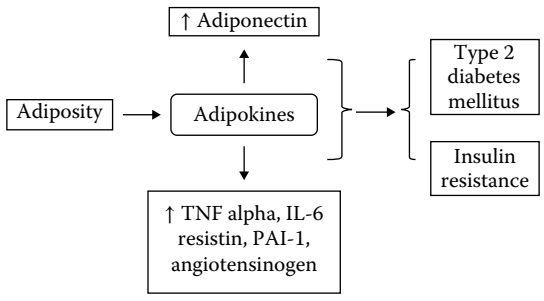

FIGURE 46.2 Adiposity leads to increased levels of adipokines and inflammatory and vascular biomarkers that foster the development of diabetes and insulin resistance.

46.4.2 Inflammatory Adipokines

As fat accumulates, the local architecture of the tissue is altered and macrophages are attracted to the site. Macrophages and other cellular elements are accompanied by increased concentrations of interleukins, TNF-alpha, resistin, leptin, adiponectin, and plasminogen activator inhibitor-1 at the sites of fat deposition and in the plasma.[50] These cytokines are highly related to the degree of insulin resistance, and a growing literature describes their effects on atherogenesis.

Interleukin-6 (IL-6) is directly produced in adipose tissue, it is associated with greater concentrations of C-reactive protein downstream, and the latter is a well-recognized determinant of greater CVD risk.[51,52] Leptin also appears to be an important determinant of IL-6 and TNF-α levels. Leptin concentrations are increased in persons who are obese, and leptin resistance is common in these individuals. A greater risk for stroke and myocardial infarction has been identified in persons with increased leptin levels.[53] Adiponectin is a cytokine that is produced in adipose tissue, and low concentrations have been associated with altered function of the arterial endothelium and increased risk for coronary artery disease.[54]

46.4.3 Oxidation

Investigators have reported increased isoprostanes in the urine of obese adults.[55] The increased formation of reactive oxygen species is believed to be atherogenic. Other potential sources for greater oxidation include plasma triglycerides and free fatty acids.[56] Increased concentrations of reactive oxygen species have been linked to abnormal regulation of nicotinamide adenine dinucleotide phosphate oxidase and altered concentrations of atherogenic cytokines that potentially foster greater atherogenesis.[57]

46.4.4 Renin–Angiotensin System

The renin–angiotensin system is inextricably linked to the growth and maturation of adipocytes in adults. Upregulation of this system is associated with increased fat deposition and greater insulin resistance. In turn, there is greater angiotensin II production and dysregulation of endothelial and myocardial functions. Some individuals develop hyperaldosteronism, and increased kallikrein concentrations and connective tissue growth factor have also been noted, especially in persons with type 2 diabetes mellitus.[58–60]

46.4.5 Electrocardiogram

Obesity is associated with a variety of abnormalities on the electrocardiogram (ECG). These can include prolongation of the QT interval on the electrocardiogram and left ventricular hypertrophy, especially if blood pressure is not controlled.[61] It may be difficult to accurately quantify voltages on the ECG because of the presence of a large amount of fat in the chest and breast area where the precordial ECG leads are placed. In this situation, it is possible that ECG-left ventricular hypertrophy

would be underdiagnosed. Pericardial fat, hypertension, and diabetes along with other risk factors have been associated with atrial fibrillation.[62,63]

46.5 ESTIMATING RISK FOR CARDIOVASCULAR DISEASE OUTCOMES

The traditional variables age, sex, total cholesterol, HDL-cholesterol, systolic blood pressure, blood pressure treatment, diabetes mellitus, and cigarette smoking have been used to estimate risk for initial CHD events. A measure of adiposity, such as BMI, waist girth, or waist/hip ratio, has not been included in most CHD or CVD risk protection algorithms.[64] It is well recognized that greater adiposity is associated with different levels of several of these factors, including HDL-cholesterol, systolic blood pressure, and diabetes mellitus.

Risk estimates for initial CVD events have focused on follow-up intervals of approximately 10 years. Analyses that have considered a potential role for adiposity in these prediction algorithms have shown no association between adiposity measure and CVD risk if the formulation already includes all of the aforementioned traditional risk factors. An etiologic analysis that focused on the role of adiposity and risk of first CVD events was undertaken using Framingham data, as shown in Table 46.4.[65] Different prediction models were used to assess CVD risk, and the role of BMI was examined in detail. For example, in model A the relative risk associated with a standard deviation of BMI (4.33 kg/m^2) was 1.28 when only age, sex, smoking, and BMI were included in the model. On the other hand, the relative risk associated with a standard deviation of BMI was 1.10 in the full model that included the preceding variables plus diabetes mellitus, systolic blood pressure, and cholesterol/HDL-cholesterol. The difference between these relative risks is the etiologic fraction associated with a standard deviation of BMI, and the authors estimated that approximately 60% of the increased risk associated with BMI was accountable to diabetes mellitus, systolic pressure, and cholesterol/HDL-cholesterol ratio.

Gaziano and colleagues[66] developed a simple CVD risk score using BMI that could easily be used in developing areas around the globe. They analyzed NHANES data in prospective analyses and compared prediction models with the traditional variables (age, systolic blood pressure, smoking status, total cholesterol, reported diabetes status, and current treatment for hypertension) using a laboratory-based approach and results obtained with traditional variables plus BMI instead of cholesterol. The authors concluded that a method that uses non-laboratory-based risk factors predicted cardiovascular events as accurately as one that relied on laboratory-based values, and they proposed that BMI could be used to help predict CVD risk efficiently, particularly in parts of the world where laboratory testing was not available.

D'Agostino and colleagues[67] published a CVD prediction algorithm that included BMI and recommended using it when traditional risk factor measurement may not be available. Additionally, a patient-friendly CVD risk algorithm was developed with the Atherosclerosis Risk in Communities data and the investigators included factors known to individuals that could potentially be used as a simple estimate of CVD risk prior to a full clinical evaluation and measurement of traditional risk factors.[68] The variables evaluated for inclusion in these analyses were age, history of diabetes mellitus, history of hypercholesterolemia, history of hypertension, family history of CHD, smoking, physical activity, and BMI. The significant variables for men included age, diabetes, hypertension, hypercholesterolemia, smoking, physical activity, and family history. In corresponding analyses for women, the significant variables were age, diabetes, hypertension, hypercholesterolemia, smoking, and BMI.

Analyses with longer follow-up intervals have shown an effect of adiposity on CVD risk even when traditional risk factors were included in the prediction model. It generally took longer than 20 years of follow-up to observe an effect of adiposity on the CVD outcome.[65]

Investigators from the Reduction in Atherothrombosis and Continuing Health (REACH) study analyzed the determinants of CVD events in persons who had survived a myocardial infarction. In this worldwide registry, they found that traditional risk factors, burden of disease, and treatments affected the risk for a subsequent CVD event or for CVD death.[69] Adiposity was investigated as a potential contributor to CVD risk in these analyses, and they reported an increase in risk for persons with reduced adiposity and no increase in risk for persons who were overweight or obese.

TABLE 46.4
Etiologic Analysis for Obesity Levels and CVD Risk: Prospective Analyses in the Framingham Offspring Study

		CVD Prediction Model Relative Risk Estimates	
Predictor	**Units**	**A**	**B**
BMI	4.33 kg/m^2	1.28	1.10
Cholesterol/HDL-C	1.61 mmol/L	—	1.38
Systolic pressure	16.67 mmHg	—	1.17
Diabetes mellitus	Yes/no	—	1.60
Age	5 year	1.55	1.48
Female	Yes/no	0.38	0.49
Current smoker	Yes/no	2.09	1.97
C-statistic		0.791	0.813

Source: Wilson et al., *Circulation*, 118, 124–30, 2008.

46.6 CARDIAC FAILURE AND CARDIOMYOPATHY

Cardiac failure occurs at a greater frequency than expected in persons with increased adiposity. It is believed that obesity accounts for approximately 10%–15% of heart failure in American adults.[70] Cardiac failure may occur following a myocardial infarction and may be associated with

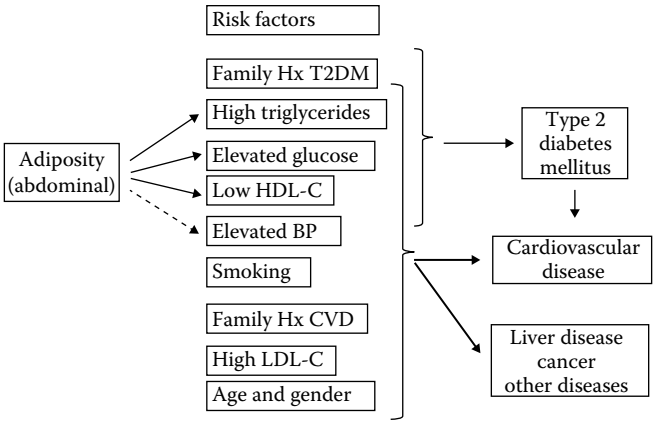

FIGURE 46.3 Adiposity leads to a variety of common risk factors, and specific subgroups of factors facilitate the development of diabetes mellitus, cardiovascular disease, liver disease, and other conditions. T2DM, type 2 diabetes mellitus.

uncontrolled hypertension, or it may occur as a result of cardiomyopathy. The overlap for persons with increased adiposity and diabetes mellitus is probably quite large.[71] Newer imaging techniques have suggested that myocardial fibers may accumulate fat, which may affect cardiac systolic function.[72] Pathologic changes in the heart may include hypertrophy of the ventricles, myocardial fibrosis, and increased capillary density, factors that may adversely affect diastolic function of the myocardium. A variety of atherogenic plasma abnormalities may be present in persons with obesity or with cardiac failure, including increased triglycerides, low HDL-cholesterol, and elevated adipokines.[73,74]

As depicted in Figure 46.3, excess adiposity, especially abdominal adiposity, appears to promote the development of clinical risk factors for diabetes mellitus, CVD, and other conditions. These risk factors work in concert to augment risk for disease, and most of the factors are strongly associated with CVD outcomes. Metabolic syndrome factors, especially adiposity itself, triglycerides, glucose, HDL-cholesterol, and blood pressure contribute to diabetes mellitus risk. Factors such as smoking and high LDL-cholesterol are not highly associated with diabetes mellitus risk, but they do increase the risk for CVD outcomes and other conditions such as cancer and fatty liver disease. Up to now, the prevention of CVD has largely focused on risk factor interventions and not on adiposity itself. Hopefully, in the future we will have improved lifestyle and pharmacological interventions to reduce risk factors and adiposity itself and these interventions will translate into a lower risk for initial and recurrent CVD events, including cardiac failure and CVD death.

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47 Obesity and Hypertension

Raj S. Padwal and Arya M. Sharma

CONTENTS

47.1 INTRODUCTION AND EPIDEMIOLOGY

Hypertension, a major risk factor for stroke, heart disease, end-stage renal failure, peripheral vascular disease, cardiovascular mortality, and total mortality, is one of the most common and devastating comorbidities in individuals with overweight and obesity.[1] Fortunately, it is also highly amenable to treatment. In 2000, the global prevalence of hypertension in adults was 26% and varied widely across the world, from 2.5% in rural India to more than 70% in Poland.[2,3] The prevalence of hypertension in adults in the United States in 2007–2008 was 30%, a level that was stable for the previous decade.[4] Approximately 80% of American adults are aware that they have high blood pressure, which is controlled to target in nearly 50%.[4]

It is estimated that 60%–70% of hypertension in adults may be directly attributed to excess adiposity.[5] In addition, excess adiposity increases the risk of resistant hypertension, which is defined as the failure to achieve target blood pressure levels despite treatment with three different agents at optimal doses. Ideally, one of the three agents should be a diuretic. For each 1 kg/m^2 increase in body mass index (BMI), the risk of resistant hypertension increases by 4% (95% confidence interval [CI]: 2%–5%).[6] Data from the U.S. Third National Health and Nutrition Examination Survey (NHANES III) 1988–1994 showed that the prevalence of hypertension rises in a linear fashion, from 25% in normal-weight subjects to 65% in those with moderate to severe obesity (Figure 47.1).[7] This linear relationship has also been described in other populations outside the United States.[8] Compared to normal-weight individuals, individuals aged <55 years with class I obesity have a 2.5- to 3.2-fold greater prevalence of hypertension.[7] This increased prevalence is attenuated in class I individuals who are ≥55 years old. Nevertheless, even in this older age group hypertension is still 1.2- to 1.4-fold more common compared to normal-weight individuals.[7] Furthermore, the risk of developing hypertension increases with increasing weight gain. For example, in 46,224 women enrolled in the Nurses' Health Study who were free of hypertension at baseline, the risk of high blood pressure increased by 20% (95% CI: 15%–25%) over a 4-year period for each 10 kg weight gained.[9]

Central or visceral adiposity is a particularly strong predictor for the development of hypertension, and this association is independent of BMI.[10,11] Visceral adiposity and high blood pressure often coexist with additional cardiovascular risk factors including insulin resistance, glucose intolerance, and dyslipidemia characterized by high triglyceride levels; low high-density lipoprotein cholesterol; and small, atherogenic low-density lipoprotein particles.[12] A low-grade inflammatory prothrombotic state is often also present.[13] This constellation of cardiovascular risk factors was characterized by Reaven[13,14] in 1988 and is now commonly referred to as the metabolic syndrome.

47.2 PATHOPHYSIOLOGY

The pathophysiology of hypertension in the setting of obesity is complex, and many factors may contribute to elevated blood pressure levels (Figure 47.2). By virtue of their larger size, obese individuals exhibit increased blood volumes

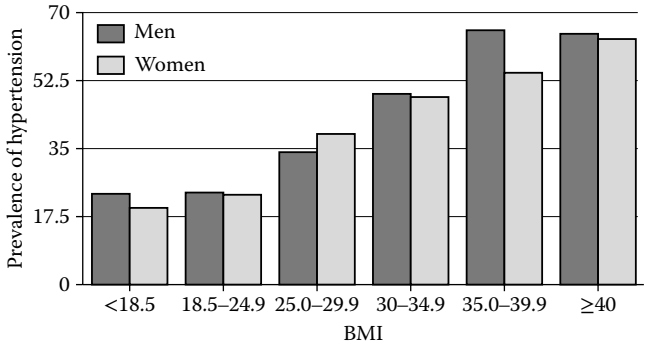

FIGURE 47.1 Relationship between body mass index (BMI) and the prevalence of hypertension in the U.S. population: data are from the Third National Health and Nutrition Examination Survey. (From Must A et al., *JAMA*, 282, 1523–1529, 1999.)

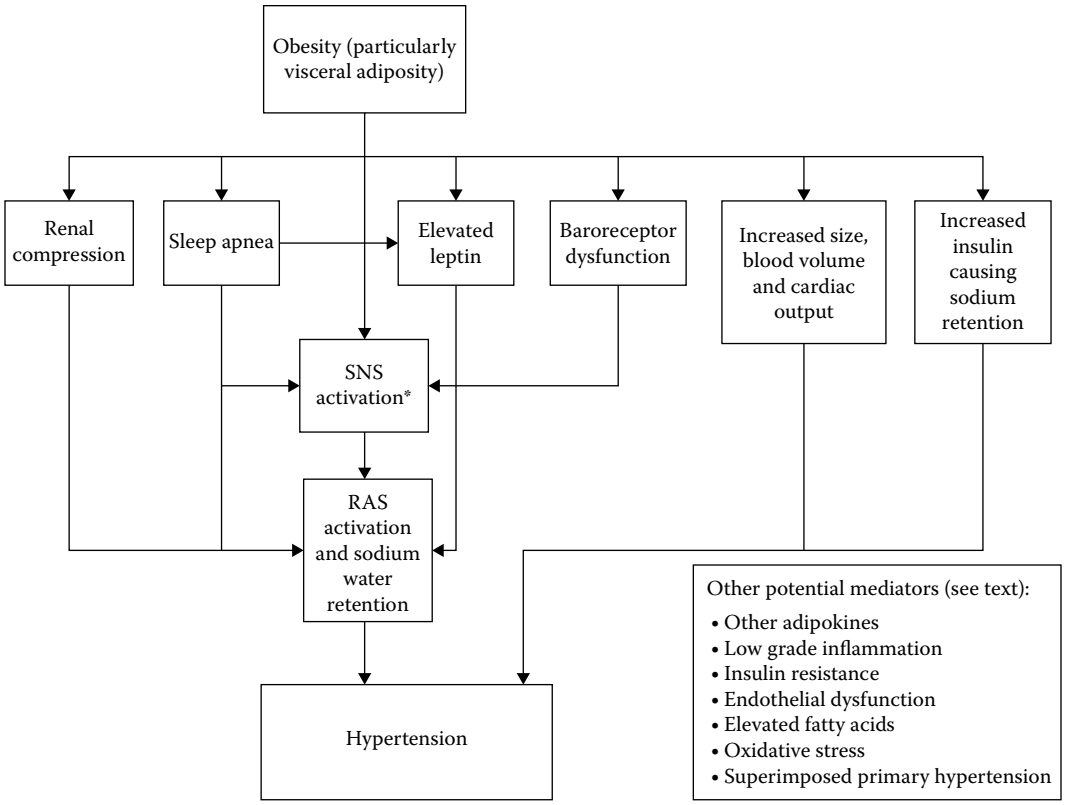

FIGURE 47.2 Major putative mechanisms linking obesity and hypertension: SNS = sympathetic nervous system; RAS = renin–angiotensin system. *SNS activation can lead to hypertension through RAS activation, sodium and water retention, or other independent mechanisms.

and cardiac outputs compared to lean individuals, and this accounts for some of the blood pressure elevation.[15] In addition, sodium retention is an important contributor to increased blood volume.[16] Thus, obesity tends to primarily lead to a volume-expanded hypertensive state. Superimposed primary hypertension can further increase blood pressure, primarily by also increasing total peripheral resistance.[15]

47.2.1 Genetic Influences

Genetic influences contribute to both the predisposition to obesity and the pathogenesis of primary hypertension, and in some individuals these influences may overlap.[17–19] Just as obese individuals are predisposed toward becoming hypertensive, observational data suggest that individuals with primary hypertension appear to be predisposed to overweight and obesity.[20] A genetic predisposition toward a sensitized hypothalamic defense mechanism, manifesting as a pressor response to low-grade stress (causing blood pressure elevation) and as increased food intake in response to stress (causing weight gain), has been proposed as a common mechanism.[16] Importantly, not all individuals with excess adiposity develop high blood pressure and, ultimately, each individual phenotype depends on both genetic and environmental factors (including dietary intake and activity levels independent of body weight).

Although genetic factors are undoubtedly important to the development of both hypertension and obesity, efforts to

deconstruct these factors from other etiological influences have been hampered by the complex and polygenic nature of these influences.[21,22] Many genetic variants have been associated with both conditions in large genome-wide association studies; however, current knowledge is not yet at a stage where the information gained from these associative studies can be translated into novel therapies. Nonetheless, insights obtained from studying patients afflicted by monogenic forms of obesity (particularly mutations affecting central melanocortin pathways in the central nervous system) have markedly improved current knowledge of the mechanisms linking obesity to hypertension.[23]

47.2.2 Sympathetic Nervous System Activation

Sympathetic nervous system activity, particularly in the kidney and skeletal muscle, is increased in obese individuals, and this appears to be an important mechanism by which hypertension occurs (Figure 47.2).[11,24,25] Adipose tissue expresses angiotensin-converting enzyme (ACE) and angiotensinogen, which are secreted into the systemic circulation.[17,26] Visceral obesity elicits greater sympathetic activity compared to subcutaneous adiposity.[27] Furthermore, weight gain increases and weight loss decreases sympathetic activity.[28,29] Multiple factors potentially contribute to sympathetic nervous system activation in obese individuals, including activation of central melanocortin pathways, alterations in adipocytokine levels (primarily hyperleptinemia), increased angiotensin II levels, baroreceptor dysfunction, and intermittent hypoxemia, in subjects with obstructive sleep apnea.[11,19]

47.2.3 Leptin

Leptin, a 16 kDa peptide hormone secreted by adipose tissue in proportion to fat mass, binds to multiple receptors in the central nervous system, including the hypothalamus.[30,31] Leptin acts on two distinct sets of neural pathways, and this combined effect acts to decrease food intake and increase energy expenditure.[23,32] First, leptin stimulates proopiomelanocortin (POMC)-expressing neurons, and the posttranslational modification of POMC results in the generation of a number of biologically active substances including α-melanocyte-stimulating hormone (α-MSH).[32,33] α-MSH acts on the melanocortin 3 and 4 receptors (MC3R and MC4R) located primarily within the hypothalamus and other sites in the brain. The end result of α-MSH action is a decrease in food intake and an increase in energy expenditure.[23,32] Second, leptin inhibits neurons that coexpress neuropeptide Y and agouti-related protein, neurohormones that ultimately act to increase food intake and antagonize MC3R and MC4R activity.[33]

Unfortunately, the vast majority of obese individuals are resistant to the anorexic actions of leptin and have high circulating leptin levels.[23,30,31] Conversely, the ability of leptin to increase energy expenditure through sympathetic nervous system stimulation appears intact. This phenomenon has been termed "selective leptin resistance" and may contribute to the inability of obese individuals to normalize their body weight and, at the same time, to their predisposition toward the development of high blood pressure.[30]

Leptin itself does not cause a pressor response in animals when acutely infused, possibly because of the occurrence of compensatory vasodilation due to nitric oxide release.[11] However, chronic leptin administration is associated with increased blood pressure in rodent models, and humans with homozygous congenital leptin deficiency exhibit postural hypotension and impaired sympathetic nervous system activity.[34] The pressor response to leptin appears to be primarily mediated through MC3R and MC4R stimulation, as pharmacological blockade of these receptors abolishes the leptin-induced, centrally mediated increase in renal sympathetic nervous system activity.[35] Furthermore, *MC4R*-deficient humans exhibit reduced blood pressure and heart rate, and administration of an MC4R agonist to humans acutely raises blood pressure.[36] Additional putative mechanisms by which leptin may increase blood pressure include increasing energy expenditure by stimulating brown adipose tissue and increasing vascular smooth muscle proliferation.[30,37]

47.2.4 Renal Influences

Although insulin is a vasodilator, it can increase blood pressure by increasing renal sodium reabsorption.[38] In this manner, elevated insulin levels can increase blood volume expansion.[16] In addition, increased renal sympathetic nervous system activity occurring through the mechanisms described earlier in Section 47.2.2 leads to activation of the renin–angiotensin system, promotes aldosterone synthesis, and leads to renal sodium and water retention (Figure 47.2).[11,19] Obese hypertensive individuals exhibit impaired pressure natriuresis,[18,39] and this hypertension is often characterized by a low-renin, volume-expanded state.[19] Increased intrarenal pressure due to perinephric fat and visceral adiposity also has been postulated to lead to renin–angiotensin system activation and sodium retention.[19]

47.2.5 Sleep Apnea

Sleep apnea is present in approximately 40% of obese individuals, and approximately 70% of patients with sleep apnea are obese; both conditions predispose toward the development of hypertension.[40,41] Sleep apnea is associated with increased sympathetic nervous system activity and hyperleptinemia independent of obesity.[42,43] Furthermore, the risk of incident hypertension increases with increasing severity of sleep-disordered breathing, as measured by the apnea–hypopnea index.[44] Intermittent hypoxemia and hypercapnia stimulate arterial chemoreceptors, leading to sympathetic nervous system activation.[45] Because treatment of sleep apnea with continuous positive airway pressure (CPAP) reduces blood pressure (see Section 47.3.2), it is likely that there is an independent contribution of this condition to hypertension independent of excess adiposity.[41,46]

47.2.6 Baroreceptor Dysfunction

Baroreflexes are primarily mediated by receptors located in the aortic arch, carotid sinuses, heart, and pulmonary vessels.[45] Baroreceptors are stretch-sensitive mechanoreceptors that signal the medullary nucleus of the tractus solitarius when blood pressure rises.[45,47] This signaling mechanism ultimately results in reduced sympathetic nervous system and increased parasympathetic nervous system activity.[45,47] Obese individuals, particularly those with central adiposity, exhibit baroreceptor dysfunction, causing elevated sympathetic nervous system activity and hypertension.[27,48] In canine models of obesity and hypertension electrical stimulation of carotid baroreceptors attenuates the increase in blood pressure seen in the obese state, and baroreceptor stimulation is currently being evaluated in humans as a novel treatment for resistant hypertension.[49–51]

47.2.7 Other Potential Mechanisms

Other potential factors that have been implicated in the pathogenesis of obesity-related hypertension include elevated levels of fatty acids, endothelial dysfunction, hyperinsulinemia, insulin resistance, low-grade systemic inflammation, oxidative stress, and hypoadiponectinemia.[11,41] Many of these mechanisms are linked to adipocyte hypertrophy and secretory dysfunction.[17] Overall, the evidence for these factors is either inconsistent or emerging, and further research is required to better delineate and define putative mechanisms.

47.3 TREATMENT

Lifestyle modification can effectively reduce blood pressure.[52] Effective lifestyle measures include weight reduction in those with excess adiposity, with sodium restriction, consuming a Dietary Approaches to Stop Hypertension (DASH)-type diet, increasing physical activity, limiting excess alcohol intake, and practicing meditation to lower stress (Tables 47.1 and 47.2). The low-renin, volume-expanded type of high blood pressure that is present in most obese individuals is often responsive to salt restriction.[19]

In a meta-analysis of 25 randomized controlled trials (RCTs) ($n = 4874$) with a mean follow-up duration of 1.3 years, mean weight reductions of 5.1 kg (95% CI: 4.3–6.0 kg) achieved through lifestyle modification led to mean systolic blood pressure (SBP) reductions of 4.4 mmHg (95% CI: 3.0–5.9) and mean diastolic blood pressure (DBP) reductions of 3.6 mmHg (95% CI: 2.3–4.9).[53] For each kilogram of weight lost, SBP was reduced by 1.1 mmHg (95% CI: 0.7–1.4) and DBP by 0.9 mmHg (95% CI: 0.6–1.3).[53] The baseline BMI in these studies ranged between 27.5 and 37.8 kg/m^2; however, BMI was not a significant predictor of the blood pressure response to weight loss.

TABLE 47.1
DASH Diet

Food Group	Recommended Number of Daily Servings	Sample Foods
Grains	6–8	Whole-wheat bread, pasta, oatmeal, cereals, brown rice.
Fruits	4, 5	Apples, bananas, grapes, apricots, oranges, mangoes.
Vegetables	4, 5	Broccoli, carrots, green beans, tomatoes, potatoes, spinach, peas, squash.
Low-fat dairy products	2, 3	Fat-free (skim) or low-fat (1%) milk, buttermilk, cheese, yogurt.
Lean meats, poultry, fish	≤6	Select lean meats, trim fat and broil, roast, or poach. Remove skin from poultry.
Nuts, seeds, legumes	4, 5/week	Almonds, peanuts, walnuts, split peas, lentils.
Fats and oils	2, 3	Soft margarines, vegetable oil (e.g., olive, corn, canola, and safflower).
Sweets	≤5/week	Sugar, jam, jelly, hard candy, sorbet.

Note: Serving sizes assume a 2000 kcal/day total intake. The full DASH eating plan is available at http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/dash_brief.pdf.

TABLE 47.2
Lifestyle Interventions to Reduce Blood Pressure in Hypertensive Individuals

Intervention	Blood Pressure Reduction (95% CI)	
	SBP (mmHg)	DBP (mmHg)
Weight loss (per kg)[53]	1.1 (0.7–1.4)	0.9 (0.6–1.3)
Sodium restriction[54]	4.4 (2.5–6.0)	2.0 (0.8–3.2)
DASH diet[61]	11.4 (7.0–16.0)	5.5 (2.7–8.2)
Aerobic exercise[64]	4.9 (2.7–7.2)	3.7 (1.8–5.7)
Alcohol restriction[55]	3.3 (2.5–4.1)	2.0 (1.5–2.6)
Stress management (transcendental meditation)[56]	5.0 (2.3–7.6)	2.8 (0.5–5.0)

Data from longer term studies of lifestyle modification and pharmacotherapy show that the blood pressure response to weight loss may be attenuated over the long term. A meta-analysis of seven observational studies and RCTs ($n = 1833$) lasting ≥2 years and including lifestyle modification and drug treatments (orlistat and metformin) reported that blood pressure reductions following weight loss were only about half those predicted by shorter term studies.[57] This analysis estimated that weight reductions of 10 kg were associated with reductions in DBP of 4.6 mmHg and in SBP of 6.0 mmHg. The reasons for the attenuation of the blood pressure response are not known, but it is possible that a lack of adherence to these treatments over the long term plays a major role.[58,59]

For each kilogram of weight lost, lifestyle modification appears to be a particularly effective method to reduce blood pressure compared to drug therapy or surgery.[57] This may be because both dietary factors (such as sodium restriction or eating a DASH-type diet) and aerobic exercise can reduce blood pressure independent of weight loss.[52,60] The original 8-week DASH trial enrolled 459 participants with a mean BMI level of 27.8 kg/m^2, SBP levels <160 mmHg, and DBPs of 80–95 mmHg.[61] Subjects randomized to the DASH diet experienced significantly greater reductions in SBP (5.5 mmHg, 97.5% CI: 3.7–7.4) and DBP (3.0 mmHg, 97.5% CI: 1.6–4.3) compared to the control group despite a between-group difference in weight of only 0.3 kg.[61] Exercise alone can improve endothelial function and reduce sympathetic nervous system activity and inflammation.[62,63] A meta-analysis of 54 RCTs ($n = 2419$) found that aerobic exercise reduced SBP by 4.9 mmHg (95% CI: 2.7–7.2) and DBP by 3.7 mmHg (95% CI: 1.8–5.7) in hypertensive individuals and that these effects were independent of baseline BMI and weight change.[64]

In contrast, the blood pressure reductions associated with antiobesity drug treatments vary according to the underlying drug class and mechanism of action. Orlistat, a lipase inhibitor, is currently the only drug approved for long-term use in the treatment of obesity. In a meta-analysis of 16 RCTs ($n = 10,631$), subjects randomized to orlistat plus lifestyle modification averaged 5.7 kg of weight loss compared to 2.8 kg in those randomized to placebo and lifestyle modification (mean difference: 2.9 kg; 95% CI: 2.5–3.2 kg).[65] Orlistat reduced SBP by 1.5 mmHg (95% CI: 0.9–2.2) and DBP by 1.4 mmHg (95% CI: 0.8–2.0) compared to placebo.[65] In 10 trials and 2623 subjects, sibutramine, a centrally acting serotonin–norepinephrine reuptake inhibitor, was compared to placebo (all patients received lifestyle modification). On average, subjects in the sibutramine arm lost 6.4 kg compared to 2.2 kg in those randomized to placebo (mean difference: 4.2 kg; 95% CI: 3.6–4.7 kg). Sibutramine therapy led to placebo-subtracted increases in SBP (1.7 mmHg, 95% CI: 0.1–3.3) and DBP (2.4 mmHg, 95% CI: 1.5–3.3) despite reducing weight.[65] Sibutramine's effect on blood pressure is a likely explanation for its tendency to increase cardiovascular events, an effect that resulted in the withdrawal of this agent from the market in 2010–2011.[66]

Although bariatric surgery has consistently been associated with improvements in blood pressure, the quality of most of the studies examining blood pressure as an outcome is low and few RCT-level data are available. In a meta-analysis of 136 studies ($n = 22,095$), 76% of which were before–after uncontrolled comparisons, the mean absolute weight loss following bariatric surgery was 39.7 kg (95% CI: 37.2–42.2 kg).[67] In the subset of patients with blood pressure outcomes ($n = 4805$), hypertension resolved in 62% (95% CI: 56%–68%) and resolved or improved in 79% (95% CI: 71%–86%). In contrast to these findings, in the Swedish Obese Subjects (SOS) study, a high-quality, matched cohort study, only slight reductions in blood pressure levels were reported when 641 surgical cases were compared with 627 controls after 10 years.[68] An increase in SBP of 1.1% (95% CI: 0.3% to –2.6%) accompanied by a DBP reduction of 2.3% (95% CI: –1.0% to –2.5%) was observed in the surgery group compared to controls despite differences in weight reduction of 16.3 kg (95% CI: 14.9–17.6 kg) favoring the surgery group. It is also notable that no statistically significant reduction in the incidence of hypertension was observed in the SOS study after 10 years (odds ratio [OR] = 0.75, 95% CI: 0.52–1.08). Since the mean blood pressure in the SOS study was only about 140/88 mmHg, it is possible that greater differences in blood pressure would have been observed if the study sample was composed entirely of hypertensive patients. It is also possible that the presence of antihypertensive treatment is confounding the effect of surgery on blood pressure.

In a 2-year RCT involving 60 patients with type 2 diabetes, subjects receiving laparoscopic gastric banding lost 20.0% of their initial body weight compared to a 1.4% weight loss for subjects receiving lifestyle modification alone (P for the comparison was <.001).[69] Although the difference in SBP change between the groups was not statistically significant (–6.0 mmHg for banding vs. –1.7 mmHg for lifestyle modification; $P = .37$), there was a 48% absolute reduction in the proportion of subjects taking antihypertensive drugs in the surgery group compared to the control group ($P < .001$).[69] Overall, more rigorous trials are required to clarify the effect of bariatric surgery on blood pressure levels and, in particular, trials need to specifically enroll obese hypertensive patients and carefully account for changes in antihypertensive drug therapy.

47.3.1 Choice of Antihypertensive Drug Therapy

Obesity is a major risk factor for resistant hypertension.[70] Thus, most obese individuals require multiple agents to achieve target blood pressure levels, particularly in the absence of successful lifestyle modification. Studies published over the past decade have indicated that renin–angiotensin inhibitors may be potentially advantageous compared to β-blockers and thiazide diuretics in terms of improved glycemic parameters in obese patients. However, the available data are not definitive, and current hypertension guidelines notably avoid making specific recommendations regarding the choice of drug class in obese patients.[71]

In the Hypertension-Obesity-Sibutramine (HOS) study, 171 obese patients were placed on one of three different antihypertensive drug combinations—felodipine/ramipril, verapamil/trandolapril, or metoprolol/hydrochlorothiazide—and then randomized to sibutramine or placebo for 16 weeks.[72]

When blood pressure control was examined separately within the two study arms, no significant differences were found among the three drug combination regimens.[72] However, the metoprolol/hydrocholorthiazide combination was associated with less weight loss compared to the other antihypertensive combinations. The results of additional studies indicate that the β-blocker component of this drug combination was likely responsible for the smaller weight loss.[73] β-Blocker and thiazide diuretics also have been associated with an increased risk of type 2 diabetes.[74] In comparison, ACE inhibitors and angiotensin receptor blockers have not been shown to increase diabetes risk and may even increase the proportion of individuals with impaired glucose tolerance or impaired fasting glucose who improve to normoglycemia.[75] Nevertheless, it should be noted that a large placebo-controlled RCT of 5269 prediabetic subjects failed to demonstrate a statistically significant reduction in the incidence of type 2 diabetes with ACE inhibitor therapy.[75]

Overall, the accumulated literature, although not definitive, favors the selection of ACE inhibitors or angiotensin receptor blockers over thiazide diuretics and β-blockers in obese hypertensive patients, especially those at high risk for developing type 2 diabetes.

47.3.2 Devices or Procedures for Reducing Blood Pressure

47.3.2.1 Continuous Positive Airway Pressure for Sleep Apnea

CPAP therapy can reduce blood pressure in patients with obstructive sleep apnea; however, the overall treatment effect size is small. In a meta-analysis of 16 RCTs of 2–24 weeks in duration ($n = 818$), subjects receiving CPAP therapy experienced greater reductions in SBP (2.5 mmHg, 95% CI: 0.6–4.3) and DBP (1.8 mmHg, 95% CI: 0.6–3.1) compared to controls.[76]

47.3.2.2 Novel Procedures for Treating Resistant Hypertension

Given the importance that increased sympathetic nervous system activity plays in the pathogenesis of hypertension in obesity, two novel procedures aimed at dampening the sympathetic response have been developed and show promise in improving blood pressure control. Although these devices are being studied in all types of resistant hypertensives and not just obese patients, the vast majority of subjects enrolled in the studies are overweight or obese.

In renal sympathetic denervation, catheter-based radiofrequency ablation of the renal afferent and efferent sympathetic nerves is performed. In a 6-month RCT of 106 subjects with resistant hypertension (mean BMI = 31 kg/m^2), blood pressure was reduced by 33/11 mmHg compared to controls ($P < .001$).[77] One advantage of renal sympathetic denervation is that it is a relatively simple outpatient procedure. Potential disadvantages include the largely irreversible nature of the nerve ablation and the unknown long-term effects on renal hemodynamics and function.

Carotid baroreceptor stimulation is a procedure that involves the implantation of a pacemaker-sized device in the upper thoracic subcutaneous tissue. A thin wire is tunneled under the skin to the carotid artery, and a lead at the distal end is mapped onto the carotid sinus region intraoperatively by verifying a blood pressure drop. Low-grade electrical impulses are used to stimulate the carotid baroreceptors and reduce blood pressure. In a 6-month RCT of 265 subjects (mean BMI = 32.5 kg/m^2), those who received active carotid baroreceptor stimulation were more likely to achieve an SBP ≤ 140 mmHg (42% vs. 24%; $P = .005$).[51] The device is currently inserted under general anesthetic; thus, the procedure is longer and more invasive than renal nerve ablation. Conversely, the dose (amount and frequency of carotid sinus stimulation) is titratable and also easily reversible by deactivating the device with a magnet.

47.4 CONCLUSIONS

Hypertension is one of the most common and deadly consequences of obesity. Complex interrelationships link obesity with hypertension, and a major contributor to this pathophysiology appears to be activation of the sympathetic nervous system via multiple mechanisms. Downstream activation of the renin–angiotensin system and sodium and water retention both contribute to elevated blood pressure. Sleep apnea is commonly also present in obese patients and appears to increase blood pressure independent of excess adiposity.

High blood pressure in obese individuals is highly amenable to treatment, especially weight reduction achieved through lifestyle modification. In addition, both dietary modification and aerobic exercise can reduce blood pressure independent of weight loss. Currently, no specific antihypertensive drug class is recommended for first-line therapy in obese hypertensive patients, although inhibitors of the renin–angiotensin system may have a relative advantage over β-blockers and thiazide-like diuretics in terms of their effect on glycemic parameters. Further study is needed to improve our understanding of the pathophysiology of hypertension in obesity so that novel therapies can be devised, studied, and utilized. Novel device- and procedure-based treatments designed to reduce sympathetic nervous system activity in obese patients with resistant hypertension are currently under evaluation.

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48 Obesity and Lipoprotein Metabolism

Sally Chiu and Ronald M. Krauss

CONTENTS

48.1 OBESITY-RELATED DYSLIPIDEMIA

The dyslipidemia most commonly associated with obesity is characterized by elevated plasma triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-C). While low-density lipoprotein cholesterol (LDL-C) levels are often normal in obese individuals, there is a preponderance of small, dense LDL particles.[1] This clustering of high TG, low HDL-C (primarily large HDL2 particles), and high levels of small, dense LDL particles, termed atherogenic dyslipidemia, is also a feature of insulin resistance and the metabolic syndrome. Atherogenic dyslipidemia is associated with increased cardiovascular risk[2,3] and its interrelated features arise from a common pathway of abnormal lipoprotein metabolism.

48.2 CLINICAL SIGNIFICANCE OF OBESITY-RELATED DYSLIPIDEMIA

48.2.1 Low-Density Lipoprotein

LDL-C is predictive of incident cardiovascular events and is the primary target for reducing cardiovascular disease (CVD) risk. However, LDL-C levels are often normal in obese, dyslipidemic individuals, making LDL-C measurements less informative when assessing risk in this population. The LDL class comprises a heterogeneous spectrum of particles ranging from small, dense, cholesterol-depleted species to large, buoyant, lipid-enriched particles, and the distribution of these particles is not reflected in the LDL-C measurement. Normolipidemic individuals have a predominance of the larger, more buoyant LDL particles (LDL phenotype A). In overweight and obese individuals, levels of small, dense LDL particles are commonly increased (LDL phenotype B) in conjunction with elevated plasma TGs and/or reduced HDL-C.

As reviewed recently,[4] a number of large prospective cohort studies have examined the relationships of LDL subfractions to CVD risk, including the Québec Cardiovascular Study,[5] which used gradient gel electrophoresis, the Women's Health Study,[6] which used nuclear magnetic resonance (NMR) spectroscopy, and the Malmö Diet and Cancer Study,[3] which used ion mobility. While levels of small LDL particles were predictive of CVD risk in each of these studies, these relationships were not significant in multiple regression models including one or more covariates, reflecting the strong interrelationships of small LDL with other lipid and lipoprotein measurements. In the Malmö Diet and Cancer Study, principal component (PC) analysis, a statistical method that captures independent clusters of interrelated variables, was used to identify correlated combinations of lipoprotein subfractions. One of the three major PCs (PC2), which closely matched atherogenic dyslipidemia, was found to be most highly associated with risk for CVD in both men and women. On average, individuals with a higher PC2 score had higher BMI.[7] Thus, increased levels of small LDL particles can serve as both a marker for an atherogenic lipoprotein pathway and a determinant of CVD risk in obese individuals. As shown in Figure 48.1, concentrations of small LDL, as well as larger very-low-density lipoprotein (VLDL) particles,

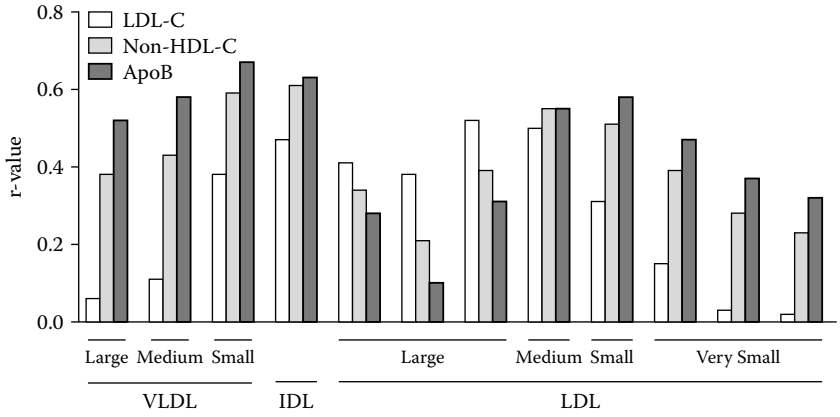

FIGURE 48.1 Correlation of plasma VLDL, IDL, and LDL particle concentrations with LDL-cholesterol (C), non-HDL-C, and apolipoprotein B levels. Data are from 158 healthy overweight and obese but otherwise healthy men and women after 4 weeks on a diet containing 15% protein, 55% carbohydrate, and 30% fat. Plasma concentrations of lipoprotein particle subfractions were measured by ion mobility (unpublished data). HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein

are more accurately assessed by measuring plasma apolipoprotein (apo) B or non-HDL-C (total cholesterol minus HDL-C) than by LDL-C, which is disproportionately influenced by relatively cholesterol-enriched larger LDL.

48.2.2 High-Density Lipoprotein

Multiple prospective epidemiological studies have shown an inverse correlation of HDL-C with CVD risk[9–11] and hence this measure is incorporated in CVD risk assessment algorithms.[12] Overexpression of the gene for apoAI, the major HDL protein component, has been shown to inhibit atherogenesis in transgenic mice.[13] It has been reported recently that variation in the capacity of plasma HDL particles to promote cholesterol efflux from macrophages is inversely associated with both carotid intima–media thickness and the presence of angiographic coronary artery disease, independently of HDL-C level.[14] The specific HDL component(s) responsible for this effect are not known, but it is likely that apoAI, by virtue of its interaction with cellular transporters involved in cholesterol efflux, plays an important role.[15]

Currently, clinical evaluation of HDL focuses exclusively on the total combined cholesterol content of all HDL particles.[12] The causal relationship of increased HDL-C and reduced CVD risk has been questioned due to failure of HDL-C raising therapies to modify risk in human trials.[16,17] This is further supported by human genetic studies[18] suggesting that the relationship between HDL-C and CVD may not be causal or that the mechanism by which HDL-C is raised may determine the effects on CVD. Therefore, increasing attention has been given to identifying and assessing functions of HDL that may confer protection from CVD and to determining specific features of HDL particles that may influence these functions.

HDL particles consist of multiple subclasses that differ by density, migration characteristics, apo content, relationships to CVD, and response to therapeutic interventions.[19] As reviewed by others,[20] there is considerable evidence that reduced levels of large, buoyant HDL2 particles are more strongly predictive of CVD risk than are concentrations of smaller, denser HDL3. Levels of particles corresponding to the largest HDL (HDL2b) have been strongly and inversely associated with coronary heart disease (CHD) or coronary atherosclerosis independent of HDL-C.[21–23] In two recent large prospective studies described in 48.2.1, levels of large HDL measured by NMR[6] and IM[3] but not smaller HDL were significantly inversely associated with incident CVD although these relationships were not independent of other lipid measures, consistent with the strong interrelationships among lipid and lipoprotein risk markers. Hence, while reduced HDL-C in obese individuals is due to reduced large HDL2b and a shift to smaller HDL particles with varying degrees of TG enrichment, it is difficult to assess the extent to which these changes directly contribute to increased CVD risk.

48.2.3 Plasma Triglycerides

Evidence for an independent relationship between plasma TG levels and CVD risk is mixed, with a lack of consensus as to whether TGs add predictive value to traditional CVD risk assessment. Analyses adjusting for nonlipid risk factors link high TG levels, either fasting or nonfasting, with increased CVD risk, but further adjustment for other lipid risk factors, particularly HDL-C, attenuates or nullifies the relationship.[24–26] Recent analyses of very large datasets highlight the difficulty of establishing TG levels as an independent risk factor for CVD. A meta-analysis of 29 prospective studies reported an odds ratio of ~1.7 for the highest versus lowest tertile of TG levels, adjusted for established CVD risk factors including LDL-C and HDL-C.[27] However, the Emerging Risk Factors Collaboration analyzed data from prospective studies including over 300,000 individuals and found no association between TG levels and CVD risk after adjusting for both HDL-C and non-HDL-C, with no differences by gender or fasted state.[28]

Detection of an independent contribution of TG to CVD risk is confounded by the interrelatedness of TG levels and other CVD risk factors including insulin resistance, obesity, and lipoprotein measures including low HDL-C and HDL2 and increased apoCIII and small, dense LDL particles. Plasma TGs themselves are likely not atherogenic, but are a biomarker for atherogenic particles that are derived from metabolism of TG-rich lipoproteins (remnant particles).[29] Indeed, among the components of the metabolic syndrome, high plasma TGs have been independently associated with atherosclerosis progression[30] and history of CVD,[31] supporting a role for TGs as a biomarker for pro-atherogenic metabolic processes.

48.2.4 Apolipoprotein CIII

ApoCIII is a modulator of TG metabolism and increased levels are a feature of atherogenic dyslipidemia. ApoCIII is bound to apoB containing lipoproteins and HDL particles and inhibits lipolysis and apoE-mediated clearance of particles. In hypertriglyceridemic individuals, apoCIII is redistributed to apoB-containing particles, increasing plasma levels. There is considerable evidence for an independent relationship of apoCIII with risk for CVD,[32–34] and this is thought to be mediated by both impaired clearance of VLDL and intermediate-density lipoprotein particles[35] and possibly by a direct inflammatory effect.[36] When adjusted for other lipid risk factors, concentrations of LDL particles containing apoCIII are much more strongly associated with risk of CHD than are LDL particles without apoCIII.[37] Thus, LDL particles containing apoCIII may confer much of the atherogenicity of LDL, despite comprising only 10%–20% of total LDL.[35] It has also been shown that apoB-bound apoCIII is enriched in small, dense LDL particles, independent of TG levels.[38]

48.3 MECHANISMS OF OBESITY-RELATED DYSLIPIDEMIA

Atherogenic dyslipidemia is strongly associated with multiple measures of adiposity, most specifically with increased visceral fat.[39–41] Recent studies have suggested that increased visceral adiposity is a marker for ectopic fat depots, such as intrahepatic fat, that are more directly responsible for the metabolic abnormalities associated with excess body fat, including dyslipidemia and insulin resistance.[42,43] Although it remains unclear whether dyslipidemia associated with obesity is more closely linked to the accumulation of intrahepatic or visceral fat, it is generally accepted that ectopic fat deposition leads to the alterations in the trafficking of fatty acids and TGs that underlie the manifestations of atherogenic dyslipidemia. In insulin-resistant states, plasma free fatty acids are elevated due to an inability to adequately suppress adipose tissue lipolysis, leading to ectopic fat deposition in tissues including the liver. This is exacerbated in individuals with excess total fat accumulation. Increased free fatty acid flux to the liver impairs insulin function and stimulates overproduction and secretion of large, TG-rich VLDL particles.[44] In normolipidemic individuals, hepatic TG is packaged and primarily secreted as smaller VLDL particles that are rapidly metabolized to relatively large and buoyant LDL particles by the action of lipoprotein lipase, and these LDL particles are efficiently cleared from plasma by hepatic LDL receptors (Figure 48.2). In individuals with atherogenic dyslipidemia, increased intrahepatic TG leads to greater hepatic secretion of large, TG-rich VLDL particles in which apoCIII enrichment leads to reduced plasma clearance and hence greater plasma residence time.[37] Through a series of steps involving remodeling by hepatic lipase and cholesteryl ester transfer protein (CETP), remnant particles ultimately give rise to small, dense LDL.[45] These metabolic processes

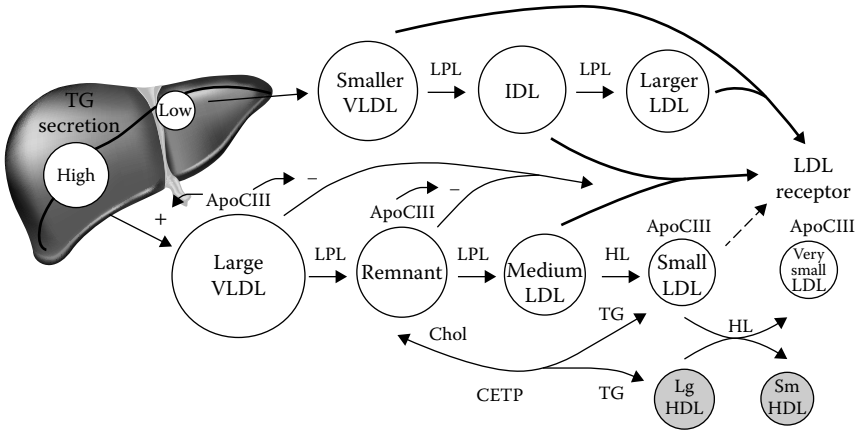

FIGURE 48.2 Model of lipoprotein metabolism in normal and atherogenic dyslipidemia states. When hepatic triglyceride content is low, smaller VLDL are produced and secreted by the liver, which are metabolized to IDL and larger LDL particles that are more readily taken up by the LDL receptor. In states where hepatic triglyceride content is high, as often seen in obesity, triglyceride-rich large VLDL-containing apolipoprotein CIII are produced and secreted. These particles ultimately give rise to smaller LDL particles, which are less efficiently taken up by LDL receptor. CETP, cholesteryl ester transfer protein; Chol, cholesterol; HDL, high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.

also lead to reduced levels of larger HDL particles and HDL-C as well as renal clearance of lipid-depleted apoAI.

We have hypothesized that when hepatic TG transport through this pathway reaches a threshold,[45] there can be a quantum effect on VLDL assembly and secretion that leads to increased production of large VLDL1 and a corresponding discrete shift in the distribution of plasma LDL particles from LDL phenotype A to LDL phenotype B. Relatively reduced affinity of smaller LDL for LDL receptor–mediated uptake contributes further to increased plasma concentrations of these particles.[45]

48.4 DIETARY EFFECTS ON OBESITY-RELATED DYSLIPIDEMIA

Weight loss can significantly improve obesity-related dyslipidemia, as extensively described elsewhere.[46,47] Here, we focus on dietary effects on this dyslipidemia that are independent of weight loss.

48.4.1 Carbohydrate Quantity

Increased carbohydrate intake can induce or amplify all features of atherogenic dyslipidemia[48,53] including total and non-HDL-associated apoCIII.[54] In combined data from seven dietary intervention studies from our group[48,50,55,56] (also unpublished studies) in which carbohydrate intakes varied over a broad range, with constant energy intake and ratio of simple to complex carbohydrates, there was a strong correlation between increasing carbohydrate intake and TG:HDL-C ratio (Figure 48.3). Consistent with this relationship, there was also a linear increase between dietary carbohydrate and the proportion of healthy men who expressed LDL phenotype B.[49]

There is also evidence that all components of atherogenic dyslipidemia can be improved or normalized by carbohydrate limitation without weight loss.[48,50,57,58] In a randomized multiparallel 13-week dietary intervention trial in 178 overweight and obese men,[50] lowering of carbohydrate intake (from 54% to 39% to 26% of energy intake, achieved through isoenergetic increases in protein and monounsaturated fat) resulted in significant reductions of total cholesterol and LDL-C, non-HDL-C, apoB, total:HDL-C ratio, TGs, and small LDL mass. Interestingly, these effects were very similar to those seen after weight loss and stabilization (7% weight loss) on a high-carbohydrate diet, suggesting that reduced carbohydrate intake may affect lipoprotein metabolism through pathways common to those influenced by weight loss.

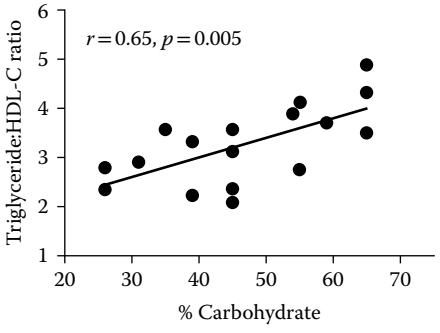

FIGURE 48.3 Correlation of carbohydrate content and triglyceride: HDL-cholesterol (high-density lipoprotein-cholesterol) ratio. Combined data from seven dietary intervention studies from our group consisting of 17 experimental diets varying in carbohydrate content demonstrates a positive correlation between percent energy as carbohydrate and triglyceride:HDL-C ratio.

48.4.2 Carbohydrate Quality

Rapidly digested simple sugars and starches have been more strongly implicated in exacerbating the components of atherogenic dyslipidemia than complex carbohydrates.[59–62] Analysis of data from the National Health and Nutrition Survey showed a linear relationship between intake of added sugars and components of atherogenic dyslipidemia including low HDL-C, high TGs, and TG:HDL-C ratio.[62] Of the simple sugars, fructose has gained the most attention as having particularly deleterious effects on a host of metabolic abnormalities. Very high intake of added fructose versus glucose (25% of total energy for each) resulted in increased visceral fat deposition, mean 24-hour TG levels, total cholesterol and LDL-C, apoB, and small LDL-C.[63] In individuals with the metabolic syndrome, small, dense LDL levels were twice as high with fructose than with glucose consumption.[63] Fructose increases postprandial hepatic de novo lipogenesis, which likely drives the dyslipidemia by promoting synthesis and secretion of TG-rich lipoproteins. Fructose may also decrease lipoprotein lipase activity, resulting in reduced clearance of and increased plasma retention time of these particles, with subsequent remodeling to produce small LDL.[63] Unlike glucose, fructose uptake in the liver is not regulated by energy status and therefore the majority of fructose consumed is taken up by the liver, allowing for the conversion of substrates for de novo lipogenesis. While there is increasing evidence that high intakes of fructose can stimulate de novo lipogenesis,[64,65] there appears to be less of an impact of fructose on TG levels at more moderate intakes (100 g/day).[66]

In the Women's Health Initiative Dietary Modification Trial, replacement of 7%–8% dietary fat with increased complex carbohydrates resulted in no deleterious effects on plasma TGs or HDL-C at year 6. Subset analyses showed an increase in TG level on the higher carbohydrate, low-fat diet in white diabetic women, but not in obese women or in those with the metabolic syndrome.[67] Although there are limitations to long-term dietary trials, the study suggests that modestly increasing dietary carbohydrate content in the form of fruits, vegetables, and whole grains does not significantly exacerbate atherogenic dyslipidemia.

The glycemic index (GI) is a measure of the ability of a food to raise blood glucose when consumed compared to white bread or standard glucose solution and has been proposed as an indicator of the metabolic effects of carbohydrate-rich foods.[68] Glycemic load (GL) accounts for the quantity

of carbohydrate in the food and is the product of GI and carbohydrate content. Several cross-sectional studies have shown an association of lower GI or GL diets with increased HDL-C and reduced TG levels.[59–61] Evidence from interventional studies is more mixed. In a trial of obese men consuming a low-GI diet and an energy-matched American Heart Association (AHA) Step I diet, the low-GI diet improved atherogenic dyslipidemia by decreasing total:HDL-C ratio and increasing LDL peak particle size compared to the AHA diet.[69] A meta-analysis of intervention trials showed a TG-lowering effect of low-GL diets, when controlled for fat intake.[70] The DiOGenes study tested high- versus low-GI diets in 932 overweight adults during a post-weight-loss weight-maintenance period of 26 weeks and found no effect on lipid profiles,[71] supporting a lack of effect of GI or GL on plasma lipids seen in other trials.[72] Discrepancies in trials may reflect inherent difficulties in matching experimental diets for other dietary components, or differences in population studied, or that GI/GL in observational studies may be a marker for an overall dietary pattern that is related to CVD risk.

Other classifications of carbohydrate quality based on digestibility have been suggested to influence components of atherogenic dyslipidemia. Resistant starches are incompletely degraded by α-amylases, and their incomplete digestion in the small intestine makes them available for fermentation by gut bacteria in the colon. Available data from a small number of human trials investigating diets supplemented with resistant versus easily digestible starch show that at high doses, resistant starches may reduce plasma TG levels,[73,74] whereas lower levels of consumption (<10% daily energy intake) do not appear to affect plasma lipids.[75,76] Animal data support a mechanism by which the slow digestion of resistant starches reduces de novo lipogenesis compared to easily digestible starches.[77,78]

48.5 PHARMACOLOGIC EFFECTS ON OBESITY-RELATED DYSLIPIDEMIA

We here briefly summarize effects of those pharmacologic agents reported to substantially ameliorate or reverse obesity-related dyslipidemia, other than those aimed at achieving weight loss.

48.5.1 Niacin

Niacin, or nicotinic acid, when administered in amounts much higher than its Recommended Dietary Allowance as a vitamin, can improve all features of atherogenic dyslipidemia.[79] The mechanisms for niacin's effects on lipoprotein metabolism are complex and not well understood. Its G-protein coupled receptor, GPR109A, is present on immune cells and adipocytes. Activation of GPR109A decreases activity of hormone sensitive lipase, leading to reduced TG hydrolysis and subsequent free fatty acid flux to the liver, reducing substrate for VLDL synthesis. HDL-C is thought to be increased by reduced CETP transfer of TGs for cholesteryl esters from VLDL to HDL particles. Other possible mechanisms include promotion of apoB degradation, inhibition of apoA1 catabolism, and stimulation of cholesterol efflux to apoAI to increase HDL biogenesis.[80,81]

48.5.2 Fibrates (Peroxisome Proliferator-Activated Receptor-α Agonists)

Fibrates activate the nuclear hormone receptor peroxisome proliferator-activated receptor (PPAR)-α, and they lower plasma TG, raise HDL-C, and, to a lesser extent, lower LDL-C.[82] Activation of PPAR-α modulates the expression of genes regulating lipid and lipoprotein metabolism. Fibrates lower plasma TG by increasing lipolysis and clearance of VLDL-TG due in part to suppressing expression of apoCIII. Some, but not all, classes of fibrates also decrease hepatic VLDL-TG secretion. Fibrates increase HDL by increasing the expression of apoAI and apoAII to varying extents.[83] LDL-C lowering is modest and variable, but levels of small LDL particles are reduced, with a shift toward larger particles and normalization of atherogenic dyslipidemia in individuals with dyslipidemia of obesity or type 2 diabetes.[84–87]

48.5.3 Peroxisome Proliferator-Activated Receptor-γ Agonists

Thiazolidinediones (TZDs) activate PPAR-γ and improve insulin sensitivity and glycemic control in type 2 diabetes. They can also improve components of atherogenic dyslipidemia through raising HDL-C and/or decreasing TGs, even while they produce an increase in body fat. Of the two currently available TZDs, rosiglitazone and pioglitazone, only pioglitazone has been shown to decrease TGs, increase HDL-C, and decrease levels of small, dense LDL and apoCIII.[88] In nondiabetic patients, the reported effects of pioglitazone on components of atherogenic dyslipidemia are variable with individual trials showing improvements in some, but often not all components.[89–92] The inconsistent effect may be dependent on baseline lipid levels or degree of insulin resistance of the study population.

48.5.4 Peroxisome Proliferator-Activated Receptor-δ Agonists

Although there are currently no FDA-approved PPAR-δ agonists for the treatment of dyslipidemia, recent studies have demonstrated their therapeutic potential. A trial of one such agent in patients with mixed dyslipidemia resulted in reductions of small plus very small LDL particles and increased levels of large LDL, with a concomitant reduction in large VLDL, and an increase in LDL peak diameter, which translated to reversal of LDL phenotype B in 90% of study participants. Modest increases in HDL particles were confined to the smaller HDL fractions.[93]

48.6 CONCLUSIONS

Excess adiposity, particularly in intra-abdominal sites, can contribute to dysregulation of lipid and lipoprotein metabolism that results in an atherogenic dyslipidemia characterized by increased plasma TG levels, reduced HDL-C, and increased levels of small, dense LDL particles. The components of this dyslipidemia are metabolically interrelated and result in part from alterations in pathways of hepatic TG trafficking. Restriction of dietary carbohydrate, particularly fructose, can improve atherogenic dyslipidemia even in the absence of weight loss. Several pharmacological agents can reverse atherogenic dyslipidemia or improve one or more of its components, although the benefits of these treatments on CVD risk remain uncertain.

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49 Obesity and Type 2 Diabetes

Henna Cederberg and Markku Laakso

CONTENTS

49.1 INTRODUCTION

Simultaneous increases in the incidence and prevalence of obesity have occurred in almost all countries during the past three decades. The major drivers of the obesity pandemic have been changes in the global food system resulting in more processed and energy-rich food that has generated an obesogenic environment. This has resulted in wide variation in the prevalence of obesity across populations, especially in adults.

The obesity epidemic seems to have begun in the 1970s and 1980s in most high-income countries, spreading later on to many low-income countries. The flipping point occurred in the 1960s–1970s with an increasing food energy supply, which in combination with low physical activity resulted in increases in population weight. Between 1980 and 2008, mean global body mass index (BMI) increased by 0.4–0.5 kg/m^2 per decade both in men and in women.[1] By 2008, 1.46 billion adults globally were overweight (BMI > 25 kg/m^2) and 502 million adults were obese (BMI > 30 kg/m^2).[1] Obesity especially affects wealthy, urban, female, middle-aged adults in low-income countries, whereas in high-income countries, it affects both sexes and all ages.[2] Encouraging trends have been reported from some European countries indicating that obesity prevalence in children and adolescents, though at high levels, has recently remained stable or is even decreasing.[3]

The global pandemic of obesity has serious health consequences. Obesity is an established risk factor for type 2 diabetes, cardiovascular disease and cancers, and nonmetabolic complications (e.g., osteoarthritis and sleep apnea). Most patients with type 2 diabetes are obese, and visceral obesity in particular is the most important predisposing factor for the development of type 2 diabetes. However, not all obese people develop diabetes, and they typically have significantly less abnormal cardiovascular risk factor levels than those who convert to diabetes. In the National Health and Nutrition Examination Survey III, approximately 80% of obese participants had metabolic abnormalities while 20% maintained normal levels of glucose and cardiovascular risk factors.[4] Subsequent studies have estimated that about 30% of obese adults are metabolically healthy.[5] People with metabolically benign obesity are characterized by a low amount of fat in the abdominal region, liver, and skeletal muscle. Thus, metabolically healthy obese individuals have the ability to store free fatty acids in adipose tissue.[6]

Although the mechanisms linking obesity to type 2 diabetes remain largely unknown, insulin resistance is a shared characteristic finding in both conditions. Obesity could be linked to insulin resistance through several mechanisms including increased visceral fat, subtypes of adipose tissue that are functionally different and affect glucose homeostasis differentially, altered production of adipokines/cytokines,

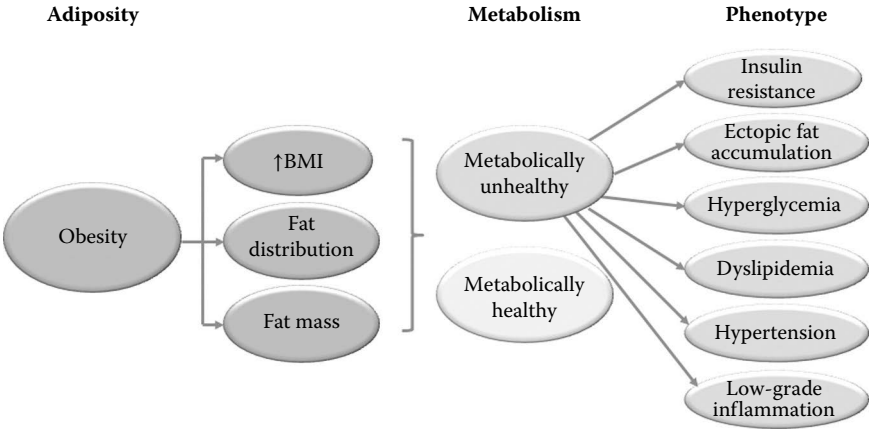

FIGURE 49.1 Schematic representation of metabolically unhealthy and healthy obese phenotypes.

and low-grade chronic inflammation. In this chapter, we discuss the parallel pandemics of obesity and type 2 diabetes, especially from the point of view of metabolically healthy/unhealthy obesity, which explains why a subgroup of obese people develop type 2 diabetes while others do not. The determinants of metabolically healthy and unhealthy obesity include not only increased BMI but also the distribution of fat, the amount of fat mass, and the size and metabolism of adipocytes. Metabolically unhealthy obese individuals are characterized by insulin resistance, ectopic fat accumulation (e.g., in the liver, skeletal muscle, and pancreas), low-grade chronic inflammation, and hyperglycemia leading to type 2 diabetes. In addition, metabolically unhealthy obese people often suffer from coexistent dyslipidemia and hypertension (Figure 49.1).

49.2 PARALLEL PANDEMICS OF OBESITY AND TYPE 2 DIABETES

Currently, 366 million people suffer from diabetes globally. By 2030, this number is expected to be 552 million,[7] largely attributable to the increase in the incidence of type 2 diabetes. The number of people with type 2 diabetes is increasing in every country, and 80% of people with diabetes now live in low- and middle-income countries.[7] Similarly, the rise in the prevalence and incidence of diabetes is predicted to be much greater in low- and middle-income countries than in high-income countries (69% vs. 20%, respectively).[8] In low- and middle-income countries, working-age people (40–60 years old) are affected most, in contrast to high-income countries, where type 2 diabetes predominantly affects those older than 60 years.[8] Obesity-related type 2 diabetes is being diagnosed at increasing frequency in young people, particularly in the United States, whereas in other countries such as Germany the prevalence of type 2 diabetes in young individuals is still relatively low.[9–11] Fifty percent of people with diabetes (183 million) are estimated to be currently undiagnosed.[7]

The increase in the occurrence of overweight has been followed by a parallel increase in the incidence of type 2 diabetes. A dramatic global increase in the mean BMI occurred from 1980 to 2008, with 35% of adults aged over 20 years being overweight (BMI $\geq$ 25 kg/m^2) and 12% obese (BMI $\geq$ 30 kg/m^2) in 2008.[12] Comparison of the geographical variation in obesity and type 2 diabetes from country to country shows clear parallel trends in obesity and overweight in regions such as North America and Europe (Figure 49.2). However, not all countries with a high prevalence of diabetes have a high prevalence of obesity (such as in Southeast Asia). People in Asia develop diabetes with a lesser degree of obesity and at younger ages; Asian populations also show a high proportion of body fat and prominent abdominal obesity compared to those of European origin with similar BMI values, probably attributable to genetic influences.[13] In Asian countries, the rate at which diabetes has increased during recent decades exceeds that in Western countries. In contrast, in some regions with a high prevalence of obesity, the rates of diabetes are lower than one might expect.

Hyperglycemia is a continuous spectrum associated with comorbidities. People with type 2 diabetes as well as those with prediabetes and undiagnosed type 2 diabetes are typically obese and have a high risk of cardiovascular complications, including coronary artery disease, stroke, and peripheral vascular disease.[14] Cardiovascular causes account for over 70% of mortality among individuals with type 2 diabetes.[15] Thus, the obesity pandemic will not only be followed by a type 2 diabetes pandemic but also by a subsequent pandemic of diabetes-related cardiovascular disease.

49.3 LINK BETWEEN OBESITY AND TYPE 2 DIABETES

49.3.1 Prediabetes and Diabetes

Type 2 diabetes is preceded by a stage of prediabetes characterized by either impaired glucose tolerance (IGT) or impaired fasting glucose or a combination of both, which can be diagnosed by an oral glucose tolerance test. In the prediabetic state, hyperinsulinemia compensates for impaired insulin action, but for type 2 diabetes to develop, a β-cell dysfunction causing impaired insulin secretion is required. Type 2 diabetes is defined by the degree of hyperglycemia

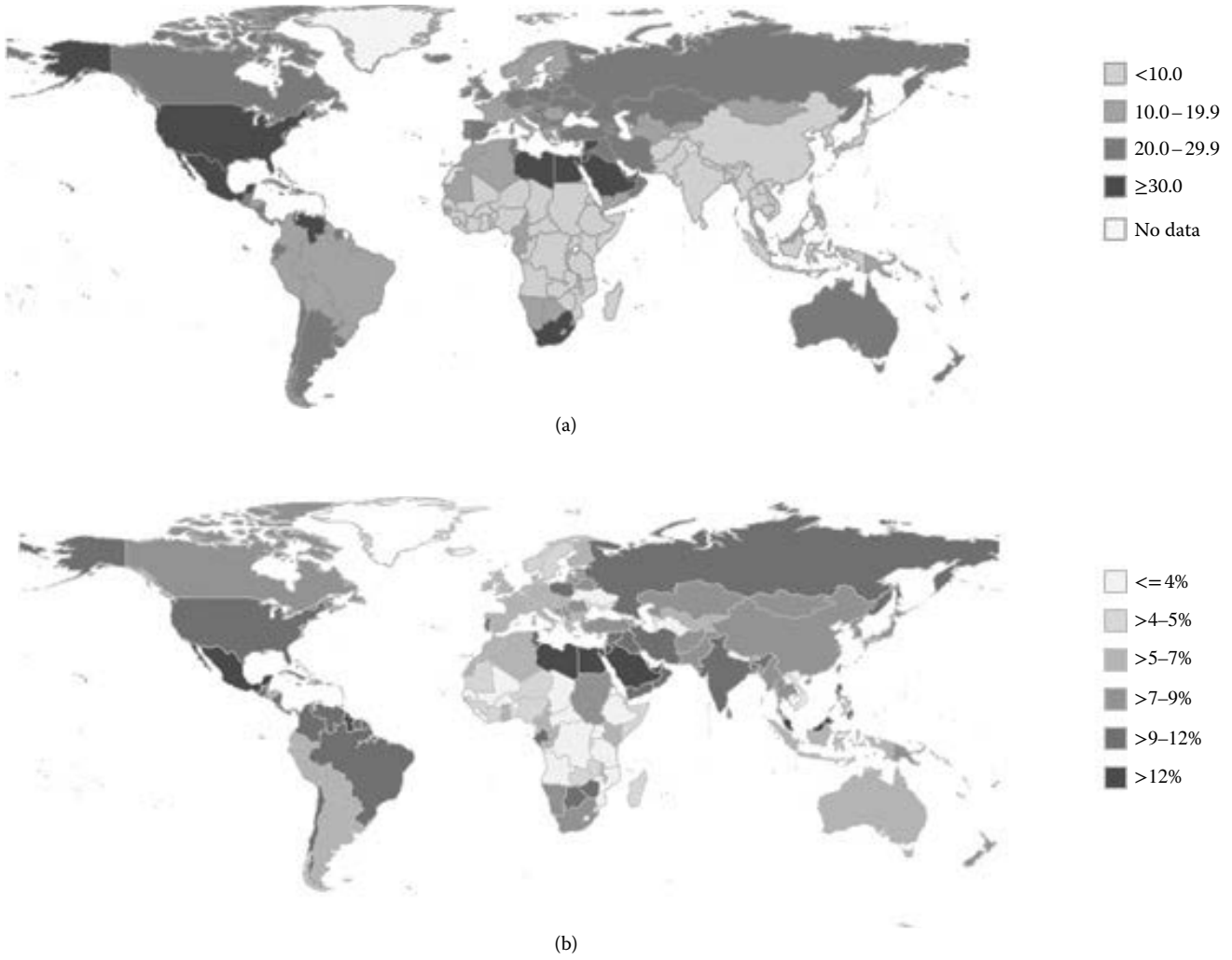

FIGURE 49.2 Prevalence of (a) obesity (%, BMI ≥ 30 kg/m^2) in 2008 and (b) diabetes (%) in 2011 by country. (Modified from World Health Organization, available at http://www.who.int/gho/ncd/risk_factors/overweight/en/index.html; and International Diabetes Federation, available at http://www.idf.org/diabetesatlas/5e/the-global-burden; http://www.idf.org/atlasmap/atlasmap, accessed March 4, 2012.)

and is currently diagnosed as fasting plasma glucose levels of ≥7.0 mmol/L or 2-hour plasma glucose levels of >11.0 mmol/L in an oral glucose tolerance test or more recently as glycated hemoglobin A1c ≥6.5%.[16–18]

Type 2 diabetes, which accounts for at least 90% of the cases of diabetes, is characterized by an inadequate β-cell insulin secretion in response to chronic fuel excess.[19] Type 2 diabetes is attributable to the interaction of environmental and lifestyle factors that increase insulin resistance (obesity, central obesity, physical inactivity, high-calorie and high-fat diet, and smoking) and inherited, progressive pancreatic β-cell dysfunction leading to progressive deterioration of insulin secretion[20] (Figure 49.3).

49.3.2 Metabolic Processes Leading from Obesity to Type 2 Diabetes

The defect most strongly associated with the development of type 2 diabetes in overweight and obese individuals is insulin resistance, whereas the association of obesity with impaired insulin secretion is less well understood. Predisposition to insulin resistance in obesity relates to adipocyte lipid turnover, deposition of fat, and adipocyte number and mass, as well as the endocrine and inflammatory properties of adipose tissue, as discussed later in Sections 49.3.2.1–49.3.2.4.

49.3.2.1 Adipocyte Lipid Turnover and Deposition of Fat

Adipose tissue mass is determined by the storage and removal of triglycerides in adipocytes and/or ectopic deposition in non-adipose tissues. In obese individuals, triglyceride turnover rate, determined by lipolysis followed by oxidation, is decreased, and the amount of triglycerides stored over time is increased.[21] Distribution of fat, that is, the site of deposition of the chronic fuel excess differentiates overweight and obese individuals who develop type 2 diabetes from those who do not.

Deposition of excess calories in the subcutaneous adipose tissue (SAT) rather than in the visceral adipose tissue

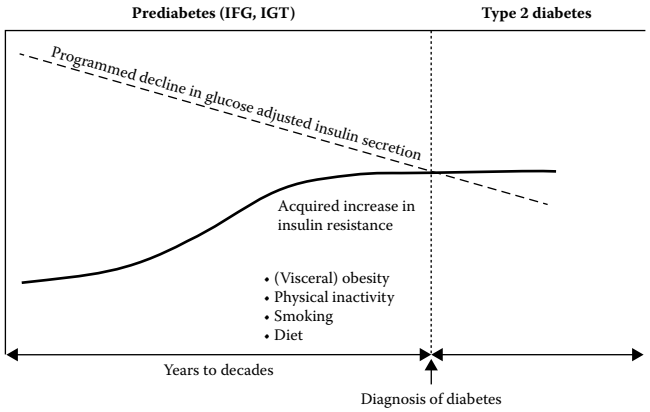

FIGURE 49.3 The development of type 2 diabetes over time in the presence of multiple risk factors. IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

(VAT; heart, skeletal muscle, liver, and pancreatic β cells) protects the key organs of the body from excess nutrient-induced metabolic stress.[19] Key adaptive mechanisms favoring fat storage in SAT include greater relative expansion of SAT than VAT, limited increase in liver fat, pancreatic β-cell compensation for insulin resistance, maintenance of near-normal nutrient concentrations, and the development of minimal insulin resistance.[6,19,22] In contrast, in metabolically susceptible individuals, the adaptive mechanisms fail and adipose tissue is preferentially deposited in the visceral compartment and in other organs. The defective mechanisms underlying visceral fat deposition in metabolically susceptible obese individuals include the development of peripheral insulin resistance, increased glucagon secretion, increased endogenous glucose production, failure of pancreatic β-cell response to hyperglycemia, impaired expansion of SAT, attenuated incretin hormone response, hypoadiponectinemia, and low-grade inflammation in adipose tissue.[19,23–26.]

What makes VAT metabolically more hazardous than SAT? Subcutaneous fat is a more active energy storage depot with greater readiness for proliferation and expansion and greater responsiveness to insulin than VAT.[27,28] VAT is a more active endocrine organ with greater release of adipokines and proinflammatory markers and reduced release of adiponectin. The proximity of VAT to the portal vein has lead to the "portal vein hypothesis" stating that increased visceral adiposity is associated with increased free fatty acid flux into the liver and inhibition of insulin action through Randle cycle.[29]

49.3.2.2 Heterogeneity of Adipose Tissue

Emerging evidence suggests that different subtypes of adipose tissue exert variable effects on glucose metabolism. Brown adipose tissue (BAT) plays an important role in thermogenesis and influences energy expenditure and thus susceptibility to obesity.[30–32] However, a limited amount of BAT is found in adult humans, with the majority of fat stored as white adipose tissue.[31,32] Improved understanding of metabolic properties of BAT in the future may lead to better understanding of the metabolic consequences of obesity.

Adipocytes, which are derived from mesenchymal stem cells through differentiation of preadipocytes, can vary in size or number. Increases in both adipocyte size and number may occur in response to weight gain.[33] However, fat mass is mainly determined by an increase in the average cell volume. The presence of enlarged adipocytes with greater lipid content correlates more strongly with insulin resistance than any other measure of adiposity.[29] Adipose tissue hyperplasia, an increase in the number of adipocytes, can occur when adipocytes reach a critical size and precursor differentiation is triggered.[27] Of these two processes of adipose tissue expansion, hyperplasia has been considered more benign whereas enlarged adipocyte size with decreased triglyceride storage in fat cells has been associated with the development of metabolic derangements and inflammation.[27,28,34,35]

49.3.2.3 Adipose Tissue as an Endocrine Organ

Adipose tissue is an active endocrine organ and secretes several hormones, or adipokines, involved in glucose homeostasis and insulin resistance.[36] Adiponectin, secreted solely from adipose tissue with higher expression in SAT than in VAT, is associated with improved insulin sensitivity and is present at lower levels in obesity.[37] Leptin, an adipokine with levels proportional to the amount of body fat, inhibits insulin binding, insulin-mediated glucose transport, lipogenesis, and glycogen synthase activity in adipose tissue.[27] Additional adipokines implicated in glucose homeostasis include resistin, visfatin (also known as nicotinamide phosphoribosyltransferase), omentin (also known as intelectin-1), and vaspin (also known as serpin A12).[27]

49.3.2.4 Low-Grade Inflammation and Endoplasmic Reticulum Stress

Obesity and type 2 diabetes are both characterized by chronic low-grade inflammation, which has been proposed to be one of the key triggers of metabolic derangements in obesity. Proinflammatory cytokines released by adipose tissue include interleukin-6 and tumor necrosis factor-α (TNF-α).[30] Inflammatory processes are observed both locally in adipose tissue (with macrophage infiltration and resistance to hormones such as leptin) and systemically in obesity, associated with elevated high-sensitivity C-reactive protein and proinflammatory markers plasminogen activator inhibitor 1 and fibrinogen.[19,27,30] Visceral and subcutaneous fat differ in their proinflammatory profiles, with higher levels of complement C3 expressed in VAT and higher levels of retinol-binding protein 4 expressed in SAT.[38]

Endoplasmic reticulum (ER) stress and mitochondrial dysfunction have a central role in determining the metabolic consequences of obesity.[39,40] The ER is a major site for protein folding and trafficking, and ER stress has been associated with the unfolded protein response, which intersects with inflammatory pathways and oxidative stress pathways, all of which can influence metabolism and impair glucose homeostasis.[39] Mitochondrial dysfunction, manifesting itself by decreased mitochondrial mass or function, is also one of the key mechanisms linking obesity to diabetes through decreased insulin sensitivity and compromised β-cell function.[40]

49.3.3 Susceptibility Genes for Obesity and Type 2 Diabetes

Obesity and type 2 diabetes are complex polygenic diseases, with disease susceptibility comprising environmental, lifestyle, endocrine, and genetic factors. The recent significant advances in the identification of common genetic variants contributing to disease susceptibility have shed light on the genetic basis of both obesity and type 2 diabetes.

49.3.3.1 Risk Variants for Obesity

The mechanisms that underlie the individual predisposition to obesity, and particularly to metabolically healthy versus unhealthy obesity, remain poorly understood.[41] Family-based linkage analyses and candidate gene studies were successful in identifying rare forms of early-onset childhood obesity including genes encoding leptin, the leptin receptor, and proopiomelanocortin.[42] Association analysis and resequencing of the gene encoding the melanocortin 4 receptor have identified low-frequency variants that explain approximately 2%–3% of cases of severe obesity.[43] Genome-wide association studies have identified approximately 30 common variants (single-nucleotide polymorphisms) influencing BMI and the risk of obesity, with the strongest signal arising from the fat mass and obesity-associated gene (*FTO*).[41,44–46] An additional 15 loci, which partly overlap with the previous loci, have been subsequently identified by case-control studies of persons representing extremes of BMI distribution.[47,48] In addition to general obesity, fat distribution and genetic determinants of visceral fat are of particular interest from the point of view of metabolically healthy versus unhealthy obesity. Fifteen distinct loci affecting fat distribution have been identified by genome-wide association analyses.[49–51] These studies demonstrate that loci for BMI and distribution of fat only partially overlap.[41]

49.3.3.2 Risk Variants for Type 2 Diabetes

Family-based linkage analyses and focused candidate gene studies have identified extreme forms of early-onset monogenic diabetes including maturity-onset diabetes of the young, mitochondrial diabetes with deafness, and neonatal diabetes. Candidate gene studies and genome-wide linkage scans have reported three common variants associated with risk of type 2 diabetes, peroxisome proliferator-activated receptor gamma, isoform 2 (*PPARG2*), potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11), and transcription factor 7-like 2 (*TCF7L2*).[52–52] Genome-wide association studies since 2007 have identified approximately 40 susceptibility variants for type 2 diabetes and confirmed previously identified variants.[55–62] Only a few of them are associated with impaired insulin action (*PPARG2*, insulin receptor substrate 1 [*IRS1*], and in some studies *TCF7L2*), while the majority of diabetes risk loci identified thus far are associated with impaired insulin secretion.[52,61,63,64]

There is only limited overlap between the risk variants for obesity and type 2 diabetes. The *FTO* gene increases the risk of type 2 diabetes not independently but secondarily through its effects on weight gain.[65] A variant in *IRS1* was initially identified as a diabetes susceptibility locus, but it has subsequently been found to affect primarily the amount of fat mass.[66]

Effect sizes of the known common genetic variants for type 2 diabetes and obesity are relatively modest and account for approximately 5%–10% of the susceptibility to type 2 diabetes and 1% to obesity. The strongest obesity variant in *FTO* alone accounts for 0.5% of the overall variance in BMI, equivalent to 2–3 kg of body weight.[45,55,56] Taken together, while evidence for genetic predisposition to both type 2 diabetes and obesity has been obtained especially in the past decade, the determinants of the susceptibility to metabolically unhealthy obesity remain poorly understood.

49.4 RISK OF TYPE 2 DIABETES IN METABOLICALLY HEALTHY AND UNHEALTHY INDIVIDUALS: EVIDENCE FROM PROSPECTIVE STUDIES

Only a limited number of prospective population-based studies have investigated the significance of metabolically unhealthy obesity on the future risk of type 2 diabetes and cardiovascular disease. In the Framingham Offspring Study, obese individuals (BMI $\geq$ 30 kg/m^2) with the metabolic syndrome (indicating unhealthy obesity) were at increased risk of incident type 2 diabetes compared to obese individuals without the metabolic syndrome during a 7-year follow-up (16% vs. 3%, respectively).[67] However, conflicting results have been obtained from studies comparing the risk of incident cardiovascular disease in metabolically healthy and unhealthy individuals.[67–69]

49.5 WEIGHT LOSS IN PREVENTION OF TYPE 2 DIABETES: TRIAL EVIDENCE

The strong etiological role of obesity in the development of acquired insulin resistance has put weight reduction in the forefront of diabetes prevention. Randomized controlled lifestyle intervention trials have, in the past decade, repeatedly shown that the progression of IGT to overt type 2 diabetes can be delayed or prevented by weight loss, achieved through dietary modifications and increased physical activity.[70–74] However, only limited data are available from these trials to compare the results between metabolically unhealthy and healthy participants.

49.5.1 Randomized Controlled Trials Targeting Diabetes Prevention

The Finnish Diabetes Prevention Study (DPS) included 522 Finns aged 40–64 years and at high risk for type 2 diabetes (IGT and BMI > 25 kg/m^2).[70] Multifactorial intervention (weight reduction $\geq$5%, moderate exercise for $\geq$30 minutes per day, and total fat intake <30% of energy consumed) resulted in greater reduction in weight (–3.5 vs. –0.9 kg in

3 years, $p < .001$) and central adiposity and greater improvement in glucose tolerance[75] and components of the metabolic syndrome.[76] Risk of diabetes was reduced by 58% in the intervention group compared to the control group,[70] and this difference persisted for at least 8 years after the trial.[77]

The Diabetes Prevention Program (DPP), a multicenter randomized clinical trial in the United States, evaluated the prevention of type 2 diabetes in 3234 individuals with IGT and fasting plasma glucose >5.5 mmol/L in three different treatment arms: lifestyle intervention, metformin, and placebo.[71] Lifestyle intervention targets included achieving and maintaining a 7% weight loss by healthy, low-calorie, low-fat diet, and moderate-intensity physical activity of ≥150 minutes per week. Identical to the DPS, the lifestyle intervention group had a 58% reduced risk of diabetes compared to placebo in the DPP, while metformin reduced the incidence by 31%.[71] Body weight at baseline and weight loss achieved by the intervention were the most important predictors of incident diabetes, with a 16% reduction in diabetes risk with each kilogram of weight lost.[78]

Significant reductions in the risk of type 2 diabetes by weight loss also have been reported in lifestyle intervention trials in Asia. In a Chinese study with a randomization by clinic design (diet alone, exercise alone, or combined diet and exercise intervention with 6-year follow-up, $N = 577$ with IGT), a reduction in the 6-year incidence of type 2 diabetes was observed in all three intervention groups compared to the control group (41%, 44%, and 46% vs. 68%).[73] The Indian DPP, a 30-month randomized controlled trial of 531 people with IGT and with a lower intensity of lifestyle intervention than in the DPP or DPS, achieved a 29% reduction in the incidence of diabetes with lifestyle modification advice compared to control.[72] The 4-year Japanese Prevention Trial of 458 Japanese men with IGT achieved a remarkable 67.4% reduction in the risk of diabetes in the intervention group with a positive correlation of diabetes incidence with body weight change in the control group.[74]

These trials offer compelling evidence for the reversibility of IGT by lifestyle intervention-induced weight loss. However, they included heterogeneous cohorts of overweight and obese individuals and did not differentiate between metabolically healthy and unhealthy individuals. The difference between healthy and unhealthy obese people in their metabolic response to lifestyle intervention is a key issue from the point of view of resources and choice of treatment.

49.5.2 Efficacy of Lifestyle Intervention in Metabolically Healthy and Unhealthy Obese Individuals

Comparison of the responses to weight loss in metabolically healthy obese individuals and insulin-resistant obese individuals has yielded conflicting results. Improvement in cardiometabolic health by weight loss in insulin-resistant obese people has been reported in some studies,[79–81] while other studies have reported that insulin sensitivity is also improved in metabolically healthy obese individuals in response to diet- or exercise-induced weight loss.[82] Metabolically unhealthy obese Korean women were reported to have significant benefits from weight loss based on favorable changes in blood lipids, C-reactive protein, and oxidized low-density lipoprotein after a 12-week caloric restriction; however, there was no measurable effect of weight loss on lipid profiles or inflammation in metabolically healthy obese women.[79]

The German Tübingen Lifestyle Intervention Program (TULIP), with intervention goals similar to those of the Finnish DPS and aiming for weight reduction of ≥5%, recently compared the effects of lifestyle intervention on the metabolism of insulin-resistant obese and metabolically healthy obese individuals ($N = 262$).[81] Reductions in visceral fat were observed in both the metabolically healthy and insulin-resistant groups during the follow-up, but total body and liver fat decreased only in the insulin-resistant group. Lifestyle intervention improved insulin sensitivity significantly in the insulin-resistant group but not in the healthy obese group. However, insulin sensitivity did not improve enough in the insulin-resistant group to provide adequate protection from type 2 diabetes.[81] This evidence indicates that lifestyle intervention may be more effective at improving insulin sensitivity in those who are insulin resistant and obese than in those who are metabolically healthy and obese. Both lifestyle intervention and pharmacological treatment may be required to adequately protect metabolically susceptible individuals from developing type 2 diabetes.[81]

49.5.3 Improvement of Insulin Sensitivity after Weight Loss

The impact of weight loss on the two main pathophysiological disturbances leading to type 2 diabetes—insulin secretion and insulin sensitivity—has been studied in short- and long-term studies.[83,84] Among individuals with type 2 diabetes, a degree of enhancement in insulin secretion has been observed after weight loss.[85] Weight loss and increased physical activity improve insulin action and attenuate hepatic glucose production.[83] Long-term data from the Finnish DPS suggest that improved insulin sensitivity is the key mechanism associated with weight loss–induced reduction in the risk of developing diabetes. In the DPS, the magnitude of weight loss was proportional to the improvement in insulin sensitivity[83] (Figure 49.4).

49.5.4 Weight Loss Achieved by Surgery and Glucose Homeostasis

Studies comparing bariatric surgery with lifestyle intervention-induced weight loss have demonstrated that bariatric surgery is the most effective treatment option for obesity and that it considerably attenuates hyperglycemia in individuals with type 2 diabetes.[86–89]

The Swedish Obese Subjects (SOS) Study, which is a large observational prospective trial including 4047 participants,

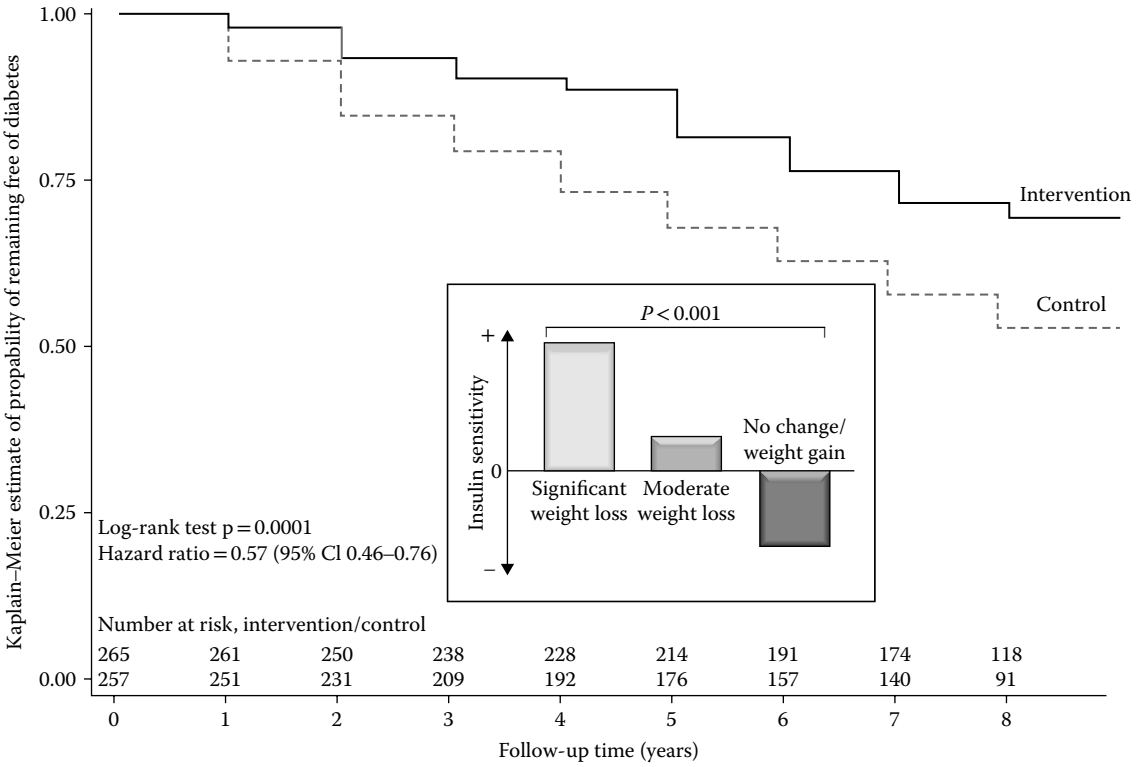

FIGURE 49.4 Effect of lifestyle intervention on the prevention of type 2 diabetes and insulin sensitivity in the Finnish Diabetes Prevention Study (DPS). (Modified from Lindström J et al., *Lancet*, 368, 1673–9, 2006; Uusitupa M et al., *Diabetes*, 52, 2532–8, 2003.)

reported that weight loss ranged from 21% to 38% (for adjustable gastric banding [AGB] and gastric bypass groups, respectively) at 1 year postoperatively and from 3% to 21% at 10 years.[86] In a meta-analysis, obese patients with type 2 diabetes lost from 26 kg (41% of excess weight) to 50.5 kg (66% of excess weight) with AGB and gastric bypass, respectively.[88] In several studies, the weight loss in patients with type 2 diabetes has been more modest than in nondiabetic patients, possibly attributable to the use of insulin and oral antidiabetic medication, which increase circulating insulin levels and enhance lipogenesis and muscle protein synthesis.[87–91]

A dramatic decrease in the incidence of new type 2 diabetes was observed in the SOS Study at 10-year follow-up in the surgery group as compared to the control group (incidence = 7% and 24%, respectively), with a relative risk reduction of 71%.[86] Significant improvement in glucose control and the "reversal" of type 2 diabetes also were reported postoperatively, marked by no further need for antidiabetic medication, in the SOS Study.[86] The reversal is largely dependent on the severity and duration of diabetes. The use of insulin treatment and high levels of hemoglobin A1c in diabetes with a long duration were negative predictors of diabetes remission.[92,93]

In a recent study, changes in glycemic control in metabolically healthy individuals were compared to those in insulin-resistant obese individuals after AGB during a 6-month postoperative follow-up.[94] Metabolically healthy obese and insulin-resistant obese patients had similar weight loss and reductions in BMI and waist circumference, and the changes in insulin sensitivity correlated with the changes in BMI.[94] Comparable improvement in fasting glucose and 2-hour plasma glucose levels occurred in both groups. Insulin sensitivity improved in both groups, but significantly more in the insulin-resistant group.[94]

The mechanisms associated with the improvement of glucose homeostasis after bariatric surgery are in part weight-independent, given the fact of a very rapid reversal of type 2 diabetes before significant weight loss in some cases. Caloric restriction is associated with decreased glycemic load and increased insulin sensitivity through a weight loss–associated decrease in hepatic fat and peripheral adipose tissue. A loss of adipose tissue mass is associated with increased levels of adiponectin and decreased levels of leptin, TNF-α, and interleukin-6.[89] Independent of weight loss, gastric bypass has been reported to affect the incretin system by increasing the levels of glucagon-like peptide 1, thereby stimulating endogenous insulin secretion from pancreatic β cells and also by decreasing ghrelin levels.[89] In addition, a decrease in the acylated form of ghrelin, a gut-brain peptide, attenuates appetite, thereby decreasing the calorie intake further.

Taken together, results from lifestyle intervention and bariatric surgery studies strongly suggest that obesity-associated insulin resistance is reversible by weight loss, at least in part. In most studies, metabolically unhealthy and insulin-resistant obese individuals have shown greater metabolic improvement in response to weight loss than metabolically healthy obese individuals.[6]

49.5.5 Gene–Lifestyle Interactions

The role of lifestyle in modifying genetic susceptibility for type 2 diabetes in high-risk individuals has been evaluated in the DPS, DPP, and some other intervention studies. In both the DPS and DPP, significant gene–lifestyle interactions were observed for variants in *PPARG2* and *TCF7L2* for weight loss and progression to type 2 diabetes.[95,96] In the DPS, increased susceptibility for type 2 diabetes in obese subjects with IGT who were carriers of the diabetogenic Pro12Pro allele of *PPARG2* was to some extent reversed by beneficial changes in diet and an increase in physical activity, possibly because of improved insulin sensitivity.[95] Similarly, in the DPP, the Ala12Ala carriers had the greatest degree of central obesity at baseline, but with lifestyle intervention, they lost the most weight, indicating a significant gene–lifestyle interaction with the Pro12Ala polymorphism of *PPARG2*.[97] In the DPP and TULIP studies, gene–lifestyle interactions for body composition changes were identified for variants of *PPARG* and *TCF7L2*.[96,98] These data suggest that the susceptibility to diabetogenic weight gain and unbeneficial body fat distribution conveyed by common genetic risk variants for type 2 diabetes is at least partly reversible by weight loss and an increase in physical activity, thereby reducing the risk of developing type 2 diabetes.

49.6 CONCLUDING REMARKS

Obesity is the most important risk factor for type 2 diabetes. Approximately 70%–80% of obese individuals have coexistent metabolic and/or cardiovascular disease, while 20%–30% are free of any apparent metabolic comorbidity. The link between obesity and impaired glucose homeostasis is complex. The site of fat deposition and type of adipose tissue and adipose cells, as well as the endocrine and proinflammatory properties of adipose tissue and cellular processes of ER stress and mitochondrial dysfunction, have been suggested to underlie the development of insulin resistance and type 2 diabetes in obesity. Lifestyle intervention trials and bariatric surgery offer compelling evidence for the reversibility of abnormal glucose tolerance by weight loss. Indeed, even genetic predisposition to type 2 diabetes can be overcome by favorable changes in lifestyle. Metabolically unhealthy and insulin-resistant patients have in most lifestyle intervention studies shown a greater improvement in insulin sensitivity than metabolically healthy obese individuals. Studies evaluating pathophysiological mechanisms behind metabolically unhealthy obesity and insulin resistance are likely to provide further insights into the complex link between obesity and type 2 diabetes.

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50 Obesity and Metabolic Syndrome

Jean-Pierre Després

CONTENTS

50.1 INTRODUCTION

In 1988, during the Banting Award lecture of the American Diabetes Association, Gerald Reaven made a landmark contribution not only to the field of endocrinology and metabolism but also to cardiovascular medicine when he introduced the notion of syndrome X.[1] Reaven made the point that there is a significant proportion of sedentary individuals who are characterized by insulin resistance and who are also at increased risk of cardiovascular disease (CVD) even if some of them never develop type 2 diabetes (T2DM). Thus, he proposed that beyond the well-recognized increased risk of T2DM associated with this condition, insulin resistance was also central to the development of abnormalities increasing the risk of CVD. As initial features of his metabolic syndrome X, Reaven made the link between insulin resistance and hypertriglyceridemia, low levels of high-density lipoprotein (HDL)-cholesterol, fasting hyperinsulinemia, and hypertension. Through a series of studies conducted over several decades he was able to document and expand the list of metabolic abnormalities associated with syndrome X, and they are presented in Table 50.1.[2,3]

After the introduction of Reaven's syndrome X, the point was made that there was another syndrome X documented in cardiology (angina with normal coronary arteries),[4–6] which led many groups to propose the term "insulin resistance syndrome" to avoid any confusion.[7,8] However, to properly acknowledge the seminal contribution of the father of this concept, we have suggested that this condition should be referred to as "Reaven's syndrome."[9]

As initially envisioned by Reaven, there is now considerable evidence that insulin resistance is a proatherogenic condition, and many prospective studies have indicated that the features of insulin resistance are associated with an increased risk of CVD.[10–12] For instance, we reported in 1996 that fasting hyperinsulinemia (as a crude marker of insulin resistance) was associated with an increased risk of coronary heart disease in initially asymptomatic and nondiabetic middle-aged men.[12] Several prospective studies that have assessed insulin resistance either by the presence of fasting hyperinsulinemia or by other indices of plasma glucose/insulin homeostasis such as the homeostasis model of assessment–insulin resistance have also reported that insulin resistance is associated with an increased risk of CVD.[12–17]

As Reaven could also detect the presence of insulin resistance in nonobese individuals (on the basis of body mass index [BMI] or total body fat content), he did not initially include obesity as one of the features of his syndrome X. However, studies initially conducted in the early 1980s[18–21] followed by a stream of metabolic and epidemiological investigations reported over the last 25 years[9,22–30] have indicated that obesity is a remarkably heterogeneous

TABLE 50.1
Metabolic Abnormalities Associated with Syndrome X as Described by Reaven

- Some degree of glucose intolerance
  - Impaired fasting glucose
  - Impaired glucose tolerance
- Dyslipidemia
  - ↑ Triglycerides
  - ↓ HDL-cholesterol
  - ↓ LDL particle diameter (small, dense LDL particles)
  - ↑ Postprandial accumulation of triglyceride-rich lipoproteins
- Endothelial dysfunction
  - ↑ Mononuclear cell adhesion
  - ↑ Plasma concentration of cellular adhesion molecules
  - ↑ Plasma concentration of asymmetric dimethylarginine
  - ↓ Endothelium-dependent vasodilatation
- Procoagulant factors
  - ↑ Plasminogen activator inhibitor-1
  - ↑ Fibrinogen
- Hemodynamic changes
  - ↑ Sympathetic nervous system activity
  - ↑ Renal sodium retention
- Markers of inflammation
  - ↑ C-reactive protein, white blood cell count, etc.
- Abnormal uric acid metabolism
  - ↑ Plasma uric acid concentration
  - ↓ Renal uric acid clearance
- Increased testosterone secretion (ovary)
- Sleep-disordered breathing

Source: Reaven GM, *Annu. Rev. Nutr.*, 25, 391–406, 2005. With permission.

condition and that not every obese patient is characterized by the metabolic abnormalities of insulin resistance, supporting Reaven's initial observations. Nevertheless, studies that have assessed regional body fat distribution using imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) have clearly shown that there is remarkable individual variation in the way we store energy in adipose tissue: some of us preferentially store fat in subcutaneous adipose depots and are less afflicted by the expected metabolic abnormalities of obesity, whereas others put on fat in intra-abdominal (visceral) adipose tissue and other nonsubcutaneous adipose depots.[9,22–30] Several cardiometabolic CT/MRI imaging studies have now clearly shown that it is the subgroup of overweight/obese individuals with high levels of intra-abdominal (also named visceral) adipose tissue who are characterized by the diabetogenic and atherogenic features of the insulin resistance syndrome. On this basis, although insulin resistance can indeed be found as a rare condition in lean individuals,[31,32] we have proposed that the most prevalent form of insulin resistance is observed among sedentary individuals with excess levels of visceral adipose tissue.[9,23,24] Several comprehensive review papers have been published over the last two decades on how body fat distribution is related to metabolic abnormalities and relevant clinical outcomes. As not to repeat extensive discussions on this topic here, the reader is referred to several reviews on this issue.[9,22–30] For the benefit of this chapter, which focuses on the metabolic syndrome, a very brief summary of some key/relevant notions are presented in Sections 50.2 to 50.7.

50.2 METABOLIC SYNDROME: FROM PATHOPHYSIOLOGY TO CLINICAL ASSESSMENT

Although we now have robust evidence that the constellation of metabolic abnormalities associated with insulin resistance increases the risk of developing several comorbidities, unfortunately, neither insulin resistance nor fasting insulin levels are measured on a routine basis in clinical practice. There is therefore a need to develop simple tools to screen for the presence of features of insulin resistance. It was with this objective in mind that the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) proposed five simple clinical criteria to diagnose a constellation of metabolic abnormalities that it called the metabolic syndrome (Table 50.2) and not the insulin resistance syndrome, as the proposed criteria did not include a direct measurement of insulin sensitivity/resistance.[33,34] On the basis of the link between abdominal obesity and insulin resistance (abdominal obesity being the most prevalent, albeit not exclusive, form of insulin resistance), the panel proposed the use of waist circumference rather than BMI as a screening tool for abdominal adiposity. As initially suggested by Reaven, it also included increased fasting triglyceride and reduced HDL-cholesterol levels, as well as elevated blood pressure, as clinical criteria. Finally, a moderately increased fasting glucose concentration was considered a very crude marker of impaired glucose homeostasis, probably revealing a state of insulin resistance. It is also important to point out that insulin resistance can sometimes be found among normotensive, normoglycemic individuals if they have abdominal obesity, elevated triglycerides, and low HDL-cholesterol concentrations. On this basis, the panel proposed that the presence of three out of the five simple criteria could be sufficient to diagnose the presence of the metabolic syndrome.

Since this initial publication, prospective studies and meta-analyses have indicated that individuals meeting the clinical criteria of the metabolic syndrome were about three to five times at greater risk of developing T2DM and about 1.5–2.0 times at greater risk of developing cardiovascular events.[35–37] The remarkable influence that the initial NCEP-ATP III position paper on metabolic syndrome has had in the biomedical literature is illustrated in Figure 50.1, which shows the progression of the number of papers published in English indexed by PubMed on a yearly basis using the search key words "metabolic syndrome."

TABLE 50.2
Criteria for Clinical Diagnosis of the Metabolic Syndrome

Measure[a]	Categorical Cut Points
Elevated waist circumference[b]	≥102 cm in men ≥88 cm in women
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator[c])	≥1.7 mmol/L
Reduced HDL-cholesterol (drug treatment for reduced HDL-cholesterol is an alternate indicator[c])	<1.0 mmol/L in men <1.3 mmol/L in women
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥5.6 mmol/L

Source: Grundy SM, *J. Am. Coll. Cardiol.*, 47, 1093–100, 2006.

[a] Any three of the five criteria constitute a diagnosis of the metabolic syndrome.

[b] It has been suggested that some U.S. adults of non-Asian origin (e.g., white, black, and Hispanic) with marginally increased waist circumference (e.g., 94–101 cm in men and 80–87 cm in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. A lower waist circumference cut point (e.g., ≥90 cm in men and ≥80 cm in women) may also be appropriate for Asian–Americans.

[c] The most commonly used drugs for elevated triglycerides and reduced HDL-cholesterol are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-cholesterol.

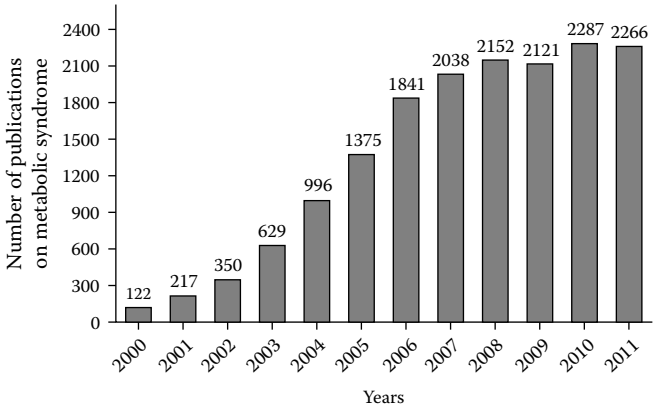


FIGURE 50.1 Number of papers published per year identified by a search in PubMed from years 2000 to 2011 using the key words "metabolic syndrome": only publications in English are illustrated in the bar chart.

50.3 METABOLIC SYNDROME: CONFUSING CLINICAL CRITERIA WITH PATHOLOGY

Since the introduction of the metabolic syndrome clinical criteria, considerable confusion has emerged around the use of this concept. First, many have referred to these criteria as the definition of the metabolic syndrome.[38,39] It is important, however, to point out that from a pathophysiological standpoint, the metabolic syndrome is generally defined as a constellation of atherothrombotic-inflammatory abnormalities for which insulin resistance is a central component.[40] Furthermore, this cluster of metabolic abnormalities is by far most frequently found among sedentary individuals who are abdominally obese.[40,41] Thus, the five clinical criteria initially proposed by NCEP-ATP III should not be referred to as the definition of the metabolic syndrome from a pathophysiological standpoint but rather as simple screening tools allowing its diagnosis in clinical practice.[9,23,24]

50.4 METABOLIC SYNDROME: STRENGTHS AND WEAKNESSES

The metabolic syndrome concept has its strengths and limitations, which have been previously discussed.[42] First, it is heterogeneous as various combinations of three out of the five criteria may define different phenotypes. Second, the severity of the metabolic syndrome is not assessed by current approaches; it is an "all or none" diagnosis. Therefore, we cannot use the presence/absence of the metabolic syndrome as a therapeutic end point. As a simple example, an individual meeting all five variables could improve on all criteria in response to whichever lifestyle modification program or therapy he/she wants to try, but if he or she still meets three out of the five criteria, he or she would nevertheless be considered as a nonresponder to treatment. This example clearly shows that the metabolic syndrome cannot be used as a therapeutic target and that changes in its individual components should rather be considered. Third, the metabolic syndrome cannot be used as a disease risk calculator. Better indices have been developed to estimate the risk of T2DM[43–45] or CVD.[46–50] For instance, for CVD the metabolic syndrome does not capture the risk associated with age, sex, low-density lipoprotein (LDL)-cholesterol, and smoking, which are key drivers of absolute CVD risk. Furthermore, some of the clinical criteria of the metabolic syndrome (blood pressure, HDL-cholesterol, diabetes, or glycemia) are already included in some risk calculators. On this basis, it has been argued that the metabolic syndrome is useless in CVD risk assessment and that such risk is driven by individual risk factors with no exacerbation of risk associated with their simultaneous presence.[38]

50.5 INTEGRATING METABOLIC SYNDROME IN GLOBAL CARDIOVASCULAR DISEASE RISK ASSESSMENT: THE NOTION OF CARDIOMETABOLIC RISK

As it became clear that the metabolic syndrome could not be used to assess global CVD risk, the next question to be asked was whether current risk assessment algorithms could capture the additional risk associated with the presence of the features of the metabolic syndrome and with insulin resistance. This issue remains very much debated today. We have suggested that the presence/absence of the metabolic syndrome could increase/decrease the level of risk predicted by the Framingham algorithm.[51] Paying attention to the presence of abdominal obesity and related features of the metabolic syndrome would particularly be relevant in subjects considered as having low or moderate risk on the basis of traditional algorithms. With the exception of individuals who are already considered to be at high risk by classical algorithms, it has been proposed that the presence of the metabolic syndrome could bring absolute CVD risk to the next category (from low to moderate or from moderate to high).[52] The global CVD risk associated with classical risk factors and the presence of abdominal obesity and features of the metabolic syndrome has been defined as "cardiometabolic risk."[24] Thus, under this model, cardiometabolic risk represents global CVD risk, which is hopefully better assessed by paying attention to abdominal obesity and simple markers of insulin resistance. However, as blood pressure and HDL-cholesterol levels are already considered by traditional approaches, an important question has been raised: what are the critical features of the metabolic syndrome that need to be added to traditional risk factors to improve CVD risk assessment? This issue is addressed in Section 50.11 of this chapter. Figure 50.2 shows that the notion of cardiometabolic risk has also been embraced by the medical community since its introduction in 2006 with a progressive increase in the number of publications (in English) identified on PubMed using the search key words "cardiometabolic risk."

50.6 DEBATING THE RELEVANCE OF ABDOMINAL OBESITY AS A KEY CRITERION FOR METABOLIC SYNDROME

In addition to the discussion on the metabolic syndrome's relevance in clinical practice, a source of heated debate has been the relevance of waist circumference as a mandatory criterion to diagnose the syndrome. After NCEP-ATP III, an International Diabetes Federation consensus group came up with essentially the same five criteria for the diagnosis of the metabolic syndrome with the exception that an elevated waist circumference (with cutoff values established on ethnicity) was mandatory for its diagnosis.[53] On the basis that many individuals with the metabolic syndrome had waist circumference values below the 102 cm and 88 cm cutoffs initially proposed for men and women, respectively, by NCEP-ATP III, it has been claimed by some that the metabolic syndrome can be observed even among lean individuals.[54,55] Although this is a valid point, the prevalence of lean individuals with the features of the metabolic syndrome remains poorly documented and appears to be very low.[54,56] When we examined this question in a representative sample of the adult population of Québec, Canada, we found that all possible combinations of the five criteria were associated with an elevated waist circumference (Figure 50.3).[54] Thus, in this study conducted in men, although values did not always reach the rather subjectively defined cutoff value of 102 cm, all individuals who were carriers of the criteria of the metabolic syndrome had markedly elevated waist circumference values compared to subjects not characterized by the syndrome (Figure 50.3). These results clearly indicate that the metabolic syndrome is infrequently observed among lean individuals and that some excess of abdominal fat accompanies this constellation of metabolic abnormalities. However, the cutoff values defining abdominal obesity have not been defined on solid scientific grounds, and further work in this area is clearly warranted. For instance, we have proposed that the 102 cm value in men was too high and that features of the metabolic syndrome

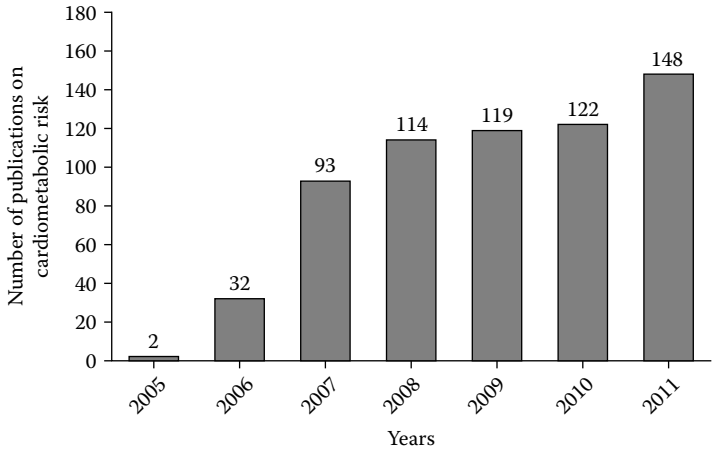
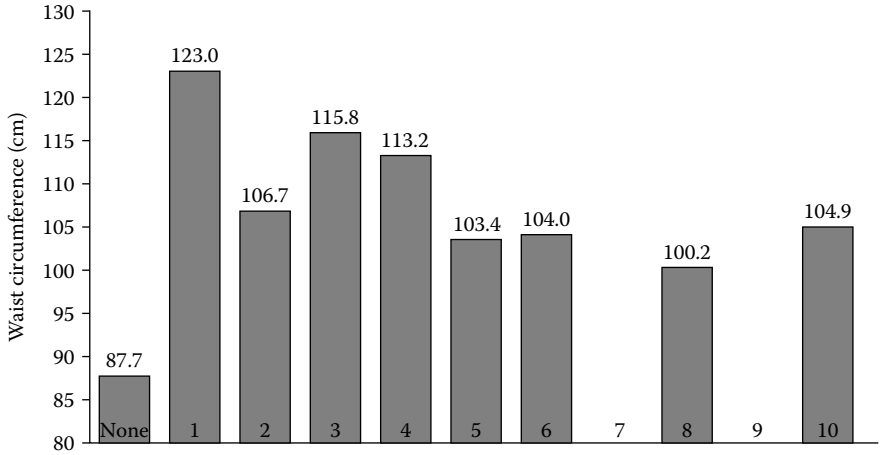


FIGURE 50.2 Number of papers published per year identified by a search in PubMed from years 2005 to 2011 using the key words "cardiometabolic risk": only publications in English are illustrated in the bar chart.



Clinical criteria	Possible combinations of 3 out of 5 clinical criteria									
Waist girth >102 cm	×	×	×	×		×	×			
Triglycerides ≥1.7 mmol/L		×		×	×	×		×		×
HDL-cholesterol <1.03 mmol/L	×		×	×	×			×	×	
Blood pressure ≥130/85 mm Hg			×			×	×	×	×	×
Fasting glucose ≥6.1 mmol/L	×	×			×		×		×	×

FIGURE 50.3 Waist circumference among men (n = 907) of the Québec Health Survey according to the different combinations of the National Cholesterol Education Program–Adult Treatment Panel III clinical criteria for the identification of the metabolic syndrome: none of the individuals were characterized by combinations 7 and 9. (Adapted from Després et al., *Eur. Heart J.*, 10, B24–33, 2008. With permission.)

could already develop at values above 90 cm in men and 85 cm in women.[51,57–59] Efforts have been made among the relevant societies to harmonize the criteria to diagnose the metabolic syndrome and the ethnicity-specific cutoff to define abdominal obesity.[60] More data are clearly needed here.

50.7 ABDOMINAL OBESITY AND METABOLIC SYNDROME: WHY?

Although the most prevalent form of the metabolic syndrome is found among sedentary individuals who have too much visceral adipose tissue, the reasons for this relationship are not fully understood and are still under investigation. Three nonexclusive scenarios have been proposed to explain this link (Figure 50.4).[9,24] First, it has been shown that visceral adipocytes have a lively lipolysis, which is resistant to the antilipolytic effect of insulin.[61,62] Thus, even in the presence of the well-documented hyperinsulinemic state of abdominal obesity, the unsuppressed lipolysis of the expanded visceral adipose tissue drains a flux of free fatty acids to the liver via the portal circulation, leading to impairments in hepatic metabolism including increased glucose production, increased secretion of triglyceride-rich very-low-density lipoprotein (VLDL), reduced apolipoprotein B degradation, and increased VLDL output, as well as decreased insulin extraction and degradation contributing to increased systemic insulin levels.[63] Thus, there is a rationale to explain the link between the expanded visceral adipose depot and some of the features of the insulin resistance syndrome. Elegant animal studies by Bergman and colleagues[64] have even suggested that the nocturnal rise in free fatty acid levels associated with excess visceral adiposity could be particularly detrimental to insulin resistance and related metabolic abnormalities. Although intuitively very appealing, this "portal free fatty acid hypothesis," first proposed by Björntorp,[65] has been debated as some investigators have documented that the majority of portal free fatty acids originate from nonportally drained subcutaneous adipose tissue.[66]

Second, another scenario to explain the visceral obesity–metabolic syndrome relationship is the remarkable endocrine function of adipose tissue.[67] When expanded, the enlarged visceral adipose depot made out of hypertrophied fat cells becomes infiltrated with inflammatory macrophages, which alter the secretory profile of adipose tissue with an increased secretion of inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α and reduced adiponectin production, to name only a few molecules from an expanding list of secretory products of the expanded visceral adipose tissue.[68–70] Under this model, the altered adipokine profile of patients with excess visceral adiposity could help explain their altered liver function, insulin resistance, and overall proinflammatory profile.

Finally, the third possibility does not exclude the two aforementioned scenarios: excess visceral adiposity may also be a marker of the relative inability of subcutaneous adipose tissue to store excess energy.[24,71,72] Under this model, when exposed to an energy surplus the individual who remains able to expand his or her adipose tissue stores should be able to channel the excess energy into the relatively abundant subcutaneous adipose tissue stores, through hyperplasia of adipocyte precursors (making new fat cells to store the energy excess). Although this process will lead to body fat gain, such

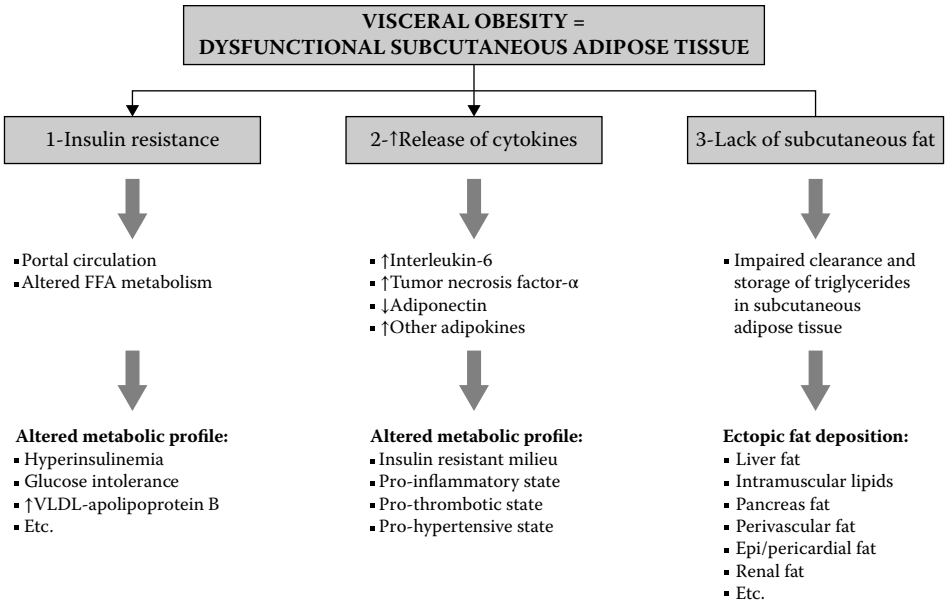


FIGURE 50.4 Proposed mechanisms by which visceral obesity could be linked to the atherothrombotic-inflammatory abnormalities of insulin resistance: excess visceral adiposity may also be a marker of the relative inability of subcutaneous adipose tissue to store excess energy, leading to fat deposition in undesired places (ectopic fat). FFA refers to free fatty acid.

an increase in subcutaneous adiposity will generally not be accompanied by major metabolic derangements. However, when facing the same energy surplus the individual who cannot expand his or her adipose tissue mass through hyperplasia will first accumulate energy through hypertrophy of adipose cells. As fat cell size expansion has limits, the storage capacity of adipose tissue will eventually reach saturation, leading to an energy spillover and to the accumulation of lipids at undesirable sites such as the liver, heart, muscle, pancreas, and kidney, a process referred to as ectopic fat deposition, which has been associated with insulin resistance and with the clustering abnormalities of the metabolic syndrome.[73,74]

50.8 ECTOPIC FAT DEPOTS: WHICH DOES WHAT?

With the development of noninvasive imaging techniques such as CT, MRI, and spectroscopy, it has been possible to accurately and reliably measure fat accumulation in organs other than adipose tissue such as the liver, heart, skeletal muscle, kidney, and pancreas. Reviewing the link between these various ectopic fat depots and features of insulin resistance is way beyond the scope of this chapter; suffice it to mention that all ectopic lipid depots are associated with various features of insulin resistance.[73,75,76] However, the respective and independent contributions of these ectopic fat depots to the development of a dysmetabolic state are much less clear. For instance, fairly strong correlations have been reported between the sizes of various ectopic fat depots (shared variance of ~25%–50%).[77,78] Thus, although considerable variation and sometimes discordance among individuals are observed in the volume of these various ectopic fat depots, subjects with increased visceral adiposity generally show evidence of overall ectopic fat deposition.[73] Clearly, because of its central role in lipid and carbohydrate metabolism, the liver is a key organ, and a fatty liver has been associated with hyperinsulinemia, hyperglycemia, elevated apolipoprotein B concentration, increased C-reactive protein levels, and hypertriglyceridemia.[79,80] Some investigators have even claimed that as we can find individuals with fatty livers but without visceral obesity who have the metabolic abnormalities of insulin resistance, liver fat rather than excess visceral adipose tissue is key in the etiology of insulin resistance.[81,82] However, as the most prevalent form of fatty liver is observed among viscerally obese individuals, one cannot exclude a role for expanded visceral adipose tissue (at least as a marker of dysfunctional subcutaneous adipose tissue). To clarify their respective roles, Britton and Fox[74] suggested that we could classify the various ectopic fat depots into those with systemic effects (visceral adipose tissue, liver, and skeletal muscle) and those more likely to have local effects (heart, kidney, pancreas, and perivascular adipose tissue). Extensive imaging studies are currently under way on large samples, which should help us better understand the respective roles of these ectopic fat depots as key players, partners in crime, or innocent bystanders. The latter possibility is a less likely scenario: it is more probable that some lipid depots have a greater influence than others depending on the metabolic variable considered, whereas some others may also contribute to the development of specific clinical outcomes. Such a proper, extensive mapping of ectopic fat depots is key to redefining what really is overweight/obesity as a condition associated with comorbidities.

50.9 LIVER: A KEY ECTOPIC FAT DEPOT

As mentioned in Section 50.8, the development of imaging technologies has allowed to estimate or even measure precisely liver fat content. Four large cohort studies, the Framingham Heart Study,[83] the Multi-Ethnic Study of Atherosclerosis,[84] the Dallas Heart Study,[85] and the International Study of Prediction

of Intra-Abdominal Adiposity and Its Relationships with Cardiometabolic Risk/Intra-Abdominal Adiposity (INSPIRE ME IAA) study,[86] are good examples of cardiometabolic/epidemiological research that has used imaging to either estimate liver fat from density using CT or to quantify liver fat content by magnetic resonance spectroscopy. All studies have shown that there is a strong correlation between visceral adiposity and liver fat content and that both adipose tissue/liver lipid depots are associated with features of the metabolic syndrome.[83–86] Men were found to have more liver and visceral fat than women and, as a consequence, were at greater risk for metabolic complications at a given level of total body fat.[87–89] Although some studies have suggested a greater role of either liver fat or visceral adipose tissue as drivers of cardiometabolic risk, the question remains very much debated and open. It is more likely that these two depots are key determinants/correlates of the systemic cardiometabolic risk profile, with the relative weight of the two variables depending on the variable/end point considered. Studies currently under way should clarify this issue.

50.10 EXCESS VISCERAL ADIPOSITY/LIVER FAT: A KEY DRIVER OF METABOLIC ABNORMALITIES IN METABOLIC SYNDROME AND IN TYPE 2 DIABETES

It is well known that obesity is a risk factor for the development of T2DM. However, not every obese patient will develop T2DM. It is now clear that a combination of insulin resistance and impaired β-cell insulin secretion is necessary to develop this metabolic disease.[90,91] Studies that have quantified visceral adiposity in these patients have clearly shown that for any given amount of total body fat, patients with T2DM have more visceral adipose tissue than nondiabetic individuals.[92,93] Furthermore, among patients with T2DM, variation in visceral adiposity was found to be a key correlate of the severity of the metabolic abnormalities found among these patients.[86,94] As there is a strong correlation between visceral adiposity and liver fat content in the general population, the finding that there is also a strong correlation between visceral adiposity and liver fat among patients with T2DM comes as no surprise. When a large cohort including nondiabetic individuals and diabetic patients were matched for visceral adiposity in the INSPIRE ME IAA study,[86] it was concluded that it is the variation in visceral adiposity and not the diabetes status by itself that is best correlated with the features of the metabolic syndrome (including triglyceride, HDL-cholesterol, and C-reactive protein levels). Liver fat content, estimated in INSPIRE ME IAA by the density of the liver, was more closely related to visceral adiposity than to the diabetes status.[86] Furthermore, prevalent CVD was entirely related to visceral adiposity and not to the diabetes status per se.[86] Finally, odds ratios for T2DM associated with 1 standard deviation increase in risk factors identified liver fat and visceral adiposity as predictors of diabetes, whereas subcutaneous adiposity measured by CT was not related to diabetes in men and even negatively related to diabetes in women.[86] These results clearly suggest that excess visceral adipose tissue and liver fat are key drivers of metabolic abnormalities and of cardiometabolic risk in T2DM, whereas subcutaneous adiposity appears to be neutral in men or even protective in women, a finding consistent with the protective "metabolic sink" hypothesis reviewed in Section 50.7 of this chapter.

50.11 HOW CAN WE FIND INDIVIDUALS WITH EXCESS VISCERAL/ECTOPIC FAT AND FEATURES OF METABOLIC SYNDROME? THE CASE FOR HYPERTRIGLYCERIDEMIC WAIST

We therefore now have substantial evidence that visceral adiposity and liver fat content are two important adipose tissue/ectopic fat depots associated with insulin resistance and features of the metabolic syndrome. More than 15 years ago, we proposed the use of waist circumference to discriminate, at a given BMI level, subjects more likely to have an excess of abdominal adipose tissue.[95] However, one key limitation of waist circumference is that it cannot distinguish abdominal subcutaneous from visceral adiposity. There was therefore a need to identify simple markers of excess visceral adiposity associated with a given waistline. In 2000, we proposed that the simultaneous elevation of waist circumference and of fasting triglyceride levels, a phenotype that we have described as "hypertriglyceridemic waist," was predictive of a very high probability (between 75% and 85% depending on the study/sample considered) of being characterized by excess visceral adiposity, insulin resistance, and features of the metabolic syndrome.[59] Since this original publication, many studies have documented the value of this simple screening procedure.[51] Again, it is very important to emphasize that hypertriglyceridemic waist cannot replace a direct measurement of insulin resistance or of visceral adiposity and liver fat content and that it should not be used as a diabetes or a CVD risk calculator. However, a large prospective study conducted in Norfolk County in the United Kingdom has shown that the presence of hypertriglyceridemic waist was not only associated with the features of the metabolic syndrome but also predictive of an increased risk of CVD in both men and women.[57] Thus, combining a simple tape measurement with the assessment and interpretation of a common blood marker, triglycerides, can be useful for the rapid screening of a subgroup of individuals at greater risk for excess visceral adiposity and liver fat, insulin resistance, and features of the metabolic syndrome.

50.12 MANAGEMENT OF METABOLIC SYNDROME: TARGETING LIFESTYLE, FITNESS, AND HYPERTRIGLYCERIDEMIC WAIST

A frequent critique addressed to the metabolic syndrome concept is that it has invented a new disease and created a new platform to justify pharmacotherapy in an expanding new subgroup of

asymptomatic patients. As a sedentary lifestyle and abdominal obesity are key underlying causes of the metabolic syndrome, it will never be emphasized enough that a clinical diagnosis of the metabolic syndrome should not necessarily first lead to pharmacotherapy. Rather, it should represent "a window of opportunity" for treating physicians and their patients diagnosed with this condition. Clearly, these patients would considerably benefit from regular physical activity/exercise, leading to an improvement in their cardiorespiratory fitness and a reduction in their waist circumference. In this regard, another subanalysis of the European Prospective Investigation of Cancer (EPIC)-Norfolk study has nicely shown that men and women with a diagnosis of the metabolic syndrome but who were physically very active were characterized by a coronary heart disease risk that was reduced by half compared to physically inactive metabolic syndrome individuals.[96] These results are consistent with the concept initially put forward by Blair and Church who showed that regular vigorous exercise could reduce the risk of chronic diseases including CVD and T2DM even among overweight/obese individuals, leading to the introduction of the "fat and fit" concept.[97,98]

In addition to the weight-independent benefits of regular vigorous exercise on cardiometabolic risk, there now is considerable evidence that regular endurance exercise can selectively mobilize visceral adipose tissue and liver fat (and possibly other ectopic fat depots even in the absence of major weight loss).[99,100] These results are consistent with our cross-sectional observations in which we reported that even among individuals perfectly matched for their BMI, physically fit subjects were characterized by lower levels of visceral adipose tissue and a more favorable cardiometabolic risk profile than BMI-matched but unfit individuals.[101] These results provide evidence that regular endurance exercise programs designed for individuals with insulin resistance and features of the metabolic syndrome should focus on the improvement of cardiorespiratory fitness and the reduction of visceral adipose tissue and ectopic fat (using waist circumference and triglycerides as crude markers) rather than solely on weight loss.[73] For instance, as sedentary individuals often have a reduced skeletal muscle mass it is not uncommon for sedentary, abdominally obese patients to gain muscle mass and lose visceral and ectopic fat with endurance exercise, sometimes leading to trivial changes in body weight.[99,100] Under these circumstances, a reduction in waist circumference and fasting triglyceride levels and an increase in cardiorespiratory fitness should be considered as relevant markers of the benefits of such lifestyle modification programs.[73]

50.13 LOW-FAT-DIET PARADOX

Finally, the nutritional management of patients with insulin resistance and the metabolic syndrome is a comprehensive topic and requires a full chapter to be adequately covered. The reader is therefore referred to comprehensive reviews on the topic.[102,103] In the context of this chapter, only one marker of nutritional quality will be highlighted as a simple nutritional target to improve the condition of abdominally obese patients with the metabolic syndrome: the role of added sugar.

Because of the focus on lowering cholesterol and LDL-cholesterol levels, cardiovascular medicine has emphasized for decades the reduction of saturated fat and total fat contents of the diet.[104] As a consequence, the industry has reacted by proposing to consumers numerous products with either a reduced fat content or no fat at all. However, to make these products palatable, fat has often been replaced by refined sugar or by refined flours/starches. Thus, as a consequence, consumers have been "educated" to pay attention to the fat content of a diet; but much less focus has been placed on the risk associated with the overconsumption of energy-dense, refined-carbohydrate-rich food products, contributing to obesity and the exacerbation of insulin resistance. More recently, the American Heart Association has recognized the limits of the "low-fat-diet" approach and has rather focused on a food-oriented dietary approach, which also proposed to pay attention to the added sugar content of the diet, particularly to the extra calories provided by sugar-sweetened beverages.[105] Indeed, overconsumption of sugar-sweetened beverages has been shown to contribute to the epidemic of obesity, metabolic syndrome, T2DM, and CVD.[106–108] In addition, because of the epidemic of hypertension and the high prevalence of this condition among patients with the metabolic syndrome, attention should also be given to the salt content of refined dietary products.[109,110]

In summary, there are simple lifestyle recommendations that can tremendously benefit abdominally obese patients with features of the metabolic syndrome. Increased participation in vigorous physical activities and regular endurance exercise are important elements of a lifestyle-modification program, which should also recommend prudent consumption of food products containing large quantities of refined sugar and salt.

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51 Obesity and Cancer
Clinical Epidemiology

Andrew G. Renehan

CONTENTS

51.1 INTRODUCTION

The hazards of obesity and tumor development were first noted by Hippocrates (460–370 BC), where in the "Father of Medicine" he characterized the crab-like structure of cancer and warned of the dangers of too much food.[1] In 1811, Robert Thomas hypothesized a link between obesity and endometrial cancer.[2] However, only in the past decade did it become widely accepted that increased body adiposity is a risk factor for cancer. Given the high prevalence of excess body weight in many populations, obesity-related cancer risk is an important public health problem in several countries.

The first half of this chapter summarizes the epidemiological evidence behind the associations between obesity and cancer risk and points out several emerging caveats in these associations, for example, effect modifications of other cancer risk factors such as hormonal replacement therapy (HRT) and smoking. The second half of this chapter will make the important distinction between types of studies evaluating obesity, cancer-related mortality, and survival, and emphasize potential biases and misinterpretations in these studies.

51.2 BODY MASS INDEX AND CANCER RISK

51.2.1 Evidence

A large volume of epidemiology demonstrates associations between body mass index (BMI), as an approximation of general adiposity, and increased risk in several cancer types. This was first established, in 2001, by the report from the International Agency for Research into Cancer (IARC).[3] The World Cancer Research Fund (WCRF)[4] extended these findings in their 2007 report, a large literature review of all study design types, which concluded that the evidence that body fatness is associated with increased risk of esophageal adenocarcinoma (EAC) and with cancers of the pancreas, colorectum, postmenopausal breast, endometrium, and kidney is "convincing" and that a "probable" association exists between body fatness and the risk of gallbladder cancer.

At the same time, the present author reported, in the *Lancet*,[5] a systematic review and dose–response meta-analysis of prospective observational studies only (221 datasets including 281,137 incident cases) quantifying associations with a 5 kg/m^2 BMI increase and risk of incident cancer for

20 cancer types. The summary of the risk estimates by gender is shown in Table 51.1. By using a standardized approach across a large number of cancer types and an updated literature search (to December 2007, capturing several studies from Asia–Pacific populations not included in previous meta-analyses),[5] the analysis convincingly demonstrated that associations

- Are sex specific (e.g., men >> women for colon cancer risk).
- Are site specific (e.g., colon >> rectal cancer).
- Exist for a wider range of malignancies than previously thought; "new" obesity-related cancers added to the list were thyroid cancer, malignant melanoma in men, multiple myeloma, leukemia, and non-Hodgkin lymphoma.
- Are broadly consistent across geographic populations, namely, North American, European and Australian, and Asia-Pacific populations.
- May be ranked per given change in BMI across the cancer types by gender.

Since that meta-analysis, there has been clarification on some associations and more obesity-related cancers have been added to the risk list. Thus, for example, there is no association between BMI and prostate cancer risk when taken as all prostate cancer occurrences,[5] but a recent dose–response meta-analysis elegantly showed that increased BMI is associated with more aggressive prostate cancer (P_{trend} = 0.001, relative risk [RR] = 1.09, 95% confidence interval [CI] = 1.02–1.16, for every 5 kg/m^2 increase in BMI, based on 13 cohort studies).[6] Analyses from the National Institutes of Health (NIH)–AARP Diet and Health Study reported a modest increased-risk BMI association for bladder cancer[7] and showed that increased BMI, particularly at an early age, might be associated with an increased risk of glioma,[8] an uncommon brain tumor. There is no association (and, indeed, there is a possible inverse association) between BMI and testicular cancer.[9]

51.2.2 Body Mass Index and Second Primaries

A small number of studies have investigated links between BMI and risk of second primary cancer incidence, particularly in women with breast cancer. A recent systematic review identified 13 prospective studies, and for every 5 kg/m^2 increase there were significant increased risks for contralateral breast cancer (RR = 1.12, 95% CI = 1.06–1.20), second primary breast cancer (RR = 1.14, 95% CI = 1.07–1.21), and endometrial second primary cancers (RR = 1.46, 95% CI = 1.17–1.83).[10] These risk estimates are very similar to those for BMI and primary cancer at these sites, suggesting that there are ongoing effects of the exposure (here, obesity) on cancer risk.

51.2.3 Body Mass Index and Cancer Risk–Effect Modifications

51.2.3.1 Hormone Replacement Therapy

As hyperestrogenemia secondary to increased aromatase activity in peripheral adipose tissue is relevant to the development of obesity-related postmenopausal breast cancer,[11] it is reasonable to hypothesize that HRT use may influence BMI–breast cancer associations. This hypothesis has been tested

TABLE 51.1
Sex-Specific Estimated Risk Ratios by Cancer Types

	Men		Women	
	n[a]	Risk Ratio (95% CIs)	*n*[a]	Risk Ratio (95% CIs)
Colorectal cancer				
Colon	22	1.24 (1.20 to 1.28)	19	1.09 (1.05 to 1.13)
Rectum	18	1.09 (1.06 to 1.12)	14	1.02 (1.00 to 1.05)
Gallbladder cancer		No association	2	1.59 (1.02 to 2.47)
Leukemia	7	1.08 (1.02 to 1.14)	7	1.17 (1.04 to 1.32)
Malignant melanoma	6	1.17 (1.05 to 1.30)		No association
Multiple myeloma	7	1.11 (1.05 to 1.18)	6	1.11 (1.07 to 1.15)
Non-Hodgkin lymphoma	6	1.06 (1.03 to 1.09)	7	1.07 (1.00 to 1.14)
Esophageal adenocarcinoma	5	1.52 (1.33 to 1.74)	3	1.51 (1.31 to 1.74)
Pancreatic cancer		No association	11	1.12 (1.02 to 1.22)
Renal cancer	11	1.24 (1.15 to 1.34)	12	1.34 (1.25 to 1.43)
Thyroid cancer	4	1.33 (1.04 to 1.70)	3	1.14 (1.06 to 1.23)
Prostate cancer	27	1.03 (1.00 to 1.07)		NA
Postmenopausal breast cancer		NA	31	1.12 (1.08 to 1.16)
Endometrial cancer		NA	19	1.59 (1.50 to 1.68)

Note: Risk estimates are per increase in 5 kg/m^2 BMI (body mass index). All risk estimates are taken from the *Lancet* meta-analysis[5]. Only risk estimates for cancer types with a significant positive association with BMI are shown. NA: not applicable.

[a] Number of prospective studies.

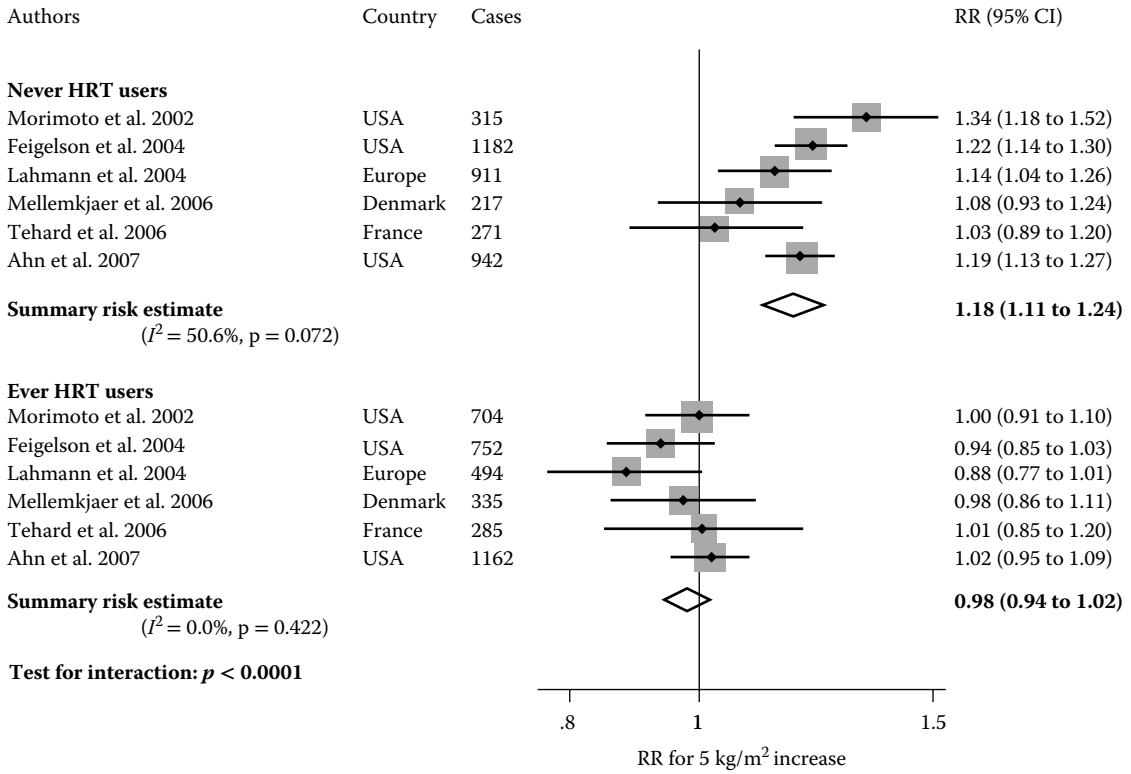

FIGURE 51.1 Forest plots of association between body mass index (BMI) and postmenopausal breast cancer stratified by hormonal replacement therapy (HRT) users: RR refers to risk ratio. I^2 is a test for between-study heterogeneity; 0% indicates no heterogeneity and 50.6% indicates moderate heterogeneity. Test for interaction was performed using metaregression.

in six cohort studies[12–17] in which risk estimates were reportedly stratified by HRT status. Figure 51.1 summarizes these studies and demonstrates that HRT is an effect modifier for associations between BMI and postmenopausal breast cancer, namely, risk estimates per 5 kg/m^2 increase are higher among never users compared with ever users of HRT (where associations are generally null).

Similarly, HRT use may influence the association between BMI and endometrial cancer risk. The author and coinvestigators[18] have previously addressed this question through meta-analysis, identifying four cohort studies reporting risk estimates stratified by HRT status. Findings similar to those for breast cancer emerged; the risk estimates per 5 kg/m^2 increase in BMI are higher among never users compared with ever users, but in this cancer type there is some residual risk in ever users.

For ovarian cancer, there is no association between BMI and cancer risk when all cases in cohort studies are taken together.[5] However, when stratified by HRT usage a different set of associations emerges. A large individual data–based analysis from 47 studies from the Collaborative Group on Epidemiological Studies of Ovarian Cancer reported that per 5 kg/m^2 increase in BMI the relative risk of ovarian cancer was 1.10 (95% CI = 1.07–1.13) in never users, but there was no association in ever users of HRT.[19]

The aforementioned observations may partly explain the higher point estimates per 5 kg/m^2 for risk of postmenopausal breast and ovarian cancers observed among cohorts from Asia–Pacific populations (areas of low HRT use) in our meta-analysis.[5]

51.2.3.2 Body Mass Index, Smoking, and Cancer Risk

In a *Lancet* meta-analysis,[5] the associations between BMI and risk were apparently inverse for two smoking-related cancers, namely, lung cancer and esophageal squamous cell carcinoma (ESCC), and for pancreatic cancer risk (another smoking-related malignancy) there were positive BMI associations in women but not men. These observations raised some questions, and recent studies are clarifying these interpretations.

When sex-specific risk estimates per 5 kg/m^2 (derived from the analysis in the study by Renehan and colleagues[5]) are plotted against the prevalence of smoking in the sex-specific populations of each study, a greater percentage of ever smoking was related to a more pronounced inverse association.[20] In the absence of smoking, the association between BMI and lung cancer was essentially null. Similar findings have also recently been reported from the NIH–AARP Diet and Cancer Study.[21]

When European Prospective Investigation into Cancer and nutrition investigators[22] examined the relationship between adiposity and esophageal cancer risk, recognizing two main histological types (ESCC and EAC), they found a strong association between BMI and EAC, which, in turn, was unaffected when the data were analyzed by smoking status. In sharp contrast, the association between BMI and ESCC, which was significantly inverse among smokers

(RR for uppermost versus lowermost quintile = 0.09, 95% CI: 0.03–0.29), was null among nonsmokers.

Recently, a pooled analysis of seven prospective studies on pancreatic cancer risk presented BMI data stratified by smoking status, finding that a 5 kg/m^2 increment was associated with an increased risk of pancreatic cancer among never and former smokers, but not among current smokers ($P_{\text{interaction}} = 0.08$).[23]

51.2.3.3 Body Mass Index, Prostate-Specific Antigen, and Prostate Cancer Risk

As noted in Section 52.2.1, there is a positive association between BMI and risk of aggressive/high-grade prostate cancer, but not for all cancers taken together. The proportion of aggressive prostate cancers in a population may reflect the level of prostate-specific antigen (PSA) screening, and hence it is reasonable to hypothesize that in populations in which the utilization of PSA screening is low, the proportion of aggressive tumors is higher and BMI associations (for all prostate cancers) are higher. Secondary analyses of the *Lancet* meta-analysis data suggest this is the case,[20] that is, there is an inverse relationship between level of PSA screening and association between BMI and prostate cancer risk (metaregression line, $p = .10$).

51.3 MEASURES OF ABDOMINAL OBESITY AND CANCER RISK

This is a research area that has not previously been comprehensively collated in the literature. The author and collaborators have recently undertaken a review of this field using the same standardized approaches that we used in the *Lancet* meta-analysis[5] to evaluate the associations between waist circumference (WC), waist–hip ratio (WHR), and cancer risk. These data are unpublished (available from the author). In men, per study standard deviation (SD) increase in WC was associated with colon (six studies: RR = 1.23) cancer and per study SD in WHR was associated with colon (three studies: RR = 1.20) and rectum (two studies: RR = 1.09) cancers. In women, associations per study SD increase in WC were recorded for colon (six studies: RR = 1.15), rectal (three studies: RR = 1.17), renal (two studies: RR = 1.21), pancreatic (four studies: RR = 1.15), postmenopausal breast (eight studies: RR = 1.10), and endometrial (five studies: RR = 1.34) cancers, and per study SD in WHR was associated with colon (five studies: RR = 1.12), rectal (two studies: RR = 1.08), renal (three studies: RR = 1.20), pancreatic (four studies: RR = 1.13), postmenopausal (eight studies: RR = 1.07), and endometrial (five studies: RR = 1.12) cancers.

In the aforementioned analyses, the summary estimates were standardized per study SD of a given anthropometric measure to allow comparability between anthropometric measures; using this approach, there appear to be no differences in the strengths of cancer associations by BMI, WC, or WHR.

51.4 CAUSAL ASSOCIATION AND ATTRIBUTABLE RISK

Although syntheses from others[4] and the author's meta-analysis[5] demonstrated associations between BMI and cancer risks, a key question (not least for the development of cancer prevention strategies) remains whether these associations are causally related. The author addressed this in a review testing the data from the *Lancet* systematic review against the nine Bradford Hill criteria[24,25] for judging causal association. The review[26] argued that the available data support strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence and analogy, suggesting that many of the observed associations are probably causal. The biological mechanisms linking obesity and cancer risk are reviewed elsewhere in the literature[11,27] and summarized in Table 51.2.

Additionally, recent studies with long-term follow-up of patients undergoing bariatric surgery for morbid obesity point to a reduction in cancer incidence (albeit this reduction seems limited to women) associated with sustained weight loss,[28,29] and, in turn, add further support to a causal association between obesity and cancer risk.

Given the likely causal association, it seems reasonable to ask the question what proportion of cancers in a population is attributable to excess body weight, as this, in turn, relates to the potential number of avoidable incident cancers. Using the summary risk estimates derived from the author's meta-analysis,[5] conservative population-attributable risks were estimated for incident cancers of 3.2% in men and 8.6% in women.[30] Across 30 European countries, this amounts to over 124,000 avoidable cancer cases per year.

Although traditional epidemiological methods assess causal associations using the Bradford Hill criteria, these approaches do not eliminate the potential of residual confounding. Mendelian randomization epidemiology offers an

TABLE 51.2
Hypothesized Mechanisms Linking Obesity and Cancer Risk

Most studied biological mechanisms
Insulin and insulin-like growth factors
Sex hormones and sex-steroid-binding globulin
Adipokines (e.g., adiponectin and leptin) and inflammatory cytokines
Other possible biological mechanisms
Altered immune response (e.g., omental invariant natural killer T cells)
Local stromal adipose cells and macrophage accumulation
Migrating adipose progenitors
Shared genetic susceptibility
Mechanical mechanisms
Hypertension and renal cancer
Acid reflux and EAC[a]
Increased iodine uptake and thyroid cancer

[a] See case study at the end of this chapter.

alternative approach and enables the estimation of causal relationships in observational studies using genetic variants as instrumental variables. Given the random assignment of alleles in gamete formation, the use of genetic variants offers an alternative method to control for confounding. The principles of Mendelian randomization are presented elsewhere in the literature.[31,32] The approach is a potentially powerful tool of causal inference and, in turn, directly informs biological mechanisms.

The relevance of Mendelian randomization to obesity and cancer risk has been studied; but to date analyses have generally been focused on one or two gene loci—for example, polymorphisms in the *CYP19A1* (encoding aromatase) gene, body weight, and endometrial cancer risk;[33] *CRP* (C-reactive protein, pentraxin-related) gene polymorphism interactions with BMI and endometrial cancer risk;[34] and the obesity-related genes *FTO* (fat mass and obesity associated) rs9939609 and *MC4R* (melanocortin 4 receptor) rs17782313 and endometrial cancer[35]; *FTO* rs9939609 and prostate cancer;[36] and *MC4R* and colorectal cancer[37]—and, in general, findings have been inconsistent. One exception has been a consortium analysis of *FTO* rs9939609 and three smoking-related cancers (lung, head and neck, and kidney), the results of which supported the inverse association of increased BMI with lung cancer.[38] With the identification of over 50 gene loci associated with the development of obesity through genome-wide association studies, there are now opportunities to scrutinize links between obesity-related polymorphisms and cancer development in more detail. Furthermore, of these obesity-related gene loci, there are approximately 15 that favor increased WHR over BMI. This will allow a further dimension of the study of the obesity–cancer link.[39,40]

51.5 OBESITY AND CANCER MORTALITY: STUDY TYPES

This chapter now turns to the question of obesity, cancer-related mortality, and survival. From the outset, a distinction must be made between two groups of mortality studies: (1) inception cohort studies that evaluate the effect of baseline measures of excess adiposity (BMI, WC, or WHR) and (2) cohorts of patients with a cancer diagnosis who also are obese (see Figure 51.2). The former are prospective cohorts or population-based studies in which measures of excess adiposity are determined at baseline and subsequent cancer-related mortality is reported (generally many years after follow-up). Thus, cancer death in these individuals is conditional on the occurrence of incident cancer prior to cancer death. The advantage of these studies is that mortality data are generally readily available and results are useful indicators of cancer burden in a population.

The second study type is associated with many different terms—treatment outcome studies; postdiagnosis survival (or prognostic) studies; or, as referred to by some epidemiologists, cancer case fatality studies. In the example of obesity as an exposure, these studies represent potentially modifiable risk factors and offer opportunities for interventions in the posttreatment patient survivorship program.

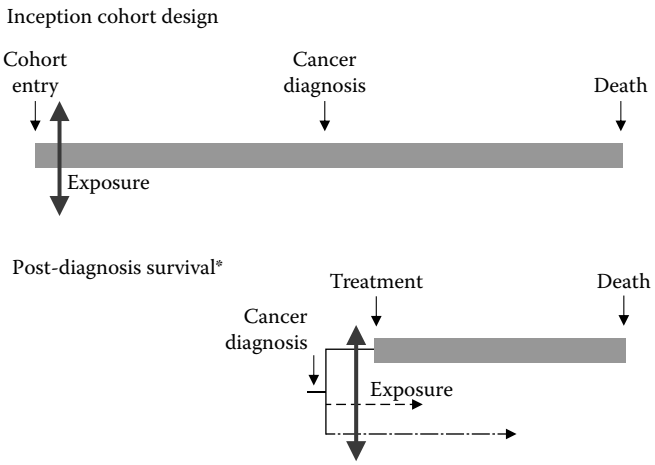

FIGURE 51.2 Schematic diagram distinguishing inception cohort studies from postdiagnosis survival studies: *The latter studies are also referred to as treatment outcome studies or case fatality studies. The upper panel demonstrates that the occurrence of cancer-related death is conditional on the earlier occurrence of incident cancer and, thus, cancer-related mortality and cancer incidence often parallel each other in these studies. The lower panel demonstrates that there can be selection processes after cancer diagnosis for treatment; this can be a major source of bias in postdiagnosis survival studies.

51.6 POPULATION-BASED COHORTS AND CANCER MORTALITY

The seminal work to this question of baseline BMI and cancer-related mortality was published in the *New England Journal of Medicine* in 2003.[41] Data from the prospective Cancer Prevention Study (900,000 U.S. adults: 404,576 men and 495,477 women) reported 57,145 deaths from cancer during 16 years of follow-up and showed that, in both men and women, BMI was significantly associated with higher rates of death due to cancer of the esophagus (distinction between ESCC and EAC was not made), colon and rectum, liver, gallbladder, pancreas, and kidney; non-Hodgkin lymphoma; and multiple myeloma. Significant trends of increasing risk with higher BMI values were observed for death from cancers of the stomach and prostate in men and for death from cancers of the breast (not classified by menopausal status), uterus, cervix, and ovary in women (findings that broadly deviate from the observations on cancer incidence).

Additional studies have confirmed these findings at cancer-specific sites—breast,[42–44] prostate (a dose–response meta-analysis including six inception cohorts; 6817 prostate cancer deaths occurred; a 5 kg/m^2 increase in BMI was associated with a 15% higher risk of dying from prostate cancer),[45] colon[44,46–49] (including Asia–Pacific populations[42,50]), endometrial,[44] renal,[44] pancreatic,[44] and liver[44,51] cancers.

51.7 OBESITY AND POSTDIAGNOSIS SURVIVAL STUDIES

Studies addressing disease recurrence and survival in patients diagnosed with cancer present many challenges. A recent Institute of Medicine workshop titled "The Role of Obesity

in Cancer Survival and Recurrence" recognized that "critical limitations of the extant research should be acknowledged."[52]

In parallel, the present authors and collaborators have developed a framework for evaluating the effect of obesity measures[53] and type 2 diabetes[54] on survival (and disease recurrence). The framework is based on the cancer patient pathway from initial diagnosis to the event of interest (death or recurrence). Eight steps are identified: step 1, delayed diagnosis (higher stage and/or more aggressive histopathology as best available surrogates); step 2, selection for initial treatment (surgery); step 3, perioperative mortality; step 4, selection for adjuvant therapy; step 5, early toxicity; step 6, altered treatment efficacy; step 7, late toxicity; and step 8, competing risks for death. An observational analysis within the context of a randomized trial reduces biases due to steps 1 and 2 (and possibly step 4) and frequently offers a more optimal setting to evaluate this research area.

Using the aforementioned framework, the author reviewed the evidence for associations between obesity, generally determined by BMI, and outcome after treatment in breast, prostate, colorectal, endometrial, and miscellaneous cancers. For each cancer type, it is imperative to consider the clinical setting, for example, postsurgical outcome, adjuvant therapy, and metastatic disease conditions. In turn, for each type there are different factors influencing survival, and obesity may have varying impacts on these.

51.7.1 Breast Cancer

Two recent meta-analyses[55,56] have evaluated the question of BMI at diagnosis and survival in women with breast cancer. Both analyses reached similar conclusions, as follows:

- Increased BMI is associated with poorer overall and breast cancer–specific survivals.
- Associations are similar for pre- and postmenopausal breast cancers (and thus contrast with associations between BMI and incident breast cancer menopausal types).

However, these meta-analyses have limitations as they draw on studies from diverse settings, treatments, and timings. One key limitation is the definitions of obese versus nonobese used across studies and, in particular, those of the nonobese referent category varied considerably. This definition is especially important given reports that the association of body size with breast cancer outcomes may be U or J shaped[57,58] (Figure 51.3a and b); thus, inclusion of either overweight (BMI $\geq$ 25 kg/m^2 and $<$ 30 kg/m^2) or underweight women (BMI $<$ 18.5 kg/m^2) in the nonobese referent category may bias the effect of obesity in both directions.

Two additional papers—one a large treatment cohort[59] and the other a population-based registry[60]—have emphasized that in women with early breast cancer (where long-term survival rates are high), the negative impact of increased BMI continues well beyond the 5-year survival landmark. The treatment cohort study reported by Goodwin and colleagues[59] also demonstrated that there is an increased risk of cancer recurrence and death for a BMI under 20 kg/m^2, which is not explained by the undiagnosed presence of metastases at time of diagnosis, as many women develop their recurrences late. These studies are unlikely to be confounded by differential presentation due to obesity, as adjustments have been made for tumor stage.

The meta-analysis by Protani and colleagues[56] also evaluated the effect of weight loss and concluded that "there is currently no evidence that weight loss after diagnosis improves survival." This question has been addressed in further detail using a pooled analysis of 12,915 women with breast cancer diagnosed between 1990 and 2006 with stage I–III tumors from four prospective cohorts in the United States and China.[61] The percentage of women who gained weight was 34.7%, and of these a weight gain $\geq$ 10% was associated with a nonsignificant increased risk of death. The percentage of women who lost weight was 14.7%, and of these a weight loss $\geq$ 10% was related to a 40% increased risk of death in the United States and over three times the risk of death in Shanghai, China.

A problem of interpretation in all these studies is the phenomenon of "capping"—chemotherapy underdosing in obese women due to toxicity-related concerns—resulting in poorer outcomes. Although capping body surface area to calculate chemotherapy doses has been common in the past,[62] there is evidence that obese women receiving standard doses of chemotherapy tolerate this therapy well[63] and indeed obese women may have fewer chemotherapy-related side effects.[64] Although chemotherapy underdosing may be a partial explanation for prognostic effects of obesity, it does not explain obesity effects in women not receiving chemotherapy.

Capping is not an issue for adjuvant hormonal therapies in breast cancer—two recent reports have examined the effects of obesity on the relative efficacy of aromatase inhibitors versus tamoxifen. For postmenopausal women, the Arimidex, Tamoxifen Alone, or in Combination trial reported that, overall, women with a BMI $>$ 35 kg/m^2 had more recurrences and more distant recurrences than those with a BMI $<$ 23 kg/m^2 (adjusted hazard ratio [HR] = 1.39 and HR = 1.46, respectively).[65] However, a higher BMI was associated with recurrence in women receiving anastrozole (HR = 1.53 for BMI $>$ 35 kg/m^2 vs. BMI $<$ 23 kg/m^2) but not in women receiving tamoxifen, and the interaction of BMI with treatment effect (anastrozole vs. tamoxifen) was significant (P = .04). For premenopausal women, the Austrian Breast Cancer Study[66] also found that overweight (vs. normal weight) was significantly associated with distant recurrence or death in those receiving anastrozole (HR = 1.53 and HR = 1.93, respectively) but null associations in those receiving tamoxifen. In the full study, anastrozole (vs. tamoxifen) was not associated with disease-free or overall survival; but for overweight and obese women, anastrozole was significantly less effective than tamoxifen in terms of overall survival (HR = 3.23), with a borderline effect for disease-free survival (HR = 1.47). One explanation for these observations is that aromatase suppression with standard-dose anastrozole was insufficient in obese women (with concomitant higher

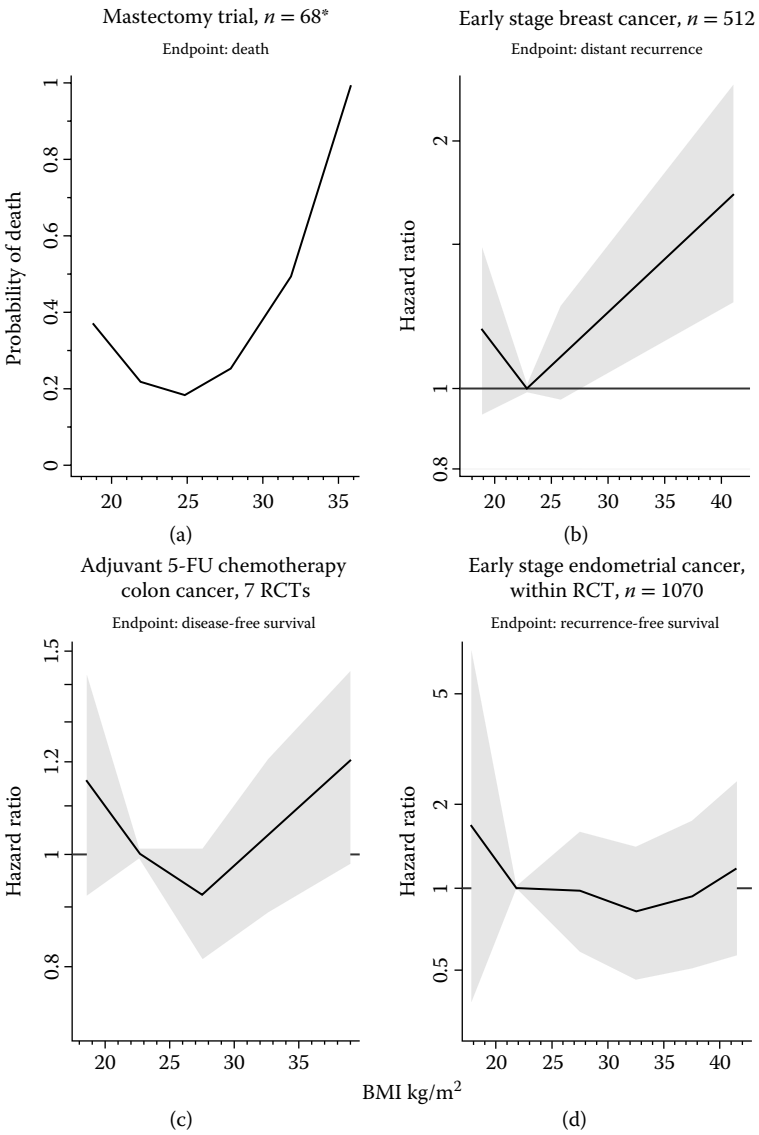

FIGURE 51.3 U- or J-shaped plots of relationships between body mass index (BMI) and risk of outcomes in breast, colon, and endometrial cancers: (a) data derived from Ref. 57, a mastectomy trial; (b) data from Ref. 58, a single-institute series of women with early breast cancer; (c) data from Ref. 77, a pooled analysis of individual patient data from seven trials of adjuvant 5-fluorouracil (5-FU) adjuvant chemotherapy in patients with stage II/III colon cancer; and (d) data from Ref. 53, from 1070 women undergoing surgery for early endometrial cancer within the Medical Research Council ASTEC trial. In the figure, *y*-axis scales are different. RCT refers to randomized controlled trial. *BMI values are estimated from reported Quarlet index.

residual estradiol levels). Supporting this hypothesis, a recent crossover study of anastrozole and letrozole (a more potent aromatase suppressor) in postmenopausal women with breast cancer, measuring plasma estradiol and estrone sulfate levels with a highly sensitive radioimmunoassay, showed that suppression of both estrogen types was correlated with BMI and was greater with letrozole across the full range of BMIs.[67]

51.7.2 Prostate Cancer

A recent dose–response meta-analysis[45] pointed to the emerging evidence that higher BMI values before or around the time of diagnosis of prostate cancer might increase the risk of biochemical recurrence (determined by PSA) and death in men with prostate cancer: a 5 kg/m^2 increase in BMI was associated with 21% increased risk of biochemical recurrence (16 studies: 26,479 prostate cancer patients followed after primary treatment) and 20% higher prostate cancer–specific mortality (six postdiagnosis survival studies: 18,203 patients with 932 prostate cancer deaths).

There are less data evaluating whether posttreatment weight gain impacts outcome, but one recent study in men who gained weight in the period from 5 years before to 1 year after prostatectomy showed a greater risk of recurrence of prostate cancer[68]; compared with men who had stable weight, those whose weight increased by more than 2.2 kg had twice the recurrence risk (HR = 1.94) after taking into account age, pathologic stage and grade, and other characteristics.

51.7.3 Colorectal Cancer

The impact of increased BMI, and other anthropometric measures, on postdiagnosis survival has been studied in several settings, including (1) analyses of cancer registry data, (2) reports of single-institution cohorts of patients undergoing surgical resection of primary tumors, (3) data from randomized adjuvant chemotherapy trials, (4) reports of single-institution cohorts of patients undergoing hepatic resection for colorectal liver metastases, and (5) the metastatic chemotherapy setting.

Data from cancer registries show no consistent association between postdiagnosis BMI and cancer-specific survival or overall survival.[49,69–71] One unique dataset from the Cancer Prevention Study II Nutrition Cohort,[49] which included pre- and postdiagnosis BMI, showed that survival is negatively impacted by prediagnosis BMI (consistent with inception cohorts) but not postdiagnosis BMI. Studies from single-institution cohorts of patients undergoing surgical resection for colorectal cancer varied by site; were small in sample size and subject to confounding (e.g., treatment selection bias); and, in general, offered no convincing evidence that increased BMI[72–75] or visceral adiposity measurements[76] are associated with poorer survival in this setting.

Several studies have examined the question of excess BMI and outcome in adjuvant chemotherapy trials of 5-fluorouracil–based regimens in patients with stage II/III colon cancer. Data from seven trials (4381 patients) have recently been pooled and reported by Sinicrope and colleagues.[77] Among colon cancer patients, 868 (20%) were obese (BMI $\geq$ 30 kg/m^2), of which 606 were class 1 (BMI = 30–34 kg/m^2) and 262 were classes 2 and 3 (BMI $\geq$ 35 kg/m^2). In the multivariate analysis, BMI was significantly associated with both disease-free survival ($P = .030$) and overall survival ($P = .0017$). Men with classes 2 and 3 obesity showed reduced overall survival compared with normal-weight men (HR = 1.35). However, across the BMI range there was a U-shaped relationship between BMI and disease-free survival (Figure 51.3c) and overall survival. BMI was not predictive of therapeutic benefit. One study, within an adjuvant radiotherapy trial for rectal cancer, reported no significant impact of BMI on overall survival[78] but did note (as earlier) that the relationship between hazard of death and BMI tends to be U shaped.

Two studies assessed the impact of obesity on oncological outcome following surgical resection of colorectal liver metastases: one paradoxically reported that median overall survival was 4 months longer in patients with a BMI $\geq$ 25 kg/m^2 compared to those with a BMI $<$ 25 kg/m^2;[79] and the second reported survival in terms of BMI and computed tomography–derived calculations of visceral and subcutaneous fat areas and found no impact on overall survival for either measure.[80] For patients with metastatic colorectal cancer undergoing conventional chemotherapy, BMI does not appear to influence disease-free survival or overall survival.[81] However, there is interest in potential interactions between BMI and anti-VEGF-targeted (VEGF refers to vascular endothelial growth factor) therapy (bevacizumab), with two studies suggesting that obesity is a predictor for bevacizumab-based therapy.[81,82]

51.7.4 Endometrial Cancer

A number of retrospective studies suggest that overweight and obesity may have no[83,84] or (paradoxically) a favorable[85–87] influence on cancer-specific survival. However, these studies have potential biases (as mentioned for breast cancer) due to the definition of normal BMI category being inclusive of patients who are underweight (reverse causality). In the setting of a randomized trial in early endometrial cancer (1070 patients), in which the treatment arms of surgery alone versus surgery and adjuvant radiotherapy showed equivalence, Crosbie and collaborators[53] showed that increasing BMI was associated with more favorable survival except for very obese women, again the relationship taking on a U shape (Figure 51.3d). These findings differ from the more consistent finding that obesity is an adverse prognosticator in breast cancer and demonstrate an important principle: an established link between an exposure and increased incident cancer risk does not necessarily translate into an inferior outcome following treatment for that cancer.

51.7.5 Other Cancers

Increasing numbers of studies in other cancer types have evaluated the associations between BMI and treatment outcome and found that increased BMI is not invariably an unfavorable prognosticator. Examples include cervical carcinoma (after excluding underweight, it is a poor prognosticator)[88] and thyroid[89] carcinoma. Indeed, a number of analyses from patients with early renal cell carcinoma report that being overweight and obese is associated with either no adverse effect[90] or a more favorable outcome[91–94] compared with normal weight. A recent meta-analysis of 24 studies addressing the impact on outcome of obese versus nonobese patients with ovarian cancer found only marginally poorer survival in obese women,[95] but as mentioned in earlier paragraphs the authors noted wide interstudy variation and potential biases due to between-study heterogeneity in definitions of nonobese.

51.8 CLINICAL IMPLICATIONS AND FUTURE

The evidence presented in this chapter shows that at least in some cancer types obesity in patients with cancer may be an unfavorable, though important, modifiable risk factor and that in many examples the relationship is complex and requires taking account of the full range of BMI (as shown in the plots in Figure 51.3). However, it is unclear whether reversing obesity effects through weight loss post diagnosis, or through pharmacologic manipulation of potential mediators, will be beneficial in patients. Nonetheless, the question should be viewed as a "testable hypothesis."[96] Current evidence is insufficient to allow obesity to guide chemotherapy and hormonal therapy selection.

In the future, there will be a need for more robustly designed analyses, along the lines of the framework described in Section 51.7. There is a need to continually reappraise the evidence and be open-minded to new findings and causal hypotheses (see the case study at end of this chapter).

This chapter demonstrates the established links between obesity and cancer risk. It equally emphasizes that there is no clear extrapolation of these observations to considerations of obesity and postdiagnosis outcome. This is an important principle: an established link between an exposure (here, obesity) and increased incident cancer risk does not necessarily translate into an inferior outcome following treatment for that cancer. A better understanding of associations between obesity and cancer and its outcomes will benefit many patients in the future.

51.9 SUMMARY

> There are known knowns; there are things we know that we know. There are known unknowns; that is to say there are things that we now know we don't know. But there are also unknown unknowns—there are things we do not know, we don't know.
>
> **U.S. Secretary of Defense Donald Rumsfeld, 2002**

A large volume of epidemiology demonstrates associations between BMI, as an approximation of general adiposity, and increased risk in several cancer types. We now know that these associations are significantly modified by other cancer risk factors, such as HRT in cancers of postmenopausal breast, endometrium, and ovaries, and by smoking in lung and pancreatic cancers and EAC. A smaller volume of epidemiology links measures of abdominal adiposity, namely, WC and WHR, with increased cancer risk. However, it is unknown whether these measures are more predictive or informative than BMI. For cancer mortality, a distinction is made between two study designs: (1) inception cohorts, evaluating the effect of baseline excess adiposity (long before cancer diagnosis) on cancer-related mortality, and (2) cancer patient cohorts, evaluating at-diagnosis adiposity measures and cancer outcome. By extrapolation from observations on incident cancer risk, we used to think that obesity at cancer diagnosis forecasts a poorer prognosis. But there are many inherent biases and misinterpretations from these postdiagnosis survival studies—the known unknowns. Consequently, at present it is unclear whether weight-reduction interventions in cancer patients are effective—the unknown unknowns.

CASE STUDY Breaking the Myth That Acid Reflux Links Obesity with Esophageal Adenocarcinoma

The conventional model of the etiology of EAC is one of a sequence of events beginning with the development of Barrett's esophagus in response to the chronic reflux of acid and bile, with progression from metaplasia through dysplasia to invasive adenocarcinoma. Increased BMI may be associated with increased prevalence of reflux and Barrett's esophagus and is a risk factor for EAC. It is tempting, therefore, to speculate that the BMI–acid reflux–cancer pathway is a major etiological mechanism for EAC. Moreover, the incidence of EAC has increased substantially in several Western populations in parallel with the rise in obesity prevalence over the past three decades.

However, there are a number of strong arguments that suggest this hypothesis is very unlikely: first, after adjustment for a history of acid reflux the associations between BMI and increased risk of EAC are unchanged.[97] Second, the absolute annual risk of transformation from Barrett's esophagus to EAC is considerably less than previously thought (0.12% rather than the assumed risk of 0.5%).[98] Third, in a recent modeling analysis using published risk estimates, only a small percentage of the rise in EAC incidence was attributed to secular trends in obesity.[99] It is more likely that EAC development involves a more complex mechanism, for example, one involving several molecular pathways (e.g., apoptosis genes: *FAS*, *FASLG*, *IL1B*, *TP53*, and *BAG6*) and interaction between chronic reflux, BMI, and smoking.[100]

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52 Inflammatory Causes of Obesity and Metabolic Diseases

Ebru Erbay and Gökhan S. Hotamışlıgil

CONTENTS

52.1 INTRODUCTION

The dramatic rise in obesity is unavoidably linked to globally changing social trends toward increased energy intake and reduced energy expenditure. With the rise in obesity, a cluster of pathologies including diabetes, atherosclerosis, steatohepatitis, hypertension, dyslipidemia, and some cancers, collectively known as the metabolic syndrome, has been climbing to disturbing proportions. The obesity-related disorders have become the leading public health challenge for not only the developed countries but also in the developing ones, and without sparing the children. Hence, the research efforts to identify the causative molecular mechanisms and effective therapeutic targets to combat this epidemic have gained great momentum in the last decade. Genetic studies that investigated the individual differences in predisposition to obesity and related disorders could identify a few obesity susceptibility genes in humans that in isolation could explain the disease phenotype. These studies clearly demonstrated that the genetic makeup of the host is an important parameter in the complex interactions between energy intake, expenditure, and deposition in fat stores that underlie weight gain. However, the phenotypic outcomes related to genetic variation with smaller effect size are a function of dynamic interactions between complex dietary input and bewildering arrays of microbes, the natural and diverse occupants of the gut, determining the metabolic health or disease of the host and contributing to the pathogenesis of obesity, insulin resistance, diabetes, and steatohepatitis. In this chapter, we present an overview of the complex molecular interactions that take place between the environment, diet, genetic, and microbial participants at the metabolic and immune interface to incite metaflammation, the low-grade, chronic, and metabolically driven inflammatory changes underlying chronic metabolic disorders associated with obesity.

52.2 OBESITY AND METABOLIC DISEASE: INTEGRATION OF THE HOST, PATHOGENS, AND DIET

Genetic studies in humans and experimental findings from mice suggest that satiety, energy intake, expenditure, and deposition are regulated by the integration of central nervous system and peripheral organs, particularly the hypothalamus and through the hypothalamic actions of factors derived from metabolic organs such as the adipose tissue. The outcome of the studies on family-based linkage analyses of monogenic (Mendelian) disorders (with severe and early-onset obesity) and common forms of population-based obesity studies links excess body weight and adiposity to an extreme tilting of an "adipostatic set point" at which body fat stores are normally stabilized.[1] For example, mutations associated with extreme and early-onset obesity were discovered in leptin (*LEP*), leptin receptor (*LEPR*), and melanocortin 4 receptor (*MC4R*) genes, all of which target the hypothalamic regulatory circuits.[2–5] Genome-wide population genetic studies contributed to the identification of additional mutations in genes that also target the central nervous system or other endocrine pathways, although the effect size in general is rather small.[6–10] While the majority of genetic studies support a strong genetic component, the target pathways remain to be established in obesity in concert with environmental influences and interactions between peripheral endocrine signals. There is yet a lack of evidence of significant associations between obesity and genetic variations related to intrinsic factors such as the basal metabolic rate, energy expenditure, or the drive to exercise.[10,11] These are important areas of current research efforts in experimental systems as well as in humans, and they indicate the power of the homeostatic drive to establish equilibrium, which is resistant to most single assaults.

The dietary components that give rise to obesity and associated metabolic pathologies are discussed in detail elsewhere in this book and hence not covered here. However, the critical contribution, as well as the complexity, of the diet needs to be emphasized here. In addition to the dietary input and the genetic contribution of the host, which is unequivocal, trillions of accompanying gut microbiota (with overwhelmingly more cells, genes, and metabolites than the host) participate in metabolic homeostasis, through their direct products or by modulation of the dietary environment. The present chapter discusses this aspect in further detail below. Hence, the metabolic health and disease in free-living humans, as well as in experimental models, are functions of the integration of three major components: diet, genetic variation, and microbiome.

52.3 EVOLUTIONARY CONNECTIONS BETWEEN METABOLISM AND IMMUNITY

Overwhelming evidence supports a close functional and molecular integration between metabolic and immune systems that is crucial for systemic homeostasis and whose deregulation is causally linked to obesity and associated diseases such as insulin resistance, diabetes, fatty liver disease, and atherosclerosis.[12–15] Evolutionarily, survival in the face of insufficient or irregular food supply and abundant new pathogens may have been the catalysis for the coevolution of nutrient- and pathogen-sensing and response systems. Integration of these systems may once have ensured energy efficiency and storage in preparation for times of food deprivation or fighting off infections. Indeed, mounting a potent immune response is energetically costly; fever, expansion of immune cells, and their recruitment, phagocytosis, and humoral responses can all place a large bioenergetic demand on the organism.[16,17] For example, sepsis increases the basal metabolic rate by 40%. The increases of 1°C in body temperature during fever requires around 10% caloric expansion.[18] On the contrary, malnutrition and starvation as well as obesity all severely impair the integrity and proper regulation of the immune response. In rodents, significant reductions in total energy depots compromise the humoral immune response. The induction of an immune response in starving insects reduces their survival. Also, biological processes like reproduction, lactation, and thermoregulation have to compete with immune defense, particularly in conditions of energy limitations or deficit. Taken together, the immune system cannot operate properly when an organism is deprived of nutrients and energy or fails to deploy energy in proper temporal and spatial order (Figure 52.1).

Modern human reality, however, is not only one of nutrient deficiency but also pertains to energy and nutrient excess as evidenced by the obesity pandemic. Many components of the immune system including macrophages, mast cells, and T-cell-mediated immune responses, as well as neutrophil and natural killer cell activities, are altered in the obese state.[19,20] The energy surplus in obesity is associated with impaired immune responses and drives a chronic, sterile inflammatory state referred to as metaflammation (referring to metabolically orchestrated chronic inflammation).[21] Metabolic

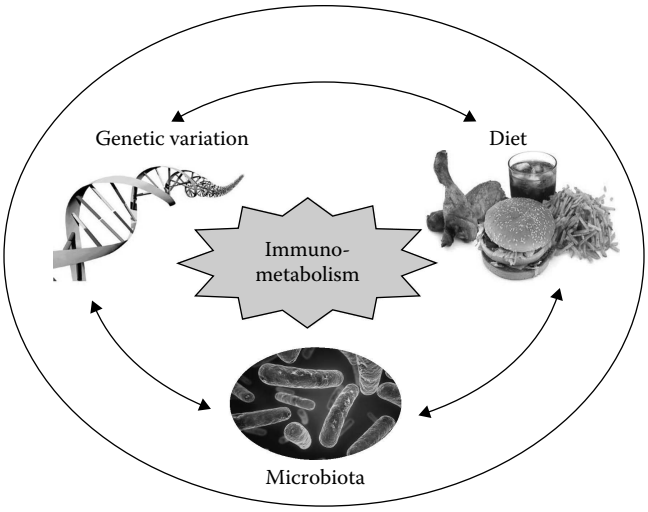

FIGURE 52.1 Immunometabolism—a network of complex interactions between metabolic and immune pathways in physiology and pathology. The complex molecular interactions that take place between genetic variation, diet and environment, and microbial occupants (of the gut) at the metabolic and immune interface incite metabolically driven, low-grade, chronic inflammatory changes named metaflammation underlying metabolic syndrome. This interface represents a rapidly growing field of research known as immunometabolism. The focus of immunometabolism research is on the close functional and molecular integration between metabolic and immune systems that is crucial for systemic homeostasis as well as these systems' deregulation that has been causally linked to obesity and associated diseases such as insulin resistance, diabetes, and fatty liver disease. The consideration of each component and their integrated output is necessary to link potential mechanisms with outcomes in a context-dependent manner.

inflammation is now recognized as a major underlying factor for reduced insulin sensitivity, abnormal glucose and lipid metabolism, and the development of type 2 diabetes and steatohepatitis, particularly, but not exclusively, in the context of obesity.[21,22] Historically, the earliest indication of the association between inflammation and insulin resistance goes back to the observations made in the late 1950s when an elusive "insulin antagonist" activity was described in the serum of a patient suffering from foot gangrene and infection; when this patient's serum was transferred to mice, it could antagonize the hypoglycemic effects of insulin.[23–25] In the 1980s, Feingold and Grunfeld demonstrated that infection or administration of tumor necrosis factor α (*TNF*α), a pro-inflammatory cytokine, caused dyslipidemia and metabolic abnormalities.[26,27] Bagby and Lang also demonstrated the impact of *TNF*α administration in inducing insulin resistance.[28,29]

The first evidence regarding the presence of inflammation in obesity and its contribution to the pathogenesis of insulin resistance and type 2 diabetes came in the early 1990s by the discovery of adipose tissue inflammatory changes associated with obesity in experimental models[30] and subsequently in humans.[31,32] Other studies showed that exposure to inflammatory cytokines in adipocytes or liver cells caused insulin resistance by blocking postinsulin receptor signaling.[33–35] Importantly, a large number of independent studies

demonstrated that insulin sensitivity could be improved in obese mice or rats by neutralization of *TNF*α using molecular or genetic approaches to block the function of this pathway.[30,36–43] Many more studies since have provided support that chronic inflammation in metabolic tissues plays a central role in the pathogenesis of insulin resistance, diabetes, steatohepatitis, and cardiovascular disease.[13–15,44,45] Important advances also came from understanding the immune components that contribute to metabolic inflammation (discussed later in Section 52.8 in further detail) and discovery of key signaling pathways that produce metaflammation.[13,15,46–49] Today, the studies starting with the obesity-induced adipose tissue inflammation have greatly expanded, leading to the establishment of the field of immunometabolism.

52.4 FEATURES AND MECHANISMS OF METABOLIC INFLAMMATION

It is critical to note that obesity leads to an aberrant form of immunity or metaflammation in a specific and unique energetic context; the inflammation in obesity occurs in the presence of excess nutrients and energy in metabolic tissues, predominantly the adipose tissue but also in many other critical organs such as liver, pancreas, and the central nervous system.[21,50] However, this inflammation does not feature an increase in energy expenditure or basal metabolic rate and raises the possibility that this may in fact have originated from an adaptive mechanism, perhaps under intermittent exposure to food, to prevent sustained insulin sensitivity, hence promotion of adipose expansion and obesity.[34] Many cytokines, including *TNF*α, interleukin-6 (IL-6), IL-1β, and monocyte chemoattractant protein-1 (MCP-1), are increasingly expressed and secreted from the adipose tissue of obese subjects as well as from other metabolic target cells and tissues.[51,52] Their local concentrations can be high with strong autocrine/paracrine influence (such as inhibiting insulin receptor signaling and recruitment and activation of immune cells), but their levels in systemic circulation remain low in comparison to classic inflammatory situations such as sepsis, infection, or trauma.[51] Furthermore, signaling pathways that may be responsible for the production of these cytokines, such as inhibitor of kappa B kinase (IKK), c-jun terminal kinase (JNK), and protein kinase RNA-activated (PKR) pathways, are also upregulated in the metabolic tissues in obesity, and their ablation through genetic or chemical approaches proved to be beneficial for insulin sensitivity or metabolic homeostasis in obese mice.[15,53–56] Unlike classic inflammation, obesity-induced metaflammation is uniquely characterized by energy conservation. Of note, blocking JNK, IKKε, and PKR derepresses energy expenditure while preventing the inflammatory responses, thereby generating the most consistent and substantial impact on systemic metabolic improvements.[53–55]

The intricate links between nutrient-sensing and pathogen-sensing systems have been weaved into the architecture of metabolic organs. For example, the fruit fly's fat body is a single organ that coordinates both the immune and metabolic responses.[57] Similar functional, temporal, and physical contiguity of energy and nutrient stores for normal function of immune cells can be found in higher organisms too. Metabolically active hepatocytes are found side by side with macrophage-like Kupffer cells in the liver.[21] The mesenteric adipose tissue is embedded with lymph nodes and harbors various immune effector cells. The activation of local immune response triggers selective lipolysis of the perinodal fat tissues, suggesting the purposeful colocalization of immune cells with energy stores in this example may be to meet the excessive energy demands of mounting an immune response.[58] While the interaction between resident immune cells and the stromal components is essential for tissue homeostasis in general, this kind of proximity to rich local energy sources can become particularly important during infection, coupled to suppression of appetite, weight loss, and the consequent systemic deficit in deliverable fuels.[20] Additionally, the perinodal adipose tissue has a high content of polyunsaturated fatty acids and could supply them to neighboring immune cells for the generation of lipid-based immune mediators such as prostaglandins and leukotrienes.[59] The intimate and dynamic relationship between immune cells and local energy depots could thus influence both the immune response and metabolism as is abundantly evident in chronic metabolic diseases such as obesity and diabetes. These intricate links also appear to be emphasized in some chronic inflammatory diseases, which are accompanied by adipose tissue remodeling such as the panniculitis associated with inflammatory bowel disease or the HIV-associated adipose tissue redistribution.[60,61] It is thus not surprising that metabolic abnormalities are also common in many chronic inflammatory diseases. For example, patients with psoriasis, a systemic autoimmune disease influencing the skin, or rheumatoid arthritis, an autoimmune disease mainly affecting the joints, carry markedly elevated risk of developing insulin resistance, diabetes, and atherosclerosis. There is also compelling emerging data that blocking inflammatory pathways, most efficiently by *TNF*α neutralization, can result in a marked reduction in the incidence of diabetes among subjects with psoriasis and rheumatoid arthritis.[62]

In addition to colocalizing anatomically, the genetic similarities and functional overlap that can be seen in metabolic and immune cells are striking and further accentuated with obesity. Despite originating from distinct lineages, macrophages and adipocytes resemble each other in relation to specific functions and genomic expression profiles. For example, preadipocytes, similar to macrophages, express nicotinamide adenine dinucleotide phosphate oxidase and can support phagocytosis.[63] Adipocytes express the pattern recognition receptors, toll-like receptor (TLR), PKR, inflammasome components, and T-cell receptors that can be activated by nutrients, pathogens, and lipopolysaccharide (LPS); activate inflammatory signaling cascades in a cell autonomous manner; and secrete various cytokines and chemokines when metabolically stressed and regulate the responses of immune cells.[64] The transdifferentiation of preadipocytes into macrophage-like cells has also been observed. Consistently, transcriptional profiling reveals a striking resemblance between preadipoctyes, adipocytes, and macrophages. The list of shared genes is further

increased when macrophages are transformed to lipid-laden, pro-atherogenic foam cells.[12,63,65] Similar to adipocytes, intestinal epithelium was also found to reactivate an ancient capacity to respond to pathogens. In a recent study, it was shown that intestinal epithelium upregulates its interferon-inducible immune response pathways at the expense of its metabolic functions when faced with microbiota under conditions when the adaptive immune system is impaired.[66]

On the contrary, immune cells also express metabolic programs and are equipped to actively monitor nutrients and energy sources to dictate the inflammatory capacity of the effector cells. For example, macrophages express the receptor for advanced glycation end products that recognize lipids and nucleic acids produced as a result of oxidative stress and hyperglycemia; activate lipid synthesis and storage programs through the activity of transcription factors like peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and sterol regulatory element-binding protein (SREBP); and generate lipid droplets as they transform to foam cells.[12,67] Furthermore, PPAR and LXR not only activate transcription of genes involved in lipogenesis, but they also limit inflammatory output.[68,69] PPARγ regulates the phenotypic switch between M1 and M2 in macrophages recruited to the adipose tissue in obesity. These studies also showed that PPARγ-induced M2 polarization is protective against insulin resistance in diet-induced obesity; mice with macrophage-specific deletion of PPARγ exhibit increased insulin resistance and obesity.[70] A recent study also demonstrated an immunoregulatory role for SREBP-1a through upregulating components of the inflammasome complex, further supporting the link between inflammation and lipid metabolism.[71] These observations underscore the coevolution of transcriptional networks to respond to a wide range of challenges from nutrient status to pathogens. Whether functional or genetic similarities exist between other metabolic cells and other immune effectors is not as well characterized. However, all immune cells rely on active metabolism in preparation for and during immune response. Glucose and lipids are important for fueling the proliferation of immune cells like lymphocytes.[72] In addition, glucose and lipids energize an immune attack by macrophages and neutrophils, particularly phagocytic activity, which consumes copious amounts of energy and requires a high rate of lipid turnover.[73] Lipids can also be important in the generation of lipid-based immune mediators secreted from these cells, and by altering membrane organization and domains, they can impair immune function.[74,75] Finally, lipids and other nutrients can serve as signals or even ligands to engage specific immune pathways.[12,54,76,77] In summary, the immune and the metabolic systems intercept at many levels, from molecules to cells to organs, and this can serve for the benefit or the detriment of the organism, depending on the context within which they interact.

52.5 ORIGINS OF INFLAMMATION IN OBESITY

The traditional initiators of inflammatory response are pathogens (such as microbes, viruses, and parasites) or tissue damage. These components engage inflammatory signaling pathways and induce a response that could contain the hazard and establish tissue homeostasis. The proximal mechanisms responsible for obesity- or high-fat diet-induced metaflammation leading to metabolic pathologies are not fully understood and remain an important area of research. Nutrients may initiate inflammation from within the metabolic cells (such as adipocytes, hepatocytes, myocytes, and pancreatic cells) or in immune cells (such as macrophages, mast cells, and lymphocytes) recruited to metabolic organs or both. One potential mechanism involves nutrients directly engaging inflammatory responses on the cell membrane through immune receptors. For instance, high concentrations of saturated fatty acids stimulate signaling through the TLR, a pattern recognition receptor pathway in adipocytes and macrophages. However, whether this is based on a direct interaction with the TLR receptor or indirectly through fatty acid metabolites like ceramide has not been determined.[78] Recently, a role for fetuin in lipid–ligand interaction with the TLR has been described, lending support to direct engagement of innate immune pathways by nutrients or some specialization for nutrients, however, distinguishing it from other signals.[76] Obesity, with high levels of saturated fatty acids, is associated with heightened TLR signaling, and the genetic ablation of TLR4 in mice was found protective against weight gain on chow diet.[79] Bone marrow transplantation chimeras for the *TLR4*$^{-/-}$ and the *Myd88*$^{-/-}$ genotype in mice display protection against insulin resistance on a high-fat diet.[80] Later studies presented a mixed picture, however, where either *TLR4*$^{-/-}$ on a different background or mice lacking the primary mediator of TLR and IL-1R, the myeloid differentiation primary response protein 88 (Myd88), were not protected against insulin resistance when compared to wild-type, control mice on a high-fat diet.[81–84] In light of recent findings, these conflicting results are likely because of the colonization of the gut microbiota that differs among facilities, handling, and specific diets, as directly demonstrated in a recent report.[85] In fact, divergent metabolic outcomes in animal models with single-gene or pathway modifications are not uncommon and most likely reflect the contribution of diet and microbiota to the impact of the underlying genetic manipulation. Further studies are needed to determine the contribution of specific pathways downstream of TLRs and other sensing and signaling molecules that are triggered by nutrients, how and which combination of these factors determines the outcomes.

In addition to membrane-based activation of inflammation, nutrients could engage inflammatory signal transduction pathways in metabolic and immune cells. For example, obesity leads to increased ceramide synthesis and production of reactive oxygen species (ROS) from the endoplasmic reticulum (ER) and the mitochondria. Both ceramide and ROS may activate the cytosolic inflammasome, a multiprotein complex that consists of nucleotide-binding domain (NOD)–, leucine-rich repeats–, and pyrin domain–containing family member protein, the adaptor molecule apoptosis-associated speck-like protein containing a caspase recruitment domain, and pro-caspase-1. This complex is

normally activated by pathogen-derived molecular patterns and cleaves pro-caspase 1, thereby activating it. The active caspase-1 then cleaves pro-IL-18 and pro-IL-1β.[86] Indeed, the activation of the inflammasome and elevated IL-1β levels are well documented in obesity in human and experimental models. Furthermore, genetic deficiency for caspase-1 and NLRP3 (and other inflammasomes including NOD1 and NOD2) improves systemic glucose homeostasis and insulin sensitivity.[87] Recently, a novel and critical role for the double-stranded RNA-dependent protein kinase (PKR) was defined in inflammasome activation.[88] Importantly, PKR deficiency in mice also leads to major metabolic phenotypes including protection against high-fat-diet-induced weight gain, inflammation, and insulin resistance and preservation of metabolic health in obesity.[54] The discovery of PKR's integral role in the inflammasome may provide an important advance in the understanding of coupling innate immune responses to metabolic stimulus and may lead to further understanding of the signals that initiate immune responses in a metabolic context and integrate insulin signaling, translational control, and immune response.

The integration between nutrients and inflammation may also potentially occur in the nucleus. Obesity is associated with an accelerated aging phenotype of the adipose tissue that impacts inflammation and insulin action. It was recently shown that cellular tumor antigen p53 is not only activated in response to shortening telomeres that happens during aging but also by excessive caloric intake and high-fat diet characterized by oxidative stress, senescence-like changes, and elevated p53 levels in the adipose tissue. Adipose tissue–specific p53 deficiency (*TRP53*$^{-/-}$) in mice protected against insulin resistance and adipose tissue inflammation induced by genetic or diet-induced obesity.[89] Overexpression of p53 in the adipose tissue resulted in inflammation and insulin resistance. Bone marrow transplantation from wild-type to adipose tissue–specific *TRP53*$^{-/-}$ mice partially improved insulin sensitivity, demonstrating the important contribution of macrophage p53 to systemic glucose homeostasis. The authors of this particular study showed that telomere shortening (that occurs in aging) is linked to metabolic deterioration; using telomerase-deficient mice, the authors demonstrated that increased DNA damage and senescence markers in the adipose tissue correlate with insulin resistance and inflammation.[89] These observations suggest that obesity-induced, aging-like changes in the adipose tissue are linked to inflammation, insulin resistance, and metabolic dysfunction through an important nuclear regulator of senescence, p53, and thus offer an additional mechanism by which metabolic derangements can trigger immune response, such as is the case in obesity.

52.6 IMPACT OF MICROBIOME ON SYSTEMIC METABOLISM

In recent years, a large body of evidence emerged demonstrating the critical importance of microbial communities in the regulation of systemic metabolism. The gut microbiota that play a critical role at the juncture of the environment and the host belong to four major bacterial phyla: the gram-negative Bacteroidetes and Proteobacteria and the gram-positive Actinobacteria and Firmicutes.[90] Early studies showed genetic obesity (in leptin-deficient mice) correlates with a reduced ratio of Bacteroidetes to Firmicutes.[91] Diet (high-fat and high-polysaccharide) generates a similar change that can be reversed with antibiotics or weight loss.[92] In most but not all human studies, a reduced Bacteroidetes/Firmicutes ratio in obesity has also been observed.[93–95] Some of the discrepancies may have been due to confounding factors such as varying diets, antibiotics usage, housing conditions, and environmental factors between the breeding facilities that could impact the initial colonization of the experimental groups as well as phenotypic outcomes.[85,96] Future studies based on the analysis of metagenomic-derived functional biomarkers rather than phylogenetic ones could help refine the data and define stronger associations with specific populations. What is consistent among the studies is that both diet, the primary nutritional source for the intestinal bacteria, and the genetic makeup of the host directly influence the microbial populations and their metabolic consequences, adding yet another level of complexity. In other words, in addition to the direct effects of diet and microbiota on their own, the energy extraction from the diet, as well as the byproducts of metabolism, could be influenced by the interactions between them. Remarkably, the metabolic phenotype associated with the microbiota could be transferred to germ-free mice in both genetic and diet-induced obesity.[92,97] Furthermore, a dietary shift from low to high fat swiftly altered the gut microbiota in humanized mice (colonized with human intestinal microbiota).[98] In the future, it may be possible to directly test the metabolic consequences of the disappearing human gut microbial complexity in mice by utilizing these humanized models. More studies in humans are also needed to determine the relevance to human disease of these conclusions derived from mouse studies.

How do the changes in the gut microbiota contribute to obesity and metabolic deterioration? Again, this paradigm is a prime example of the interactions between the genetic makeup of the host, diet, and the identity, composition, function, and output of the pathogen populations. For example, it is possible that certain microbial species are more efficient than others in extracting energy and contributing to weight gain.[97] The gut microbiota can convert nondigestible carbohydrates (fibers) into short-chain fatty acids (SCFA). These diet-derived SCFA products can be oxidized to provide energy for the host and delivered directly to the liver through the portal vein.[99] The increased flux of fatty acids could lead to steatohepatitis, followed by insulin resistance in the liver and gradual impairment of systemic glucose metabolism.[100] Whether these products are directly transported or need to interact with trafficking proteins is not known, and their exploration presents formidable experimental challenges.

In an alternative mechanism, high-fat diet and certain pathogens instigate inflammatory changes and epithelial dysfunction and thus elevate the overall permeability in

the gut. The resulting leakiness of the gut could lead to an increased delivery of gut microbiota or their metabolites to the mesenteric fat bordering on the gut.[101–103] What these microbial-derived factors are and which host metabolic targets they modify remain unanswered questions of profound interest. Recent studies elaborated angiopoietin-like protein 4 (Angptl4) as one host target, intestinal expression of which can be inhibited by the gut microbiota.[104] Angptl4 can increase plasma triglyceride levels by inhibiting lipoprotein lipase-mediated lipolysis of lipoproteins and consequent fatty acid mobilization toward adipose tissue.[105,106] Furthermore, hypothalamic actions of Anglpltl4 also suggests a potential role in central regulation of energy balance.[107] Another host target could be the endocannabinoid (EC) system engaged through LPS released by the gut microbiota.[103] A greater EC tone affected by the gut microbiota may negatively influence appetite, satiety, and adiposity.

Exposure to microbial products such as lipopolysaccharide, flagellin, or others can also engage innate immune response through the TLR or other sensing molecules. Because of inflammation and increased gut permeability, the bacterial flagellin can engage its specific TLR5 receptor on the basolateral surface of the gut epithelia to initiate an immune response against the pathogen, which is necessary for containment. Indeed, the TLR5-deficient (*TLR5*$^{-/-}$) mice displayed increased chronic inflammation, adiposity, insulin resistance, and hyperlipidemia, whereas antibiotic treatment could reduce the bacterial load and reverse the metabolic parameters to healthy levels. In this particular study, even the lean mice exhibited insulin resistance due to excess inflammatory responses in metabolic tissues.[108] Furthermore, both the gut microbiota and the associated metabolic dysfunction could be transferred from the *TLR5*$^{-/-}$ mice to germ-free, *TLR5*$^{+/+}$ mice.[108] The gut microbiota from the *TLR5*$^{-/-}$ mice differed in composition but not in the relative proportions between the major phyla.[108] However, these observations were recently challenged by another study, which did not observe inflammation of the gut or systemic metabolic dysfunction in two separate colonies of *TLR5*$^{-/-}$ mice. This latter study did confirm improper immune response to flagellated bacterial species.[109] These disparate results may have been because of the colonization of the gut microbiota that differs among facilities, handling, and specific diets and may illustrate the complexities of these experimental systems and their sensitivity to each component in place that can modify the phenotype. For example, earlier studies in germ-free mice showed that TRL2 deficiency (*TLR2*$^{-/-}$) is protective against insulin resistance and obesity. However, when grown in conventional facilities, these mice developed insulin resistance, metabolic dysfunction, and obesity. These changes in the metabolic phenotype of the *TLR2*$^{-/-}$ mice in conventional facilities accompanied changes in the gut microbial populations that resembled, at least in part, those found in obese mice and humans. In addition, the metabolic phenotype could be reversed by antibiotic treatment and transferred to wild-type mice with fecal transplant of the *TLR2*$^{-/-}$ mice's gut microbiota.[85] Collectively, these results underscore the metabolic impact of the gut microbiota that can override or modify the genetic preconditioning of an organism, at least under certain conditions, drawing attention to these interactions between dietary input and metabolic and immune responses that possibly underlie many conflicting phenotypic outcomes of similar genetic models in different studies.

Finally, the mesenteric fat, embedded with lymph nodes and in close contact with the resident immune cells and factors, is essentially an innate immune barrier and is capable of producing an inflammatory response to the incoming microbial challenge from the gut.[110] The proinflammatory cytokines, adipokines, and fatty acids released from the mesenteric fat could enter the liver through the portal vein and in turn destabilize hepatic metabolism. Consequently, steatosis and insulin resistance develop in the liver. Interestingly, the liver phenotype driven by dysbiosis, a microbial imbalance within the digestive tract, and inflammation appears to be heavily, if not completely, driven by *TNF*α action and could be rescued by blocking this pathway.[111] The development of extrahepatic insulin resistance and the growing metabolic pressure resulting from insulin resistance on the pancreas can bring about full-blown diabetes. What these microbial metabolites or factors are and their molecular targets responsible for this kind of a profound metabolic shift will become an important area for future research.

In conclusion, the three central factors contributing to the nutrient-driven metabolic and immune responses and the phenotypic outcomes include the genetic heritage of the host and genetic variation between subjects, host–pathogen interactions, and dietary exposure and diet composition (Figure 52.2).

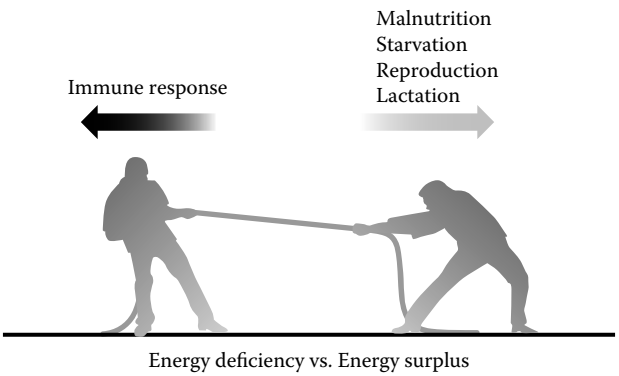

FIGURE 52.2 The competing functions of the organism at times of energy deficit and surplus. The mounting of a potent immune response is an energetically costly endeavor. Conditions such as malnutrition, reduction in energy depots, and starvation severely impair the immune system. Conditions of energy deficit lead to significant competition between immune defense and biological processes of central importance for the organism like reproduction, lactation, and thermoregulation. On the other side of the coin, the immune system is also not equipped to adapt to chronic energy surplus and associated molecular and cellular alterations, which cause it to exhibit malfunction. The best example for the latter is illustrated in obesity and associated metabolic inflammation setting the grounds for a cluster of metabolic diseases.

52.7 ORGANELLE FUNCTION IN INFLAMMATORY SIGNALING AND METABOLIC DETERIORATION

An important primer for metaflammation in obesity is the chronic metabolic overloading of anabolic and catabolic organelles leading to impairment of their function. One such organelle, the ER, serves as a critical intracellular metabolic hub for protein, lipid, and calcium metabolism and lipid droplet formation.[112] The vital functions of ER are maintained by a conserved, adaptive stress response that emanates from its membranes and is known as the unfolded protein response (UPR). Several diverse stimuli including accumulation of unfolded proteins, hypoxia, and toxins can induce the UPR.[113] UPR can also be triggered by acute or chronic excess of nutrients (including fatty acids and free cholesterol) or their deficiency (such as glucose). ER communicates its distress by engaging three signaling branches initiated by the pancreatic ER kinase (PERK), inositol-requiring transmembrane kinase/endonuclease 1 (IRE1), and activating transcription factor 6 (ATF6).[21,114,115] IRE1 possesses dual activity consisting of a kinase, which autophosphorylates itself, and an endoribonuclease, which leads to mRNA processing. The major target of the IRE1 endoribonuclease activity is an important transcriptional regulator of the UPR, the X-box-binding protein 1 (XBP1).[116–118] In synergy with IRE1, the ATF6 branch leads to transcriptional upregulation of XBP1 expression.[119] Together, XBP1 and ATF6 maintain a complex transcriptional program vital for the execution of UPR that involves upregulation of ER-resident chaperones to promote folding and components of the protein degradation apparatus.[113,115] If ER stress cannot be resolved, the UPR can engage apoptotic pathways and lead to cell death[48,120] (Figure 52.3).

The ER and the UPR play a significant role in both the physiological and pathological responses of immune cells. For example, some aspects of the UPR are important for the maturation of immune cells such as dendritic cells, lymphocytes, and plasma cells, XBP1 being a central regulator for the latter.[115] ER stress can impair adaptive immune responses

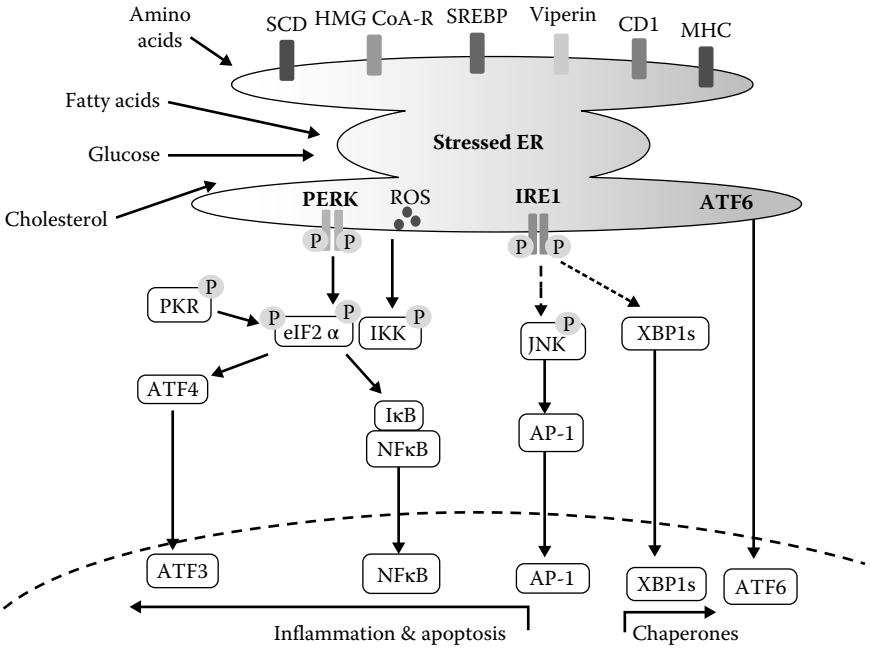

FIGURE 52.3 (See color insert.) The endoplasmic reticulum as a potential hub for metabolism, energy, immune, and stress responses. In addition to its well-known roles in protein quality control, folding, secretion, and calcium homeostasis, the endoplasmic reticulum (ER) also plays a critical role in lipid metabolism and lipid droplet formation through harboring central players such as the cholesterol-sensitive transcription factor sterol regulatory element-binding protein-1 (SREBP-1); the key regulating enzyme in cholesterol synthesis 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoAR); and in fatty acid desaturation through stearoyl CoA reductase (SCD) on its membranes. Studies have now shown that lipid droplets are released from specialized regions of the ER and regulated by proteins like viperin, also associated with ER membranes. Many links also exist between ER responses and glucose metabolism (not depicted here). These myriads of functions are maintained by an adaptive stress response system that emanates from ER membranes, known as the unfolded protein response (UPR). Various stressful situations including accumulation of unfolded proteins, hypoxia, toxins, and acute or chronic excess of nutrients (including fatty acids and free cholesterol) or their deficiency (such as glucose) can activate the UPR. Upon induction, the UPR engages three signaling branches initiated by the pancreatic ER kinase (PERK), inositol-requiring transmembrane kinase/endonuclease 1 (IRE1), and activating transcription factor 6 (ATF6). The major target of the IRE1 endoribonuclease activity is the X-box binding protein 1 (XBP1), which together with the ATF6 branch mounts a complex transcriptional program vital for the execution of UPR. The UPR can also engage inflammatory cascades such as JNK and the IKK–NF-κB pathway, leading to the production of cyclooxygeneases and other pro-inflammatory mediators. Induction of the double-stranded RNA-dependent protein kinase (PKR) can activate the inflammasome, leading to pro-inflammatory responses, and interfere with insulin action.

by reducing the processing and presentation of peptides by major histocompatibility complex (MHC)–associated antigen presentation.[121] Chronic ER stress, induced by overnutrition in obesity, for example, can also potentially serve as a primer for inflammatory and stress responses in both immune cells (such as macrophages) and metabolic cells (such as adipocytes or beta cells). During the course of obesity, unresolved stress in the ER can engage inflammatory response systems through several mechanisms. To begin with, the stressed ER and the mitochondria can produce significant amounts of ROS that can lead to oxidative damage.[122] ROS, whether originating from the mitochondria or the ER, has been shown to activate several stress and inflammatory pathways and contribute to the development of metabolic deterioration in obesity.[123,124] Regardless of the origin, in a chronic disease process, the stress can spread from one organelle to another through inter-organelle contact sites (such as the ER mitochondria encounter sites [or ERMES] found between the ER and the mitochondria), which can transmit vital information in the form of proteins or lipids or through the endomembrane system.[21,125] Thus, the ER and the mitochondria can have a strong impact on each other's function; however, it remains to be seen whether these interactions have any role in the functional deficiencies of these organelles seen in obesity and the metabolic pathologies.

Alternatively, the UPR can directly engage inflammatory cascades and stimulate cytokine production. For example, the IRE branch can stimulate JNK kinase activity, through its association with the adaptor protein *TNF* receptor–associated factor 2 (TRAF2), leading to production of pro-inflammatory gene expression by the transcription factor activator protein-1.[118] Active JNK1 can also phosphorylate the serine residues on IRS proteins and inhibit postinsulin receptor signaling. Consistent with these findings, JNK1-deficient mice exhibit reduced inflammatory cytokine levels and were protected from developing insulin resistance on a high-fat diet.[53] Inhibiting JNK by chemical or peptide inhibitors also improved insulin sensitivity in cultured cells such as macrophages, adipocytes, and whole animals.[126–130]

In another mechanism, IRE1 and PERK arms activate the IKK–nuclear factor-κB (NF-κB) pathway, leading to the production of cyclooxygenases and other pro-inflammatory mediators.[131,132] PERK activation has been associated with the degradation of IκB and nuclear transport of NF-κB. On the other hand, IRE1 activates IκB-kinaseβ [IκKβ] indirectly, through association with TRAF2. Signals through TLR2 and TLR4, but not intracellular TLRs, were recently shown to activate IRE1, through TRAF6, to induce XBP1 processing and the secretion of pro-inflammatory cytokines such as IL-6, *TNF*α, and interferon-β.[133] This study and an earlier one also showed that spliced XBP1 could bind the promoter of *TNF*α and inducible nitric oxide synthase (*iNOS)* genes, implicating XBP1 in the regulation of these pro-inflammatory cytokines.[133,134] However, clear mechanistic links between inflammatory pathways and UPR remain to be established in metabolic diseases. Recently, obesity was found to be associated with the activation of an important pathogen sensor, the double-stranded RNA-dependent protein kinase (PKR), in concert with the induction of UPR in metabolic tissues. PKR can be responsive to ER stress, but the mechanisms of its activation remain unclear. PKR deficiency in mice that fed a high-fat diet is protective against weight gain, metabolic deterioration, and insulin resistance. Lipid-induced insulin resistance also requires PKR, both in vitro and in vivo, and PKR interacts with and leads to IRS1 phosphorylation.[54] PKR can interact with and modulate the inflammasome activation and potentially contribute to inflammasome-mediated metabolic deterioration. Moreover, recent studies point out regulation of the inflammasome by a proximal ER stress sensor, IRE1 itself.[135] Collectively, these studies emphasize the integral role played by the ER in connecting the pathogen-sensing, inflammatory, and metabolic systems.[54]

The UPR is highly receptive of the nutrient status of cells. Historically, the deletion of yeast IRE1 is associated with auxotrophy for inositol.[113] Another set of UPR proteins, namely, the glucose-regulated proteins, were discovered by their induction in glucose-deprived conditions, a first implication of the nutrient-sensing function of the ER.[136] Either lowering or increasing glucose levels can activate the UPR. The PERK arm plays an important role in systemic glucose homeostasis, particularly through its actions in the liver and pancreas.[137,138] Glucose acutely regulates IRE1 activity, and when this becomes chronic, IRE1 can impinge on inflammatory cascades mediated by JNK or IKK.[113] UPR-induced transcriptional programs are also directly linked to glucose synthesis and breakdown.[139] Moreover, the ER assumes a central role in the synthesis of phospholipids and cholesterol. The UPR contributes to the lipogenic program, for example, through the activities of ATF6 and XBP1, although a great deal of uncertainty exists among reported phenotypes of the genetic mouse models with respect to lipid metabolism.[140,141] An essential sensor for intracellular cholesterol levels, the SREBP, is situated on the ER membrane.[113] Cholesterol deprivation activates this transcription factor, which upregulates key enzymes in the cholesterol synthetic pathway. Furthermore, elevated free cholesterol or free fatty acids induce ER stress and initiate all three arms of the UPR, but the molecular mechanisms for how the ER senses these changes remain unclear.[142,143]

In obesity or dyslipidemic conditions, exposure to high levels of nutrients such as saturated fatty acids and free cholesterol leads to ER stress and activation of the UPR in several metabolically active sites including the liver, hypothalamus, atherosclerotic plaque, and adipose tissue.[144] Recent studies have elaborated the causal role of ER stress in the liver and adipose tissues to the development of systemic insulin resistance and type 2 diabetes. A genetic haploinsufficiency model for the *Xbp1* gene in mice leads to elevated ER stress levels and promotes glucose intolerance, insulin resistance, and obesity. In contrast, treating obese mice with chemical chaperones has been shown to release ER stress and improve all of these metabolic parameters.[145,146] Moreover, prolonged ER stress can spur a homeostatic mechanism called autophagy to recycle damaged cellular components and organelles. In recent studies, the failure of autophagy by

genetically altering master regulators of this mechanism in obese or atherosclerotic mouse models was associated with increased inflammation, insulin resistance, and lesion progress, respectively.[147–149] Recently, autophagy was also linked to the metabolic benefits of exercise, particularly on insulin action, providing an additional layer of integration between this response and metabolic homeostasis.[150]

How do nutrients stress the ER in the first place? Recently, the metabolically stressed ERs from obese mice were carefully examined to understand the mechanisms of nutrient-induced ER stress. These studies showed that in the stressed ER from obese mice, when compared to control nonobese groups, protein synthesis is suppressed and chaperone content is not significantly changed. However, the metabolically stressed organelle exhibits prolific lipid synthetic capacity, and the specific alterations in ER lipid composition are associated with the inhibition of sarco/ER ATPase (SERCA) activity. Furthermore, reversing the lipid compositional changes or hepatic overexpression of SERCA resolved ER stress in vivo and improved glucose homeostasis and insulin sensitivity in mice.[151,152] In a recent study coupling polysome profiling to microarray analyses, the mammalian translatome was recaptured in vivo. This study showed the steady-state liver translational profile from an obese animal represented a fasting profile of liver from lean animals, suggesting the liver may become insensitive to the excessive flux of nutrients during obesity. The liver, in particular, also displays aberrations in alternative pathways of bile acid metabolism. Both the liver and the muscle profiles also emphasize mitochondrial defects. These findings suggest that translational dysfunction is another important aspect of obesity that may contribute to the associated metabolic dysregulation.[153]

Several studies elaborated on the mechanisms of ER stress-induced insulin resistance and weight gain. For example, the IRE1 arm of the UPR can inhibit insulin receptor signaling through activating JNK1, which then phosphorylates serine residues on IRS1.[145] JNK can also be activated through PKR and calcium/calmodulin-dependent kinase signaling, each of which has been shown to disrupt metabolism and insulin signaling.[154] Another mechanism has been proposed where XBP1 interacts with forkhead box protein O1, leading to its proteosomal targeting and degradation.[155] ER stress can also lead to leptin resistance in the hypothalamus that is associated with increased weight gain in mice on a high-fat diet, which can be reversed by the administration of chemical chaperones.[156] These findings highlight ER's important position as an interface between metabolism and immunity whose dysfunction plays a causal role in the development of obesity and chronic metabolic disease.[145,157–159] In summary, organelle stress and inflammation both contribute to the development of obesity-associated insulin resistance and atherosclerosis. However, it remains to be determined which is the preceding factor and how the metabolic consequences are determined through each of these potential mechanisms. Furthermore, a critical remaining question is whether inflammation itself can be proximal to disruption of ER function or its adaptive capacity and if so, in what capacity? Future studies chemically or genetically targeting intermediate genes in both UPR and inflammatory pathways should be instrumental in delineating the order of events and their isolated or combined effects. Regardless, therapeutic targeting of organelle dysfunction offers potential new opportunities for the management of chronic metabolic diseases and rare genetic diseases that display defective ER function and diabetes, such as the Wolfram syndrome (also called DIDMOAD; Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness) and the Wolcott–Rallison syndrome (WRS).[160,161] The Wolfram syndrome occurs because of a rare mutation leading to defective wolframin gene, ER function, and insulin secretion. The WRS is a rare autosomal recessive disease characterized by neonatal/early-onset, nonautoimmune, insulin-requiring diabetes associated with skeletal dysplasia and growth retardation, and it is caused by mutations in the *PERK gene*. Two chemical chaperones that are known for their ability to improve insulin sensitivity and systemic glucose homeostasis in obese mice, tauroursodeoxycholic acid (TUDCA) and phenylbutyric acid (PBA), were recently evaluated in humans. One study with TUDCA demonstrated it could increase insulin sensitivity in the liver and the muscle in obese humans.[162] PBA treatment in humans also prevented lipid-induced insulin resistance and pancreatic beta-cell dysfunction.[163] These promising outcomes warrant studies of therapeutic agents with capacity to improve ER function and folding capacity in wider clinical trials and other settings.[164]

52.8 METAFLAMMATION: OBESITY-INDUCED INFLAMMATION

The involvement of the immune system in obesity lacks resemblance to acute inflammation that is characterized by five classic signs including pain, heat, redness, swelling, and loss of function. The acute inflammatory reaction of the vascular tissues is a robust response of the immune cells to confine the injury or infection at its origin and resolves rapidly when the trigger is removed. However, none of these attributes of classic inflammation prevail in obesity-induced metabolic inflammation. Obesity leads to an atypical immune activation, also referred to as metabolic inflammation or "metaflammation," for it is triggered by metabolic cues and involves both immune (macrophages, mast cells, T cells, and eosinophils) and metabolic cells (such as adipocytes, beta cells, and hepatocytes).[21,22] This immune activation is almost undetectable at a systemic level, and the obesity-induced inflammation appears to be limited to metabolic tissues and remains unresolved over time. In particular, the obese adipose tissue shows signs of elevated inflammation, which includes infiltration of various immune effector cells and production of a variety of inflammatory mediators. Studies have shown that the stressed adipose tissue can alter the metabolic functions of the liver and muscle by releasing fatty acids, adipokines, and inflammatory cytokines. For example, the genetic ablation of JNK in the adipose tissue enhanced systemic insulin sensitivity and glucose metabolism, whereas

overexpression of MCP-1 in the adipose tissue resulted in systemic metabolic deterioration.[165–167] These findings thus argue that the adipose tissue is important for systemic metabolic deterioration as a primary site and through sustaining obesity-induced inflammation. It is, however, important to note that inflammatory alterations in obesity are prominent in many other critical metabolic sites, such as hypothalamus, pancreatic islets, and liver, and impact a wide variety of metabolic parameters such as insulin action and secretion, glucagon production, hepatic glucose production, and leptin and adiponectin sensitivity (Figure 52.4).[48] Finally, disruption of inflammatory or metabolic pathways in immune cells can also block inflammation and improve metabolism, demonstrating the critical role of immune response for metabolic control and illustrating the importance of the interactions between immune and metabolic cells.[168] It is, however, essential to note that inflammatory response is an integral component of adaptation, defense, repair, and homeostasis. Hence, it may be overly simplistic to label it "friend or foe" in an absolute manner, but rather consider this metabolic–immune interface an equilibrium where the outcome is highly dependent on where the organism resides in this continuum.

Obesity leads to enlargement of adipocytes, which becomes an abundant source of inflammatory cytokines including *TNF*α, IL-6, IL-1β, and MCP-1 as well as many lipid products.[169] Immune cells are recruited into the adipose tissue (as well as other metabolic organs).[43,170] Several immune signaling cascades are activated including TLR, IKK, JNK, and PKR and may be responsible for the cytokine production from the adipocytes and/or immune cells infiltrating adipose tissue.[48] The adipocytes are overburdened in their effort to metabolize the excess nutrients, and the resident immune cells are devoid of any significant metabolic capacity to deal with this level of nutrient assault and may die. When these stressed cells die, they invite further involvement of the immune system and thus sustain a chronic inflammatory reaction without chance for resolution.[34] The inability to resolve metaflammation in obesity is not mechanistically understood. The presence of macrophages in the obese adipose tissue was first recognized in 2003 and found in crown-like structures that form around the necrotic adipocytes.[46,47,171] Time course analysis of mice on a high-fat diet showed that macrophages arrive before the first signs of adipocyte necrosis. The adipocyte apoptosis in an inducible mouse model of lipoatrophy leads to macrophage recruitment into the adipose tissue. However, blocking adipocyte necrosis through the deletion of cyclophilin D did not stop macrophage infiltration or inflammation in the adipose tissue.[172,173] Furthermore, it was also found that human obesity did not increase adipocyte death.[174] Hence, these findings suggest that complex interactions beyond adipocyte necrosis may be required, such as genotoxic events, activation of other stress signaling cascades, or production of immunomodulators and layers of immune activation and cellular complexity for immune cell infiltration and other inflammatory responses of the adipose tissue during obesity, and these mechanisms are not yet fully understood.

Up to 60% of the adipose tissue in obesity can be populated with cells that stain positive for the macrophage marker F4/80 compared to about 10% in adipose tissue from lean

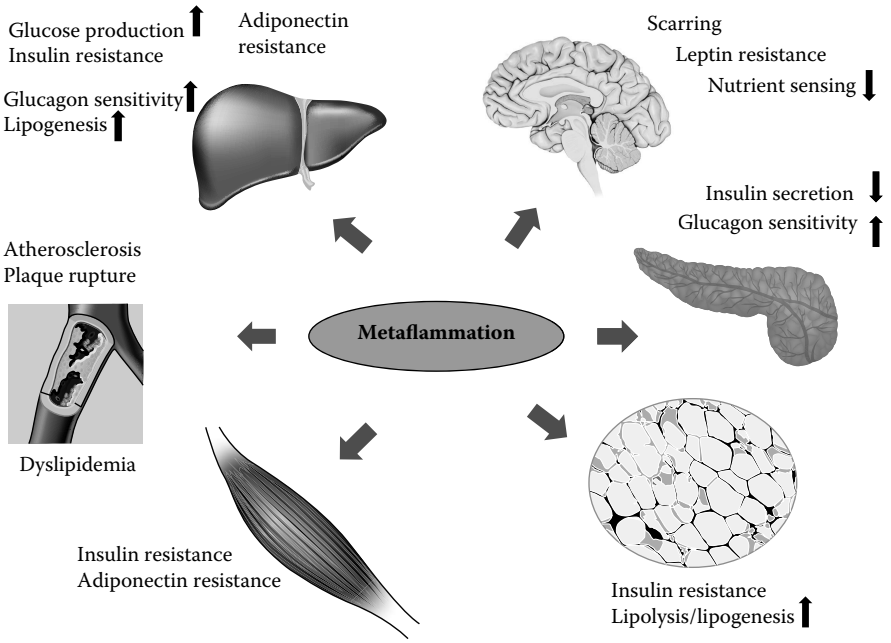

FIGURE 52.4 The impact of metaflammation on multiple organs leading to metabolic syndrome. The adipose tissue is important for systemic metabolic deterioration as a primary site of sustained obesity-induced inflammation. However, inflammatory alterations are prominent in many other critical metabolic sites including the hypothalamus, pancreas, liver, and skeletal muscle in obesity, impacting a wide variety of metabolic parameters such as insulin action and secretion, glucagon production and sensitivity, hepatic glucose production, and leptin and adiponectin sensitivity in the respective targets.

animals.[47] Interestingly, the macrophages in adipose tissue in obesity display characteristics of classical M1 phenotype (proinflammatory; nitric oxide synthase 2 and *TNF*α expression), while macrophages from adipose tissue of lean animals appear to belong to the alternatively activated M2 phenotype (anti-inflammatory; arginase 1 [ARG1]+, c-type lectin domain family member receptor [CD] 206+, CD301+, and IL-10 secreting).[175,176] The M1 type macrophages align around necrotic adipocytes, presumably to scavenge the lipids and necrotic material, and form crown-like structures.[171] The pro-inflammatory M1 macrophages and the immune mediators they secrete are thought to contribute to the pathogenesis of insulin resistance and systemic metabolic deterioration. Consistent with these observations, depletion of M1 macrophages in CD11c-DTR mice or preventing their chemotaxis to tissues in chemokine (C-C motif) receptor 2–deficient mice reduced adipose tissue inflammation and improved insulin sensitivity.[177,178] Furthermore, myeloid deficiency of IKKβ or JNK1 prevented myeloid cell–derived inflammation in adipose tissue and improved insulin action or glucose metabolism, although there are differences in the extent of contribution in different studies.[165,179–181] Adipose tissue–driven improvement in inflammatory and metabolic status is best explained in blocking multiple isoforms of JNK in the stroma rather than in the immune cells.[165,166,181] This is also evident in IKKε-deficient as well as in PKR-deficient models.[54,55] Taken together, these studies demonstrate how the recruitment and activation of macrophages to the adipose tissue contribute to systemic glucose homeostasis, but the interactions with the metabolic and stromal cellular components are also critical.

Recent studies show infiltration of the adipose tissue in obesity by several other types of immune cells, which also have systemic effects on metabolism. During obesity, the number of T helper-1 lymphocytes (T_H1; secrete pro-inflammatory cytokines) and CD8+ T cells (cytotoxic T cells; secrete pro-inflammatory cytokines) are increased in the adipose tissue, while the T helper-2 (T_H2; secrete anti-inflammatory cytokines) and regulatory T helper-2 cells (Treg; secrete anti-inflammatory cytokines) are decreased.[182,183] However, some recent studies report contradictory findings regarding the type of T cells that are increased or reduced in obesity. What is the role of T lymphocytes in obesity-induced inflammation and metabolic deterioration? One study in mice that lacked T lymphocytes (mice deficient in recombination-activating genes-1 [RAG-1]) showed they developed worse inflammation and insulin resistance when compared to control mice on a high-fat diet, arguing that certain populations of lymphocytes may play a protective role against metabolic inflammation and disease.[182] In fact, adoptive transfer experiments in RAG-1 mice showed Treg and T_H2 lymphocytes but not T_H1, and CD8+ cytotoxic T cells suppressed metaflammation and restored glucose metabolism.[182] Furthermore, targeted induction of Treg cells (by IL-2/anti-IL-2 complex) reduces adipose tissue inflammation and enhances systemic insulin sensitivity in obese mice.[183] Consistently, depleting Treg cells (in the Foxp3-DTR mice) worsened inflammation and insulin resistance. It is generally accepted that Treg and T_H2 cells improve insulin sensitivity, while T_H1 and CD8+ cytotoxic T cells promote insulin resistance. In addition to the changes in T cells, the adipose tissue B lymphocytes are found to be elevated, as is serum immunoglobulin levels, over the course of weight gain.[184] B cells function in antigen presentation to T cells and are important for humoral immunity. Mice deficient in B cells or depleted from B cells by CD20-specific immunotherapy exhibit enhanced insulin sensitivity compared to wild-type mice on a high-fat diet.[184] This positive response may be due to reduction in the number of pro-inflammatory T cells and macrophages as seen in the adipose tissue or other sites in these mice. Since adipocytes express unique T-cell receptors and MHC, it is possible that these aspects of metaflammation are also orchestrated by metabolic cells and signals. Either B-cell transfer or serum IgG from obese mice, but not from the lean control mice, to the B-cell-deficient mice induced insulin resistance.[184] In summary, obesity leads to activation of both the innate immune system and the adaptive immune response during the progression of metabolic disease. An important question remains unanswered: What are these antigens recognized by the T cells and from where do they originate?

Mast cells and eosinophils are two other types of immune cells that have attracted research interest because they are found in higher numbers in adipose tissue in obesity. Recent studies showed that either genetic depletion or pharmacological stabilization of the mast cells reduces adipose tissue inflammation and improves systemic insulin sensitivity in obese mice.[185] Furthermore, the IL-4- and IL-12-producing, anti-inflammatory M2 macrophage-promoting eosinophils are reduced in the adipose tissue during obesity. The eosinophil-deficient mice exhibit enhanced inflammation and altered insulin sensitivity, suggesting that these cells play a protective role against chronic inflammation and metabolic disease.[186]

Another important feature of metaflammation is that it is a low-grade immune response. Several immune organs, including primarily the adipose tissue, as well as liver, pancreas, muscle, and brain, display increased inflammation and local cytokine concentrations. The reflection of these inflammatory changes to circulating cytokines levels is small, if any, in obese mice and humans.[51,187] Furthermore, metaflammation does not increase energy expenditure or basal metabolic rate. This is a central issue in the exploring the role of individual immune pathways on systemic metabolism and why these systems were so closely positioned in the first place. These features of metaflammation are in contrast to the classic systemic inflammatory reaction to pathogens or trauma, which uniformly increases metabolic rate and energy expenditure, suggesting that obesity-induced inflammation remains a local but effective response that alters systemic metabolic homeostasis but preserves weight. This cycle can also be disrupted, at least in genetic models such as in PKR- and *IKK*ε-deficient mice, which exhibit reduced metabolic inflammation and increased energy expenditure, hence resulting in systemic metabolic improvement as well as better weight control in experimental models.[54,55]

Finally, metaflammation is chronic and unresolved. Inflammatory cell infiltration escalates over the time course of weight gain, cycles in intensity, but never resolves in obesity. In mice, inflammatory alterations can be detected within hours or days, and cells begin to infiltrate the adipose tissue and stabilize as early as in weeks after high-fat diet, and they reach a climax around 26 weeks on such a diet.[46,47] These studies suggested inflammation increased in parallel to the enlargement of the fat pads and potentially coincided with adipocyte cell death.[171] In this context, one can even imagine some utility for inflammation. As discussed earlier in this section, the inflammation remains local and modest. Perhaps, this kind of a low-grade inflammatory response does not trigger the mechanisms to resolve it, or alternatively, metabolic signals that initiate inflammation are not able to also engage resolution pathways or even prevent their proper responses. On the contrary, the adipose tissue turnover (adipocyte necrosis, proliferation, and differentiation occur simultaneously in the obese fat pads) appears to be an attempt at maintaining tissue homeostasis in this particular target of metaflammation. Over time, at least some aspects of inflammation will result in fibrosis and scarring and may become irreversible. Such changes have been reported in the hypothalamus and adipose tissue and may impact the outcomes of genetic or chemical interventions, again depending on time and context.[188]

52.9 CONCLUSIONS

The contribution of inflammation to metabolic deterioration is unequivocal and much better understood at the mechanistic level because of the significant amount of research reported in the past two decades. Beginning with some early observations in septic shock and severe infection, continuing with the discovery of metaflammation and arriving at the knowledge about the gut microbiota's contribution to insulin sensitivity and other metabolic phenotypes, the two seemingly afar scientific spheres of immunology and metabolism are beginning to merge into the field of immunometabolism. In this chapter, we presented overwhelming evidence for the causal role of inflammation in metabolic dysfunction associated with obesity as well as some of the unsettled issues, disparities, and potential reasons. An important future direction involves effective translation of this knowledge to shape future therapeutic approaches to metabolic syndrome. To date, several approaches have been taken to target inflammation from antibody-based neutralization of inflammatory cytokines to nutritional modification of inflammation in humans. Early studies with *TNF*α-blocking antibodies reduced inflammation without significant enhancement in insulin sensitivity in a small group of obese and diabetic patients. More recently, metabolic improvement and glucose-lowering effects have been reported following *TNF*α neutralization in obese humans.[189] Insulin resistance seen in rheumatoid arthritis patients benefited from *TNF*α antibody treatments, although some studies have reported negative results as well.[190] Blocking IL-1 receptor was also reported to improve glucose metabolism, although there have been some negative findings.[15] More substantial effects have been seen upon treatment of obese subjects with salicylates. Based on several independent studies, salicylates had beneficial impact on metabolism and improved insulin sensitivity while reducing inflammation and blood lipid levels. However, the molecular target of salicylates remains to be determined for the therapeutic window reported in these studies.[191,192] Taken together, an effective anti-inflammatory strategy has not yet been applied and vigorously tested in humans. Ongoing and future studies should probably target several cytokines or combinations (e.g., *TNF*α and IL-1) or upstream regulators of metaflammation (such as JNK, IKKε, or PKR) that would impact multiple mediators, overcome potential redundancies, and regulate energetics for effective and long-lasting improvements in glucose metabolism and insulin action. Potential upstream targets could be the molecules that constitute the metaflammasome (metabolically induced inflammasome assembly), pathogen-sensing and/or stress kinases, or organelle function, as discussed in this chapter, which can produce favorable changes in systemic energy homeostasis while preventing the engagement of inflammatory responses. It is likely that such interventions should be coordinated with dietary exposures and modulation of gut microbiome for optimal and sustainable results.

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53 Obesity and Gallbladder Disease

Cynthia W. Ko and Sum P. Lee

CONTENTS

Gallstones are present in about 8% of men and 17% of women in the United States.[1] In obese patients and those losing weight, gallstones are even more common and composed primarily of cholesterol. The pathophysiological conditions involved in cholesterol gallstone formation include biliary cholesterol supersaturation, nucleation of cholesterol crystals, gallbladder dysmotility, genetic predisposition, and enhanced intestinal cholesterol absorption. Recent work has elucidated the pathophysiological changes in obesity that predispose to cholesterol gallstone formation and has provided the possibility of pharmacologic reduction in gallstone risk. This chapter reviews the epidemiology and pathogenesis of cholesterol gallstones, with special attention to obesity, and discusses the effects of weight loss on gallbladder disease.

53.1 EPIDEMIOLOGY OF GALLSTONES

Gallstones occur in populations throughout the world, but their prevalence varies substantially.[1–5] The prevalence of gallstones in females varies from 3.7% in Indians and Pakistanis to 62.2% in Pima Indians.[3,4] In males, the prevalence varies from 2.9% in Thais to 25.9% in Pima Indians.[4,6] Both racial and genetic factors likely contribute to the wide variation in prevalence.

In all populations studied, the prevalence of gallstones increases with age.[7] In addition, females have a higher prevalence of gallstones than males at all ages, although the female predominance is less marked in older age groups. Increased estrogen stimulation, such as with oral contraceptive use, higher parity, and estrogen replacement therapy, also is associated with a greater risk of gallstones. Risk factors other than race/ethnicity, age, and gender are less well defined and understood. For example, patients with diabetes mellitus or glucose intolerance have a higher incidence of gallstones in some, but not all, studies, likely secondary to altered gallbladder motility and hepatic lipid metabolism.[8,9] Serum lipids are also associated with gallstones, with a weak negative association between total serum cholesterol or high-density lipoprotein (HDL) levels and gallstone formation seen in some, but not all, studies.[10] A moderate positive association has been found between serum triglyceride levels and gallstones.[8,10]

Diet has also been implicated in gallbladder disease, but there is currently no clear data on the potential effects or mechanisms. Evidence exists that higher total caloric intake correlates with symptomatic gallbladder disease.[11] In addition, diets with a high intake of carbohydrates or *trans*-fatty acids and diets with a high glycemic load or index are associated with a greater risk of symptomatic gallbladder disease, whereas the intake of *cis*-fatty acids is associated with a lower risk.[12–14]

More recently, physical activity has been implicated as a risk factor for symptomatic gallstones and cholecystectomy, independently of its effect on overall body mass index (BMI) and weight loss.[15,16] These studies, performed in both men and women, have shown that even moderate levels of recreational physical activity are protective against symptomatic gallstones. The mechanisms behind this phenomenon are unclear, although some have postulated that the effects of exercise on glucose tolerance, insulin levels, and serum lipid levels may be responsible.

53.2 RISK OF GALLSTONES IN THE OBESE

Many studies have shown the association of obesity with gallbladder disease (Table 53.1). The incidence of gallstones in obese women has been estimated at 2.6 per 100 person-years, with approximately two-thirds of these stones being asymptomatic.[17] The relative risk seems to increase as body weight increases.[10,11,18–20] However, there is no defined threshold effect, as the relative risk of gallstones increases with BMI even in normal-weight individuals. Up to 43% of men and women undergoing bariatric surgery have gallbladder disease, defined as prior cholecystectomy or gallstones.[21–23] Finally, obesity is increasingly being recognized as a risk factor for gallstones in pediatric and adolescent populations.[24] A recent study found that 69% of children undergoing cholecystectomy were overweight or obese, with marked increases in the percentage of severely obese patients between 1980–1996 and 2005–2008.[24]

In addition to the effects of overall obesity, central or truncal adiposity is correlated with the risk of gallstones in both men and women, even after adjustment for BMI.[25,26] In the San Antonio Heart Study of Mexican–American women, the risk of developing gallstone disease was 30% greater for women in the highest quartile of subscapular-triceps skinfold thickness ratio compared to those in the lowest quartile.[27] Finally, the metabolic syndrome (presence of three of the following five factors: high waist circumference, high triglycerides, low HDL-cholesterol, hypertension, and diabetes) is a risk factor for biliary stones and cancers,[28] with a significant increase in risk with the presence of each metabolic syndrome factor.

53.3 PATHOGENESIS OF GALLSTONES

Bile is an aqueous solution with varying concentrations of lipids, proteins, and electrolytes. Cholesterol, a hydrophobic molecule, is kept in solution by amphipathic bile salts and phospholipids. However, when the cholesterol-carrying capacity of bile is exceeded, cholesterol supersaturation occurs and cholesterol crystals can form. Supersaturation can occur either with excess hepatic secretion of cholesterol or with relative undersecretion of bile salts or phospholipids.

53.3.1 Synthesis and Secretion of Biliary Lipids

The primary site of cholesterol synthesis and metabolism is the liver (Figure 53.1). Cholesterol in plasma lipoproteins or chylomicrons can be taken up by hepatocytes, whereas free

TABLE 53.1
Relative Risk of Gallstones with Obesity in Various Populations

Reference	Study Population	Diagnostic Criteria	Normal Population	Obese Population	Relative Risk
11	Nurses' Health Study	Previous cholecystectomy or symptoms	BMI <24	BMI 30–35	3.69
				BMI 35–40	4.72
				BMI 40–45	5.11
				BMI >45	7.36
18	Nurses' Health Study	US if symptomatic	BMI <22	BMI 22–24.9	1.6
				BMI 25–31.9	3.3
				BMI >32	6.3
19	Nurses' Health Study	Previous cholecystectomy or symptoms	BMI 18.5–21.9	BMI 25.0–29.9	2.3
				BMI 30.0–34.9	3.2
				BMI ≥35	3.7
19	Health Professionals Follow-Up Study	Previous cholecystectomy or symptoms	BMI 18.5–21.9	BMI 25.0–29.9	1.6
				BMI 30.0–34.9	2.5
				BMI ≥35	3.3
20	Obese prior to bariatric surgery	Previous cholecystectomy and intraoperative US	BMI <20 (Reference 88)	BMI 35–40	5
				BMI 40–50	7
				BMI 50–60	8

Note: US = ultrasonography.

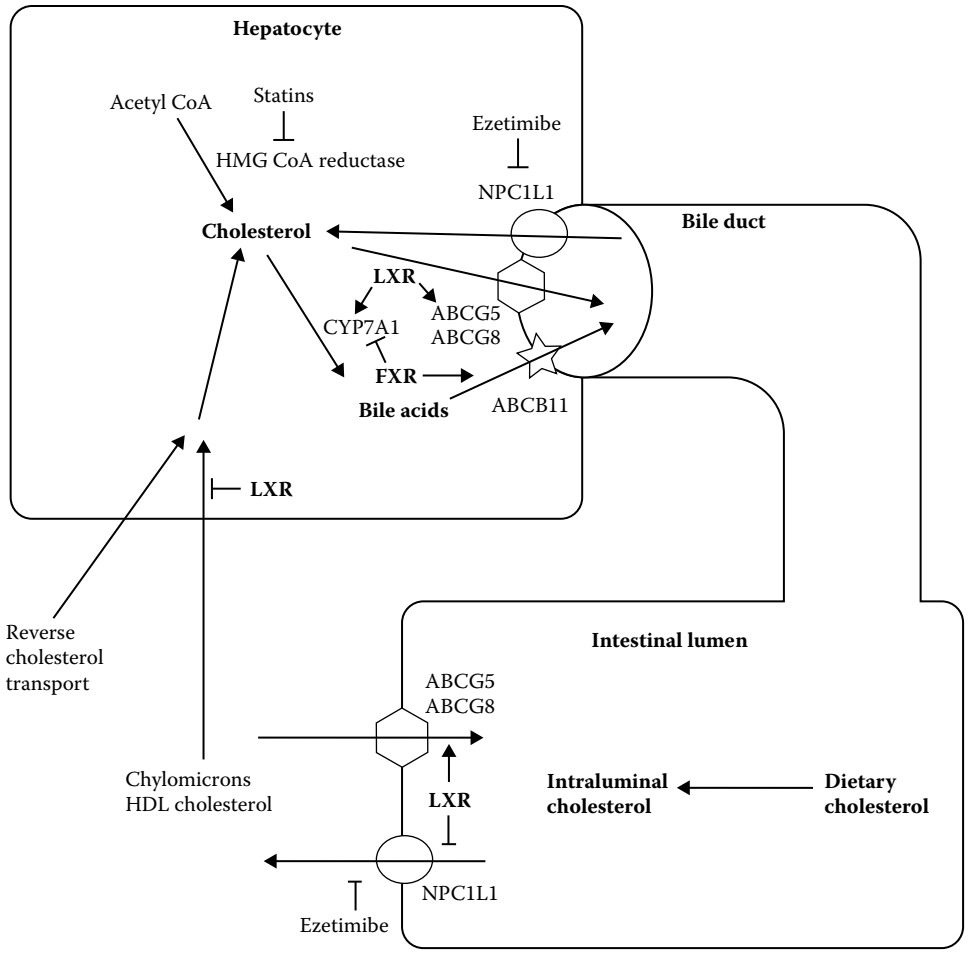

FIGURE 53.1 Hepatic cholesterol metabolism and transport: the liver is a key regulator of cholesterol metabolism and transport. Hepatic cholesterol is synthesized from acetyl-coenzyme A (acetyl-CoA) via the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase enzyme or is derived from intestinal absorption or reverse cholesterol transport from the peripheral tissues. Cholesterol can be converted into bile acids via the CYP7A1 enzyme or excreted into bile via the ABCG5/ABCG8 heterodimer. Bile acids are excreted into the biliary canaliculi via the ABCB11 pump. Many of the key enzymes in cholesterol and bile absorption are regulated by liver X receptor (LXR) and farnesoid X receptor (FXR).

cholesterol is synthesized in the hepatocyte endoplasmic reticulum or created by the de-esterification of cholesterol from plasma lipoproteins. Free cholesterol is the substrate pool for bile acid and lipoprotein synthesis and is the principal sterol found in bile. Cholesterol is excreted into bile by the adenosine triphoshate–binding cassette subfamily G member 5 (ABCG5) and member 8 (ABCG8) heterodimeric cholesterol transporters located on the biliary canalicular membrane.[29] Expression of the *ABCG5* and *ABCG8* genes is regulated by the liver X receptor (LXR), a sterol-response nuclear receptor that is a key regulator of cholesterol metabolism, bile acid synthesis, and glucose metabolism.[30] Recently, in genome-wide association studies common variants of *ABCG5* and *ABCG8* have been associated with gallstone formation, confirming the importance of cholesterol secretion in the pathogenesis of gallstones.[31,32] The Niemann–Pick C1-like protein 1 (NPC1L1), expressed on the biliary canalicular membrane, can mediate the reuptake of cholesterol from bile.[33] Thus, biliary cholesterol secretion is mediated by the overall balance between activity of the ABCG5/ABCG8 heterodimer and NPC1L1. Cholesterol hypersecretion is believed to be the primary defect in most Western patients with cholesterol gallstones, regardless of race or ethnicity.

Bile acids are synthesized from cholesterol in the liver by the rate-limiting enzyme cholesterol 7α-hydroxylase (also known as cytochrome P450, family 7, subfamily A, polypeptide 1 [CYP7A1]). After synthesis, bile acids bind to carrier proteins for transport through the hepatocyte and are conjugated with glycine or taurine, increasing their water solubility. They are then actively secreted by bile salt transporters, most prominently the ABCB11 bile salt export pump, located in the biliary canalicular membrane of the hepatocyte. This process is regulated by the farnesoid X receptor (FXR), which is activated by conjugated bile acids.[34] Bile acids pass into the small intestine with gallbladder contraction and are eventually reabsorbed in the distal small intestine via enterohepatic circulation.

Biliary phospholipids are believed to derive from membranous structures within hepatocytes, such as the endoplasmic reticulum, or from the hepatocyte canalicular membrane.

Phospholipids are amphipathic molecules and, similar to bile acids, can solubilize and transport cholesterol. Phospholipids are translocated from the inner to the outer leaflet of the canalicular membrane by the ABCB4 phospholipid transporter.[35] FXR activation also induces the *ABCB4* gene.

FXR (now known as nuclear receptor subfamily 1, group H, member 4) appears to be a key regulatory gene in gallstone pathogenesis. In mice lacking *Fxr*, bile lithogenicity is increased, with increased bile salt hydrophobicity and gallbladder inflammation.[36] In susceptible wild-type mice, treatment with a synthetic FXR agonist increased bile salt and phospholipid concentrations, improving cholesterol solubility and preventing gallstone formation. Interestingly, mice with aberrant *Fxr* expression also demonstrate metabolic abnormalities, including dyslipidemia, glucose intolerance, and fatty liver disease.[37] In high-fat-diet-induced obese mice, FXR acetylation is increased, impairing the activation of target genes such as *ABCB11*.[38] Thus, abnormalities in *FXR* activity and function in obese persons may explain the link between obesity, diabetes, and gallstone formation. *LXR*, as a key regulator of both glucose and lipid metabolisms, may also play an important role in gallstone pathogenesis related to insulin resistance.

53.3.2 Transport of Biliary Lipids

In bile, cholesterol is solubilized because of the amphipathic properties of bile salts and phospholipids.[29] Multiple forms of cholesterol carriage exist in bile, including small unilamellar vesicles, multilamellar vesicles, and mixed micelles, and these forms of transport have different levels of thermodynamic stability. Bile salts can aggregate as simple micelles, which carry small amounts of cholesterol. In addition, bile salts stimulate the secretion of unilamellar vesicles made up of cholesterol and phospholipids from the external layer of the biliary canalicular membrane which contain very little or no bile acids.[39,40] In bile with a higher concentration of bile acids, such as gallbladder bile, these vesicles may fuse and form larger multilamellar vesicles or liquid crystals[41,42] (Figure 53.2). Cholesterol is also transported in mixed micelles containing bile salts and phospholipids, which are thermodynamically stable and can have a high cholesterol-carrying capacity. Cholesterol can undergo dynamic exchange between the nonmicellar and the micellar forms of transport. The relative concentrations of bile salts, cholesterol, and phospholipids in bile determine the forms of carriage present and the cholesterol-carrying capacity of bile.[39] Cholesterol saturation index (CSI) represents the cholesterol content of bile relative to the carrying capacity, and bile with a CSI greater than 1 is, by definition, supersaturated and prone to gallstone formation.[43]

Various proteins in bile have been postulated to accelerate or retard the initial precipitation of cholesterol from supersaturated bile (crystal nucleation), although their roles have come into question recently. However, an important pronucleating role for mucin glycoprotein is likely. Mucin hypersecretion is seen early in the pathogenesis of gallstones,[44] and murine genes controlling mucin accumulation have been associated with gallstones.[45] Mucin appears to entrap cholesterol–phospholipid vesicles, which subsequently aggregate and precipitate to form cholesterol crystals, biliary sludge, and stones.

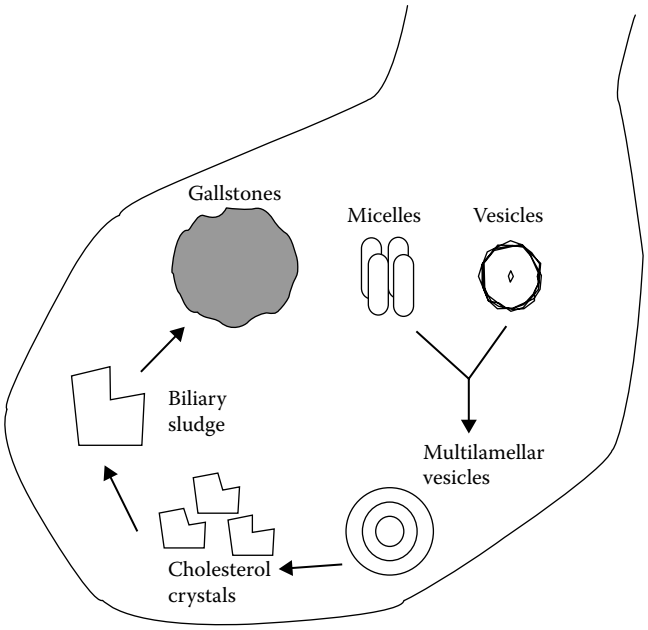

FIGURE 53.2 Cholesterol crystallization and gallstone formation: in the gallbladder, micelles and vesicles in supersaturated bile can coalesce to form multilamellar vesicles. With gallbladder dysmotility, the multilamellar vesicles can be trapped by mucin glycoprotein and cholesterol crystals can nucleate. These crystals aggregate to form biliary sludge and eventually gallstones.

53.3.3 Role of the Gallbladder

Cholesterol gallstones occur very rarely in patients who have undergone previous cholecystectomy. Therefore, the gallbladder is felt to play an important role in gallstone formation. The gallbladder has storage, absorptive, secretory, and contractile properties that may contribute to the development of gallstones.

53.3.3.1 Mucosal Function

The gallbladder is generally thought of as a storage organ. However, the gallbladder epithelium acidifies bile, actively transports sodium and chloride, absorbs lipids, and absorbs water by passive osmosis. During this process, initially dilute hepatic bile is concentrated, leading to higher concentrations of biliary lipids and predisposing to cholesterol crystal nucleation.[46] The gallbladder epithelium can also absorb cholesterol and phospholipids, potentially reducing the CSI. Defects in gallbladder cholesterol and phospholipid absorption have been seen in animal models of cholesterol gallstone disease.[47] However, cholesterol absorbed by the gallbladder can be incorporated into the sarcolemmal membranes, impairing gallbladder motility and promoting cholesterol hypersecretion.[48]

In addition to its concentrative and absorptive functions, the gallbladder epithelium secretes mucin, a glycoprotein

with extensive hydrophobic domains that can bind biliary lipids. In more concentrated bile, vesicles and micelles are entrapped in these binding sites and come into close and prolonged contact.[49] Mucin hypersecretion has been shown to precede gallstone formation in prairie dog models.[44] Multiple potential stimuli for mucin hypersecretion have been demonstrated, including hydrophobic bile salts, prostaglandins, and arachidonic acid.[44]

53.3.3.2 Motor Function

Both the endocrine and the nervous systems regulate gallbladder motility. The most important hormone regulating gallbladder contractility is cholecystokinin (CCK), which is released in the duodenum after meals and stimulates gallbladder contraction and sphincter of Oddi relaxation. Neural control is mediated through both the parasympathetic and the sympathetic nervous systems. Vagal activity enhances gallbladder contraction, whereas the role of sympathetic innervation is generally inhibitory. Gallbladder contraction allows the passage of bile into the small intestine and facilitates enterohepatic circulation of bile salts. During fasting, gallbladder contraction is weak and bile accumulates in the gallbladder, sequestering the circulating bile acid pool. With the resulting fall in bile acid secretion rates, bile becomes progressively more saturated, facilitating cholesterol crystal nucleation. Thus, adequate gallbladder motility is necessary to promote the circulation of bile salts and to empty saturated bile, sludge, and small stones before larger stones can form.

Abnormal gallbladder motility has been noted in cholesterol gallstone patients.[50,51] In many conditions that predispose to sludge or gallstone formation, gallbladder emptying is markedly inhibited because of endocrine or neurologic abnormalities. For example, patients who are fasting or receiving total parenteral nutrition have markedly diminished CCK release and gallbladder hypomotility.[52] Treatment with the CCK antagonist somatostatin, as in patients with acromegaly, can inhibit gallbladder contractility.[53] Obese persons, who are also predisposed to sludge and stone formation, may have diminished responsiveness of the gallbladder musculature to CCK.[54]

53.3.4 Nucleation of Cholesterol Crystals and Growth of Crystals into Stones

Cholesterol crystal nucleation is the first step in gallstone formation. Nucleation begins with the aggregation and fusion of unilamellar vesicles to form multilamellar vesicles, with the subsequent aggregation of cholesterol molecules to form crystals (Figure 53.2). This initial aggregation is mediated at least in part by mucin binding of these lipids. The cholesterol that precipitates is primarily derived from biliary vesicles and nucleates using mucin glycoprotein as a nidus.[49] Calcium ions are believed to be important in gallstone formation, as they can promote the fusion of phospholipid–cholesterol vesicles. Calcium salts can also serve as a nidus for cholesterol precipitation and are usually found in the central core of cholesterol gallstones.[29] Albumin and other calcium-binding proteins are found in the matrix of cholesterol gallstones and thus may also serve as sites for nucleation.[55,56] When cholesterol crystals reach a certain critical size, biliary sludge and stones form, with further cholesterol deposition on the aggregates.

Once a crystal of adequate size is formed, cholesterol, calcium bilirubinate, and other biliary lipids can deposit on its surface, leading to the formation of visible gallstones. One study suggested that bile in obese patients promotes more rapid crystal growth than that in the nonobese.[57] However, this process has not been as extensively studied as crystal nucleation and little information is available on factors that may influence the growth of stones.

53.3.5 Genetic Contributions to Cholesterol Gallstone Disease

Family and twin studies have shown that there is a complex genetic predisposition to the development of cholesterol gallstones.[58,59] Lithogenic (*Lith*) loci have been identified on mouse chromosomes, revealing novel insights and confirming the importance of biliary lipid transporters in the pathogenesis of cholesterol gallstones.[60] For example, the *Abcb11* bile salt export pump is a candidate gene for the *Lith1* locus in mice, whereas the *Abcg5/Abcg8* cholesterol transport proteins are candidate genes for the mouse *Lith9* locus.[60] Mouse models have also identified the *Abcb4* phospholipid transporter as a candidate gene associated with cholesterol cholelithiasis. Missense mutations in this gene have been associated with a particular form of cholelithiasis, characterized by mild chronic cholestasis and intrahepatic sludge.[61] Other putative genes affecting gallstone risk in mice include the CCK receptor (*Cckr*) and gallbladder mucin (*Muc1*), although these associations have not been confirmed in humans. The risk of gallstone development is most likely defined by a complex interaction between genetic factors and environmental factors, such as age, obesity, physical activity, and diet.

53.3.6 Enhanced Intestinal Cholesterol Absorption

A high-cholesterol diet and increased intestinal cholesterol absorption may both be risk factors for gallstone formation, although the magnitude of these effects is unclear.[62] In the intestinal brush border cholesterol uptake is mediated by NPC1L1, whereas, interestingly, the ABCG5/ABCG8 heterodimer mediates cholesterol transport back into the intestinal lumen. Thus, the overall balance between cholesterol influx and efflux in the intestine is mediated by the relative activity of these two transporters, similar to biliary cholesterol secretion. The importance of intestinal cholesterol absorption in gallstone pathogenesis is demonstrated by the fact that ezetimibe, a potent inhibitor of NPC1L1, reduces intestinal cholesterol absorption, maintains gallbladder motility, and prevents gallstone formation in mice and humans.[63] However, it is generally believed that biliary cholesterol hypersecretion plays a greater role in gallstone pathogenesis than enhanced intestinal cholesterol absorption.

53.4 EFFECTS OF OBESITY

Excessive body weight is associated with increased daily cholesterol synthesis and a larger pool of metabolically active cholesterol in the body. In addition, the hepatic conversion of cholesterol into bile acids is impaired in obesity. Obese persons therefore have dual mechanisms contributing to a higher body total cholesterol pool: increased synthesis and decreased degradation.

53.4.1 Biliary Cholesterol Supersaturation

Overall, biliary cholesterol secretion is increased in the obese relative to the nonobese. However, when normalized to subject weight cholesterol secretion appears normal in obese patients without gallstones. In contrast, in obese patients with gallstones cholesterol secretion is markedly elevated, even after correction for body weight.[64,65] This marked cholesterol hypersecretion, with a resulting higher CSI, is felt to be the primary mechanism predisposing to gallbladder disease in obesity.[65]

The pathophysiology of cholesterol hypersecretion in obesity is poorly understood. Putative mechanisms include increased cholesterol uptake from lipoproteins,[66] increased cholesterol synthesis by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase,[67] decreased cholesterol catabolism by CYP7A1,[67] and decreased esterification of cholesterol within the hepatocyte.[68] It seems likely that cholesterol hypersecretion is secondary to a combination of these effects. Cholesterol hypersecretion may be modulated by adipokines such as leptin or by insulin resistance.[69,70] In animal models of hepatic insulin resistance, FXR expression is decreased with subsequent changes in bile secretion.[70] These animals have a decreased expression of key enzymes in bile salt synthesis, including CYP7A1, resulting in decreased bile salt synthesis, increased hydrophobicity, and thus increased lithogenicity. However, treatment with an FXR agonist did not normalize the bile salt profile, indicating additional pathways whereby insulin resistance may affect the bile salt profile. In these mice, expression of the biliary cholesterol transporters ABCG5 and ABCG8 is also increased, with subsequent increases in biliary cholesterol secretion and saturation. Finally, these mice demonstrate increased gallbladder volume. Thus, increased expression of ABCG5/ABCG8 and altered expression of bile acid synthetic enzymes may be involved in the pathogenic mechanism linking obesity, insulin resistance, and cholesterol gallstone disease.

In contrast to the consistent data showing cholesterol hypersecretion in obesity, the data on alterations in bile acid secretion are variable. The total pool and biliary secretion of bile acids are thought to be normal to increased in obese patients. However, when normalized for body weight, bile acid secretion is lower in the obese than in the nonobese and bile lithogenicity is higher because of the marked increase in cholesterol secretion.[71] Overall, CSI and bile lithogenicity are increased in obesity because of cholesterol hypersecretion without compensatory increases in bile salt secretion.

53.4.2 Gallbladder Motility

Gallbladder stasis is an important factor that predisposes to the formation of gallstones.[54] Obesity, and in particular central fat distribution, in itself is associated with gallbladder hypomotility and stasis, with many studies showing increased fasting volumes, increased residual volumes, and decreased fractional emptying.[51,54,72,73] Multiple mechanisms may predispose to alterations in gallbladder motility in obesity. Insulin resistance, leptin resistance, hyperglycemia, and hyperlipidemia have been implicated in gallbladder dysmotility.[74,75] Diminished gallbladder responsiveness to CCK has also been proposed. Aberrant splicing of the *CCKR* gene, which is predicted to result in a nonfunctional protein, has also been found in obese gallstone patients.[76] Another proposed mechanism is accelerated gastric emptying in obesity, resulting in decreased CCK release from the duodenum and diminished gallbladder emptying[51].

53.4.3 Effects of Adipokines

Serum leptin levels are positively associated with gallstone disease,[77] and many studies have attempted to identify how leptin may influence gallstone pathophysiology. In leptin-deficient *ob/ob* mice, administration of exogenous leptin altered the expression of several genes involved in lipid metabolism and gallbladder motility, absorption, and secretion, providing a link between leptin and known gallstone risk factors.[78] Leptin resistance is also associated with gallbladder dysmotility, although the mechanisms of this effect are unclear.[79] Likewise, serum adiponectin levels have been found to be lower in cholesterol gallstone patients compared with healthy controls, after adjustment for BMI and gender.[77] Adiponectin is an adipokine with anti-inflammatory and insulin-sensitizing effects, and its serum levels are inversely correlated with BMI. Adiponectin knockout mice showed a prolithogenic bile acid profile compared to control mice, as well as low levels of apolipoprotein A-I, an inhibitor of cholesterol crystallization, and a higher expression of inflammatory markers in gallbladder mucosa.[80] Finally, serum levels of visfatin, a recently identified adipokine, have been found to be elevated in both obese and nonobese patients with cholesterol gallstones compared to healthy controls, although it is unclear whether there is a causal relationship.[81] Little work has been done to elucidate the mechanisms for the association of visfatin with cholesterol gallstones.

53.5 GALLSTONES DURING WEIGHT LOSS

Obesity is associated with a marked increase in the prevalence of gallstones, but, paradoxically, weight loss through either dieting or bariatric surgery is a risk factor for gallstone formation (Table 53.2). Sections 53.5.1 through 53.5.3.4 review the incidence, pathophysiology, and prevention of gallstone formation during weight loss.

TABLE 53.2
Risk of Gallstone Formation with Weight Reduction

Reference	Study Population	Method of Weight Loss	Diagnostic Test	Follow-Up Period	Percentage with Gallstones
83	Obese on low-calorie diet	540 kcal Diet	US screening	4 Weeks	7.8
				8 Weeks	25.5
87	Obese undergoing bariatric surgery	Gastric bypass	US screening	6 Months	36
89	Obese on low-calorie diet	520 kcal Diet	US screening	16 Weeks	10.9
101	Obese undergoing bariatric surgery	Gastric bypass	US screening	3 Months	43

53.5.1 Incidence of Gallstones during Weight Loss

In the Nurses' Health Study, women losing 4–10 kg of weight had a 44% increase and those losing more than 10 kg had a 94% increase in the risk of gallstones.[18] Interestingly, the risk of symptomatic gallstones in this population was also influenced by long-term weight patterns.[82] Women whose weight fluctuated and women with net weight loss over time had higher prevalences of gallstones than those who maintained a steady weight.

An overall incidence of gallstones of up to 25% was shown in 8–16 weeks after the initiation of a weight reduction diet.[83] It has been suggested that the risk of gallstone formation dramatically increases if the rate of weight loss exceeds 1.5 kg/week.[84] In addition, the composition of the weight loss diet, especially the amount of fat, may be important. Patients on a diet containing more than 10 g of fat per day have a lower risk of gallstone formation than those who consume less than 10 g of fat per day, perhaps because of maintained gallbladder motility.[85,86]

Patients losing weight with either low-calorie diets or bariatric surgery seem to be at risk. The incidence of gallstones may be as high as 37% in the first 6 months after bariatric surgery and as high as 71% within the first 12 months.[87,88] The risk of gallstone formation is greatest in the first postoperative year but may be increased for up to 3 years postoperatively as weight loss continues. Although these periods are coincident with the periods of greatest weight loss and ongoing weight loss, the risk of gallstone formation does not necessarily correlate with the degree of weight loss. Up to 40% of those developing gallstones after surgery will be symptomatic, and up to 67% of those symptomatic patients may undergo cholecystectomy.[87,88] Asymptomatic gallstones will resolve in about 50% after 1 to 2 years.[89]

Both initial BMI and the relative rate of weight loss are predictors of gallstone development, although absolute weight loss is more difficult to assess because of its dependence on initial BMI.[89] Likewise, the rapidity of weight loss has not been established as a definitive risk factor because it is related to the absolute and relative amounts of weight lost. Increased rates of gallstone formation during weight loss are seen in men. However, this effect is removed when controlling for the higher initial BMI, relative BMI reduction, and initial serum triglycerides seen in obese men compared with obese women.[90]

53.5.2 Pathophysiology of Gallstone Formation during Weight Loss

Changes in bile composition that lead to increased lithogenicity are seen with very-low-calorie diets or bariatric surgery. The cholesterol content of bile increases early during weight loss, most likely because of mobilization from peripheral adipose tissue, and then decreases as weight stabilizes.[91,92] However, a low caloric intake lowers cholesterol input and may reduce bile acid secretion and cholesterol synthesis. Bile acid and phospholipid secretions do not reliably change with weight loss but generally are lower after weight loss.[91] Biliary cholesterol secretion will reflect a balance of all these variables. In the weight stabilization phase after a low-calorie diet, CSI decreases below the baseline value. Nucleation time decreases concurrently with these changes.[92]

Gallbladder motility is diminished during the rapid-weight-loss phase after bariatric surgery.[93] With very-low-calorie diets, fasting and residual gallbladder volumes increase, an effect that may be reversed by the inclusion of adequate calories (over 800 kcal/day) or dietary fat (over 10 g/day) to maximally stimulate gallbladder contractility.[94]

53.5.3 Prevention

53.5.3.1 Screening for Gallstones Prior to Weight Reduction

Patients undergoing bariatric surgery are often screened with preoperative ultrasound to determine the need for concomitant cholecystectomy. Some have advocated screening for gallbladder disease prior to weight reduction dieting and possibly dietary modification if gallstones are found. However, screening prior to weight reduction has not been studied systematically, and it is not clear that screening will reduce gallstone-related complications.[95]

53.5.3.2 Prophylactic Cholecystectomy

Some authors have advocated prophylactic cholecystectomy at the time of bariatric surgery because of the greater than 30% incidence of gallstones in the initial period of rapid weight loss. Up to 25% of patients who have not had a prior cholecystectomy will already have gallstones at the time of surgery, and 95% of patients undergoing cholecystectomy with bariatric surgery will have pathologic evidence of gallbladder disease.[96] Cholecystectomy adds only minimally to

procedure time (30–45 minutes), and patients undergoing prophylactic cholecystectomy have not had a higher incidence of perioperative complications or a longer hospital stay.[97] Routine cholecystectomy has been advocated at the time of open bariatric surgery, although this is not yet the standard of care for laparoscopic surgery.[22,98] Prophylactic cholecystectomy before initiating weight reduction diets has not been advocated.

53.5.3.3 Bile Acid Supplementation during Weight Loss

Bile acid supplementation with ursodeoxycholic acid (UDCA), a hydrophilic bile acid, decreases cholesterol saturation and bile lithogenicity. Thus, UDCA has been used as a nonsurgical treatment for gallstones and is generally well tolerated and does not have significant adverse effects.

UDCA decreases hepatic cholesterol synthesis by decreasing the activity of hepatic HMG-CoA reductase, but it has no effect on the conversion of cholesterol to bile acids via the CYP7A1 enzyme.[99] Gallbladder bile from patients treated with UDCA contains only a trace of cholesterol in vesicles, the more lithogenic form of transport.[100] The molar percentage of bile acids is unchanged to slightly increased with UDCA, and UDCA becomes the predominant bile acid during therapy.[101] Overall, treatment with UDCA prolongs nucleation times and decreases the concentrations of cholesterol and phospholipids present in the vesicular phase of bile.[101] In addition, patients treated with UDCA during weight loss have preserved gallbladder motility. All these factors combined suggest that UDCA may prevent gallstones during weight loss. In fact, randomized controlled studies have provided evidence that giving 600 mg/day of UDCA during weight reduction dieting[102] or after gastric bypass surgery[103] can significantly decrease the incidence of biliary sludge and gallstones. These results were confirmed in a meta-analysis, which showed that UCDA treatment reduces the risk of gallstone formation by 60% (95% confidence interval: 26%–78%) after bariatric surgery and is cost saving.[104]

53.5.3.4 Other Pharmacologic Measures

Other pharmacologic treatments for gallstones have been proposed but not well studied during weight loss. Statins, by inhibiting HMG-CoA reductase, reduce cholesterol synthesis and biliary cholesterol secretion. Their effect in humans is mixed, with some studies reporting gallstone dissolution or reduced formation and others reporting no effect.[105,106] In prospective cohort studies in the general population, statin use has been associated with a modestly reduced risk of cholecystectomy or gallstones.[105]

Ezetimibe reduces intestinal cholesterol absorption by suppressing NPC1L1. In hamster models, ezetimibe decreased absolute and relative cholesterol levels in bile and improved cholesterol solubilization while protecting gallbladder motility.[63] In human studies, ezetimibe significantly reduced cholesterol concentration and CSI while slowing nucleation.[63] Thus, ezetimibe is a promising agent for medical treatment of gallstones but needs further study.

53.6 SUMMARY

Gallstones are a common clinical problem in obesity. Important pathophysiological conditions required for gallstone formation include secretion of supersaturated bile, nucleation of cholesterol crystals, and gallbladder stasis. In obesity, bile is more saturated because of cholesterol hypersecretion and gallbladder motor function is impaired, predisposing to gallstone formation. Newer research suggests that insulin resistance and adipokines such as leptin may mediate the association between obesity and gallstones.

Paradoxically, dietary or surgical weight reduction also predisposes to gallstone formation. The mechanisms of gallstone formation during weight reduction also involve altered bile composition and gallbladder motility. UDCA is the only medical therapy that has been shown to decrease gallstone incidence during weight reduction. Further research needs to be done on the risk factors for and the treatment of gallstone disease and its prevention in obese patients and in those losing weight.

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54 Obesity and the Liver
Cell Death, Compensatory Growth, and Repair of Damage

Giovanni Tarantino

CONTENTS

54.1 INTRODUCTION

Calorie-rich diets; consumption of energy-dense, high-fat, and/or high-sugar foods (sometimes called junk food) and beverages; and a lack of physical exercise, all habits that lead to obesity and are typical of the so-called civilized countries, have generated an explosion of hepatic steatosis or unclassified nonalcoholic fatty liver disease (NAFLD), which can evolve into nonalcoholic steatohepatitis (NASH) or, simply, fatty liver. Increased production of adipokines by adipose tissue and raised circulating levels of acute-phase proteins and inflammatory cytokines have led to the view that obese people are characterized by a state of low-grade chronic inflammation, causally linked to insulin resistance (IR) and the metabolic syndrome (MetSyn) [1]. In adult obese subjects, serum concentrations of C-reactive protein, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) have been significantly correlated with body mass index (BMI) and waist circumference [2]. Low-grade systemic inflammation also may underlie the clustering of metabolic risk factors in children and adolescents [3–6]. Through proteomics and microarray screening, Zhang et al. [7] identified lipocalin 2, a novel autocrine and paracrine adipokine that potentially links obesity with its related adipose inflammation. In contrast, data from Wistar rats suggest that diet-induced obesity affects intracellular insulin signaling mechanisms leading to hepatic IR, which plays a determinant role in inducing NAFLD independently of the inflammatory action of cytokines [8].

A fascinating observation is that fat cells, which develop from preadipocytes (themselves deriving from mesenchymal progenitors), derive from the mesoderm, although neural crest cells are able to differentiate into adipocytes [9]. The liver arises from the embryonic junction, yet the mesenchymal structure of the transverse septum, within which both blood vessels and the liver begin to form, is of mesodermal derivation [10]. The adipose tissue and liver, which share a common origin, function in an extraordinarily similar way [11]. Recent studies have demonstrated another important link between bone and fat cells, both arising from the same mesenchymal precursor cell within the bone marrow [12].

NAFLD, ranging from simple fatty liver to NASH, advanced fibrosis, and cirrhosis, is increasingly recognized as the most common liver disease in developed countries. The frequency by which NASH progresses to cirrhosis is uncertain, even though recent studies have reported rates of up to 15% [13]. Common risk factors for NAFLD include obesity, dyslipidemia, and type 2 diabetes mellitus. Although these risk factors appear to play a key role in the development of NAFLD, the precise mechanisms remain poorly understood. A growing body of evidence suggests that increased hepatocyte apoptosis is a critical mechanism contributing to inflammation and fibrosis of the liver. Hepatocytes can undergo programmed cell death via extrinsic as well as intrinsic pathways. Mitochondria play a general role in the final stage of apoptosis, but reactive oxygen species (ROSs) are thought to be the likely trigger of this process. Furthermore, the mammalian target of rapamycin (mTOR), also known as the mechanistic target of rapamycin or FK506 binding protein 12-rapamycin-associated protein 1 (FRAP1), is a highly conserved serine/threonine-protein kinase that plays a key role in cell growth, proliferation, and survival. mTOR regulates cell growth in response to growth factors, nutrients, and energy. Following research on aging, the family of nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases termed sirtuins was discovered. These proteins are important in mediating the antiaging effects of calorie restriction. Human beings have seven sirtuins, which

modulate cell cycles and various metabolisms in response to environmental stressors. This chapter reviews current thoughts on the mechanisms potentially involved in the dysregulation of liver metabolism in obese states.

54.2 MITOCHONDRIA AND REACTIVE OXYGEN SPECIES

Mitochondria convert energy for cells into adenosine triphosphate (ATP). This process, called oxidative phosphorylation, involves the transport of protons (hydrogen ions) across the inner mitochondrial membrane by means of the electron transport chain. Under normal conditions, oxygen is reduced to produce H_2O; however, in about 0.1%–2% of electrons passing through the chain, oxygen is, instead, prematurely and incompletely reduced to provide the superoxide radical $\cdot O_2^-$. Superoxide is not particularly reactive per se but can inactivate specific enzymes or initiate lipid peroxidation in its protonated form, hydroperoxyl ($HO_2\cdot$). The pK_a of hydroperoxyl (protonated superoxide) is 4.8; thus, at physiological pH most of it exists as superoxide.

Patients with NASH have increased lipid peroxidation [14], TNF-α [15], serum IL-6 levels [1], and mitochondrial β-oxidation rates [16]. The in vivo ability to resynthesize ATP was shown to be decreased after a fructose challenge in rats with acute hepatic damage [17]; hepatic mitochondria exhibited ultrastructural lesions and depletion of mitochondrial DNA, as well as decreased activity of respiratory chain complexes. ROSs may oxidize fat deposits to cause lipid peroxidation, which damages proteins and cardiolipin—an important component of the inner mitochondrial membrane—partially hampering the flow of electrons within the respiratory chain. This flow may be further decreased by TNF-α, which can release cytochrome *c* from mitochondria. Concomitantly, the increased fatty acid β-oxidation rate augments the delivery of electrons to the respiratory chain. Increased mitochondrial ROS formation can, in turn, directly oxidize mitochondrial DNA, other structural proteins, and intracellular lipids; enhance lipid peroxidation–related mitochondrial damage; trigger hepatic TNF-α formation; and deplete antioxidants, thus further blocking electron flow and increasing mitochondrial ROS formation in a vicious circle.

Mitochondrial dysfunction plays an important role in liver lesions, not only through the ROS-induced release of biologically active lipid peroxidation products but also through cytokine overexpression. In particular, the upregulation of both TNF-α and TNF receptor superfamily member 6 (Fas) triggers mitochondrial membrane permeability and apoptosis. The ingestion of apoptotic bodies by stellate cells stimulates fibrogenesis, which is further activated by lipid peroxidation products and high leptin levels [18]. Evidence is accumulating that mitochondrial dysfunction, particularly respiratory chain deficiency, plays a key role in the pathophysiology of NASH [19]. Indirect evidence of this mechanism is represented by the increased basal metabolic rate in hepatic steatosis [20], as well as by the high prevalence of drug-induced liver injury in obese patients with NAFLD [21].

Cook et al., who hypothesized that elevated β-oxidation in hepatocytes leads to IR and hepatic steatosis, suggested that an adaptive mechanism limits excessive intracellular storage of both fatty acids and triglycerides. Indeed, higher fatty acid availability could activate β-oxidation by decreasing carnitine *O*-palmitoyltransferase 1 inhibition through malonyl-coenzyme A (malonyl-CoA) [22] and by activating peroxisome proliferator-activated receptor α. The resulting high rate of β-oxidation would provide large amounts of reduced equivalents (NADH+ and flavin adenine dinucleotide) and electrons to the respiratory chain regardless of ATP demand. Thus, oxidative phosphorylation would be unbalanced, leading to high ROS production and mitochondrial and cellular damage. Yet excessive free radical production seems to activate stress proteins such as c-Jun N-terminal kinase (JNK) and the inhibitor of nuclear factor κB kinase subunit β (IKKβ), which are able to reduce insulin signal transduction with phosphorylation of serine 307 and serine 312 on insulin receptor substrate(IRS) proteins. Interestingly, some authors have suggested that IR can be explained only by excess ROS production [23], inasmuch as it could initiate mitochondrial degeneration and insulin signaling alteration. In both circumstances, generation of ROSs by the damaged respiratory chain can be augmented. ROS generation in an environment enriched with lipids, in turn, induces lipid peroxidation; this releases highly reactive malondialdehyde, which has diverse detrimental effects on hepatocytes and hepatic stellate cells.

The key point is that mitochondrial dysfunction can lead to apoptosis or necrosis, depending on the energy status of the cell. ROS and lipid peroxidation products also increase the generation of the cytokine transforming growth factor-β1 (TGF-β1) in addition to the Fas ligand, both of which play a key role in cell death, as well as TNF-α-induced inflammation and fibrosis. To confirm this hypothesis, the consequences of impairment of mitochondrial fatty acid β-oxidation and mitochondrial injury were investigated in human and rat liver slices using four inhibitors of β-oxidation. Etomoxir and CPI975 are direct inhibitors of the rate-limiting enzyme carnitine O-palmitoyltransferase 1 that regulates β-oxidation, whereas FOX988 and SDZ51-641 sequester and deplete the intramitochondrial pool of CoA. Diverse lesions were reported as a result of mitochondrial injury, including steatosis, inflammation, apoptosis, necrosis, and fibrosis [24].

Discovering a drug that is able to prevent oxidative stress and mitochondrial dysfunction in NASH represents a challenge for researchers, given that ROS is increasingly suspected to have a role in the generation of liver injury in NASH [25]. Indeed, in obese mice hepatocytes are supplied with large amounts of free fatty acids (FFAs), leading to increased mitochondrial respiratory activity. As previously emphasized, because mitochondria are a major source of ROS, an excessive fuel supply may lead to an increased production of mitochondrial ROS and may trigger oxidative stress in hepatocytes. Free radicals ($O_2^{\bullet-}$, $OH^{\bullet}$) and nonradical oxygen derivatives (H_2O_2, $ONOO^-$) can damage cellular structural proteins, membrane lipids, and DNA [26]. However, these

deleterious effects can be modulated by several enzymatic and nonenzymatic antioxidant factors that can either specifically inhibit the formation of ROSs or facilitate their conversion into inactive derivatives [27]. TNF-α inhibits insulin action, in part by activating JNK, via unknown mechanisms. However, researchers have confirmed that hyperglycemia increases mitochondrial ROS production. What is more, apoptosis signal-regulating kinase 1 (ASK1) was shown to activate the JNK and p38 mitogen-activated protein (MAP) kinase signaling pathways and to play a key role in TNF-α-induced apoptosis. Nishikawa and colleagues [28] demonstrated in Huh7 cells that TNF-α increases mitochondrial ROS production and ASK1 activity and that these TNF-α-induced phenomena were associated with JNK activation, increased serine 307 phosphorylation of IRS-1, and decreased insulin-stimulated tyrosine phosphorylation of IRS-1; these mechanisms could underlie TNF-α-induced IR.

The novel adipokine apelin-36 is associated with IR and the components of MetSyn. Through in vivo and in vitro pharmacological and genetics approaches, Dray et al. [29] demonstrated the involvement of endothelial nitric oxide synthase, adenosine monophosphate (AMP)-activated protein kinase (AMPK), and Akt in apelin-stimulated glucose uptake in soleus muscle. Remarkably, in obese and insulin-resistant mice apelin restored glucose tolerance and increased glucose utilization. The effects of apelin on glucose uptake and Akt phosphorylation are in part mediated by a Gi and AMPK-dependent pathway [30], thus representing a promising target in the management of IR beyond body weight loss. Serum levels of apelin-36 assayed in patients with biopsy-proven NAFLD showed a modest association with IR [31].

What is the link between body weight loss or exercise-induced body weight reduction and improvement of metabolic features, mainly IR? Intriguing hypotheses highlight the role of the decrease in circulating TNF-α following caloric restriction [32]. In these conditions, a decrease in TNF-α concentration contributes to the restoration of insulin sensitivity, probably by a more appropriate secretion of adiponectin. Still, a decrease in high levels of insulin stimulates lipoprotein lipase. Consequently, adipocytes modify their triglyceride turnover and FFA disposal to other deposits (i.e., the liver) decreases. It has been hypothesized that body weight loss improves hepatic IR before overt or incomplete peripheral IR. The decrease in tissue polypeptide substance antigen levels after the occurrence of body weight loss can perhaps mirror the ongoing oxidative stress recovery that lessens hepatic damage [33].

Oxidative stress, via ROSs, originates from mitochondria, cytochrome P450 2E1, peroxisome, and iron overload in hepatic steatosis. Excessive amounts of ROSs are considered to cause fatty liver progression to its more severe form, that is, NASH. Furthermore, oxidative stress worsens insulin sensitivity in hepatocytes and hepatic steatosis, in turn, causes oxidative stress, creating a vicious circle [34]. Consequently, oxidative stress and IR are strictly interconnected in NASH. Actually, Laurent et al. [35] found that the severity of hepatic steatosis correlates with serum thioredoxin levels, a marker of oxidative stress, in NASH patients. Therefore, it was hypothesized that a feedback loop of oxidative stress, IR, and steatosis would play a significant role in the development of NASH. This hypothesis was successfully tested by others [35].

54.3 MECHANISMS OF CYTOCHROME *c* RELEASE

Despite vast differences in its causes, the mode of hepatic cell death typically follows one of two patterns: necrosis or apoptosis with regeneration [36]. Whereas in necrosis large groups of contiguous cells die, in apoptosis individual dying cells separate from their neighbors and shrink rather than swell, a phenomenon described in the pathologic literature as piecemeal necrosis. Piecemeal necrosis, or interface hepatitis, is a feature of NASH as well as of viral chronic hepatitis and autoimmune hepatitis. Distinctive nuclear changes also occur in apoptosis, including nuclear lobulation and fragmentation, chromatin condensation, and internucleosomal DNA degradation. Eventually, cells fragment into apoptotic bodies (the so-called Councilman bodies) that are phagocytized by adjacent cells and macrophages for lysosomal degradation [37]. There is increasing evidence that necrosis and apoptosis are alternative outcomes of the same initiating factors and signaling pathways, a process known as necro-apoptosis. Apoptosis represents the execution of an ATP-dependent death program often initiated by death ligand/death receptor interactions, such as Fas ligand with Fas, which leads to a caspase activation cascade. Although controversies exist regarding which mode of cell death predominates in various forms of NAFLD and drug-induced liver injury [21], any mitochondrial damage caused by free radicals induces apoptosis.

Programmed cell death starts with the activation of initiator caspases (cysteine proteases) in signaling complexes: the apoptosome (on the intrinsic or mitochondrial pathway) or the degradosome (on the extrinsic or death receptor pathway). The proteolytic cascade then starts, through the activation of downstream caspases and DNases, which are responsible for DNA degradation. Mitochondria provide a crucial contribution to apoptosis by releasing cytochrome *c*, the essential component of the apoptosome, Smac/diablo, and Omil/HtrA2, which link the caspase inhibitors; endonuclease G and apoptosis-inducing factor are also released. Cytochrome *c* binds to apoptotic protease-activating factor 1 (Apaf-1), which is floating freely in the cytoplasm. Using the energy from ATP in the mitochondria, Apaf-1 and cytochrome *c* bind together to form apoptosomes, which bind to and activate caspase-9, another free-floating protein. Caspase-9 then cleaves the proteins of the mitochondrial membrane, causing it to break down and start a chain reaction of protein denaturation and subsequent phagocytosis of the cell. These factors drop out of the mitochondrial membrane through the apoptosis regulator bcl–2-associated X (Bax) protein and bcl–2 homologous antagonist/killer (Bak) protein-containing channels. The process is due to an enzyme-driven mechano-remodeling of the whole structure, as well as to phospholipid

peroxidation and proteolysis in the inner membrane. An important mechanism in apoptotic regulation is the changes in the subcellular distribution of pro- and antiapoptotic proteins. Among the proteins that change their localization and may promote apoptosis are nuclear proteins. Several nuclear proteins such as cellular tumor antigen p53, nuclear hormone receptor Nur77, histone H1.2, and nucleophosmin have been reported to accumulate in the cytosol and/or mitochondria and promote the mitochondrial apoptotic pathway in response to apoptotic stressors [38]. A common event leading to both apoptosis and necrosis is increased mitochondrial permeability and dysfunction.

The mechanisms of cytochrome *c* release remain controversial. Malhi and colleagues [39] proposed that proapoptotic bcl-2 family members, such as tBid, Bax, and Bak, promote the formation of specific cytochrome *c* release channels in the mitochondrial outer membrane. An alternative mechanism hinges on the formation of pores in the inner membrane that nonspecifically leak solutes up to 1500 Da. Opening mitochondrial permeability transition (MPT) pores leads to mitochondrial swelling [39]. Consequently, the outer membrane ruptures to release intermembrane proteins [40]. In one model, the MPT pore consists of the voltage-dependent anion channel from the outer membrane; the adenine nucleotide transporter from the inner membrane; and cyclophilin D [41,42], a binding protein for cyclosporin A (CsA), which inhibits the MPT in a fashion unrelated to its immunosuppressive properties [43]. Another model by He and Lemasters [44] proposes that MPT pores form by the aggregation of damaged, misfolded membrane proteins. Chaperone-like proteins initially block conductance through these misfolded protein clusters. It is noteworthy that increased Ca^{2+} opens these perfectly regulated MPT pores, but this effect is counteracted by CsA in vitro. It has been concluded that when protein clusters exceed the chaperones available to block conductance, unregulated pore opening occurs [44]. Malhi and colleagues [37,39] opportunely clarified this complex network.

Beclin 1 usually interacts with several autophagy-inhibiting proteins including the antiapoptotic proteins from the bcl-2 family (bcl-2, bcl-XL, and Mcl-1) and the inositol 1,4,5-trisphosphate receptor, which interacts with beclin 1 indirectly, via bcl-2. Beclin 1 possesses a BH3 domain that usually interacts with a hydrophobic cleft, the BH3 receptor domain, contained within bcl-2, causing its homologue pores to open. All these additional activities are required for optimal autophagy induction by BH3 mimetics, pointing to the existence of a coordinated autophagy regulatory network [45]. BH3-only bcl-2 family members, including tBid, which is formed by death receptor–linked caspase-8 activation, cause Bax/Bak-dependent permeabilization of the outer membrane. Permeabilization may involve formation of channels in the outer membrane or induction of a CsA-sensitive MPT followed by mitochondrial swelling and outer membrane rupture. After membrane permeabilization, cytochrome *c* is released to the cytosol, activating in sequence caspase-9 and caspase-3 in a reaction requiring Apaf-1 and desossi-ATP (or ATP). The X-linked inhibitor of apoptosis blocks caspase-9/3 activation, whereas DEVDcho is a substrate analog inhibitor that also blocks caspase-3 activity. In the presence of constant and deep mitochondrial dysfunction, ATP is partially lowered as a consequence of the activation of a step-limiting enzyme, that is, the mitochondrial uncoupler–stimulated ATPase. Attributable to ATP depletion, caspase activation is blocked, leading to cell necrosis. Fructose, the main source of ATP via the glycolytic pathway, inhibits membrane failure and the resulting cell death [46]. Again, the elucidation of this system has been reviewed by Malhi et al. [37,39].

In studies of signaling pathways involved in the protection of cells against death induced by ATP depletion, recent results indicated that growing the ATP-depleted Madine–Darby canine kidney cells in glycine-containing media increased the level of phosphorylated extracellular signal-regulated kinase 1 and 2 (ERK1/2), Ets-like transcription factor-1 (Elk1), Akt, and forkhead box protein O1 and decreased the level of phosphorylated p38 MAP kinase, with little effect on the phosphorylation status of JNK 1 and 2 [47].

54.4 OTHER PATHWAYS INDUCING/INHIBITING APOPTOSIS, INSULIN RESISTANCE RELATED

The mechanism by which FFAs mediate apoptosis in NAFLD is unclear. JNK activation is pivotal in both MetSyn accompanying NAFLD and cellular programmed death. Multiple hepatocyte cell lines and primary mouse hepatocytes were treated in culture with monounsaturated fatty acids and saturated fatty acids. Collectively, the data indicated that saturated FFAs induce JNK-dependent hepatocyte lipoapoptosis by activating the proapoptotic proteins Bim and Bax of the bcl-2 family, which trigger the mitochondrial apoptotic pathway [39]. Low values of serum bcl-2 predict a greater prevalence of metabolically unhealthy overweight/obese patients [48]. Data strongly suggest that adipocyte apoptosis is a key initial event that contributes to macrophage infiltration into adipose tissue, IR, and the hepatic steatosis associated with obesity in both mice and humans [49].

Heat shock proteins (HSPs) are a family of ubiquitously expressed, highly homologous chaperone proteins that are induced in response to environmental, physical, and chemical stresses to attenuate the consequences of unfolded or misfolded proteins. These chaperone molecules restrict cellular damage and facilitate its recovery [50]. The ability of HSPs to maintain cell survival depends mainly on inhibition of caspase activation and programmed cell death. HSPs, particularly HSP70, can inhibit the activity of proapoptotic bcl-2 proteins to prevent permeabilization of the outer mitochondrial membrane and release of proapoptotic factors. The disruption of apoptosome formation represents another mechanism by which HSPs can prevent caspase activation and induction of apoptosis. For instance, HSP70 blocks the recruitment of procaspase-9 to the Apaf-1/dATP/cytochrome *c* apoptosome complex [50]. This likely induces

a conformational change that hinders procaspase-9 binding. Several signaling cascades involved in the regulation of key elements within the apoptotic cascade are in part under the control of HSPs, including those involving JNK, nuclear factor κB, and AKT [50].

HSP70 is a key molecule in the relationship between hepatic steatosis and carotid intima-media thickness [51]. Petersen et al. [52] examined the hypothesis that IR promotes the development of atherogenic dyslipidemia by altering the distribution pattern of postprandial energy storage via reduced mitochondrial oxidative and phosphorylation activity in skeletal muscle. They concluded that IR in skeletal muscle is sufficient to promote atherogenic dyslipidemia by changing the pattern of ingested carbohydrate from glycogen synthesis in skeletal muscle into hepatic de novo lipogenesis. This shift leads to an increase in plasma triglyceride concentrations and a reduction in plasma high-density lipoprotein concentrations [52].

An average adult is made up of 42% (male) or 36% (female) skeletal muscle as a percentage of body mass [53]. In skeletal muscle, insulin increases glucose uptake by increasing the expression of GLUT4 transporters at the plasma membrane, oxidation is enhanced by glycolysis, and glucose is stored as glycogen; in addition, fatty acid β-oxidation and glycogenolysis are inhibited. Insulin acts on skeletal muscle, leading to fatty acid storage at the expense of postprandial reduction in glycemia and lipemia, even though via other routes it increases fat content and adipose tissue mass. In contrast, in the presence of hypoglycemia glucagon attempts to counter low energy loads and reverts the aforementioned effects by switching on processes that mobilize energy reserves while promoting the use of fatty acids by tissues instead of glucose. Glucagon, via protein kinase A, activates hormone-sensitive lipase in the fat tissue [54], thus generating significant glycerol amounts that the liver uses in the synthesis of glucose and FFAs, to be used as fuel by most tissues. At a molecular level, a drop in the energy load in cells activates a fuel sensor (i.e., AMPK) [55], which in turn activates lipogenesis. Research suggests that the exposure of a special type of hepatic cells (rat hepatoma cell line derived from H35 cells [FaO]) to lipid emulsion increases mitochondrial ROS production and decreases cellular energy levels, followed by cell death [56]. Reduced circulating and muscle tissue carnitine levels, possibly leading to impaired mitochondrial function, have been postulated to be involved in the pathogenesis of IR [57]. Carnitine is involved in energy metabolism by carrying acyl groups into mitochondria and transporting acetate from mitochondria to cytosol. Also, carnitine is critical in glucose metabolism because it reduces the acyl-CoA/CoA ratio in mitochondria, which in turn increases the activity of pyruvate dehydrogenase and facilitates glucose disposal [58].

Obesity is accompanied by hyperleptinemia. The failure of elevated leptin levels to suppress feeding and mediate weight loss in common forms of obesity is defined as leptin resistance [59]. Leptin acts by binding to specific receptors, which are expressed in the central nervous system, mostly in afferent satiety centers of the hypothalamus, but also in adipose tissue, skeletal muscle, pancreatic β-cells, and the liver [60]. Of the six isoforms of the leptin receptor, ObRb is the one that mediates most of the biological effects of leptin through the activation of the Janus kinase 2 (JAK-2)/signal transducer and activator of transcription 3 (STAT3) pathway. More specifically, leptin binding to ObRb results in autophosphorylation and activation of JAK-2, which then leads to phosphorylation of the highly conserved tyrosine residues located in the intracellular domain of ObRb [61]. STAT3 activation ultimately leads to increased transcription and expression of suppressor of cytokine signaling 3 (SOCS-3). Although SOCS proteins were thought to be primarily involved in the attenuation of cytokine signaling through classic negative feedback, there is now growing evidence that SOCS-3 also attenuates insulin signaling [62]. Leptin receptor signaling also results in the activation of phosphoinositide-3-kinase (PI3K). Under normal conditions, leptin improves peripheral insulin sensitivity through PI3K in the liver by suppressing hepatic glucose production [63].

Src homology 2 (SH2) domain–containing protein B (SH2-B), a JAK-2-interacting protein, has been identified as a key regulator of leptin and insulin sensitivity, glucose homeostasis, and body weight in mice [64]. It seems that the SH2-B protein interacts with both JAK-2 and IRS-2 and promotes IRS-1/2-mediated activation of PI3K in response to leptin [65]. In mice, SH2-B loss of function has been shown to lead to significant metabolic defects, including hyperinsulinemia and hepatic steatosis [66]. Leptin, as a cytokine, can have important effects on both innate and adaptive immune responses. Owing to its broad action, signaling pathways triggered by leptin receptors can promote cross talk among different cells [67]. mTOR and AMPK also have been proposed to play a role in leptin signaling.

54.5 MAMMALIAN TARGET OF RAPAMYCIN SIGNALING PATHWAY

Complex networks are involved in ensuring that various tissues have sufficient energy to meet basic metabolic processes, beyond a basal reservoir of nutrients. Among these systems, an important one is the mTOR-raptor (regulatory-associated protein of mTOR) signaling pathway (Figure 54.1), which assesses intracellular amino acid disposal and cellular energy status. This information is coupled with signals from cell surface receptors (i.e., insulin receptor, PI3K, and *Akt*). Many of the discoveries and insights into TOR signaling and function were gathered from genetics studies in yeast, worms, and *Drosophila*; from biochemical studies in mammalian cells; and from pharmacological studies using rapamycin, a specific inhibitor of mTOR [68].

mTOR is a serine/threonine-protein kinase that contains several regulatory domains. These include a catalytic domain, which binds an associated protein (GßL); an FKBP12 rapamycin–binding domain; a protocadherin FAT domain comprehending ferric reducing antioxidant power (FRAP); ataxia telangiectasia mutated (ATM);

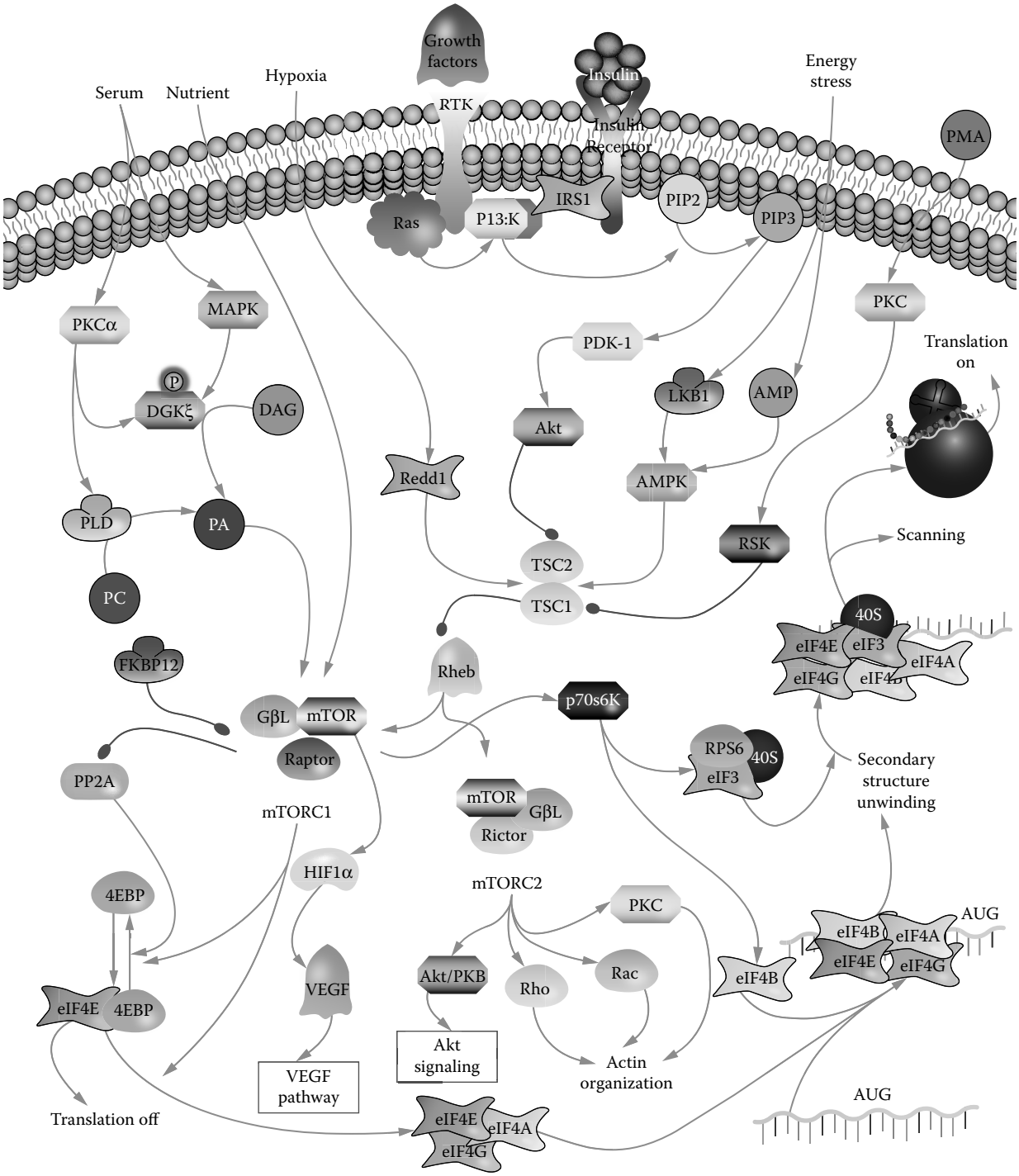

FIGURE 54.1 (**See color insert.**) Mammalian target of rapamycin (mTOR) pathway: VEGF, vascular endothelial growth factor. (Kind permission of Qiagen Company.)

transformation/transcription domain–associated protein (TRRAP); and a smaller FRAP, ATM, TRRAP C-terminal domain that acts with the FAT domain to influence kinase activity by facilitating protein–protein interaction. Within the N-terminal half of mTOR, there is a series of Huntingtin elongation factor 1A–protein phosphatase 2A-A subunit–TOR repeats that bind cytosolic proteins such as raptor and rictor (rapamycin-insensitive companion of mTOR). These processes and pathways are described in a recent publication [69]. When raptor is bound, mTOR kinase activity can be inhibited by rapamycin and stimulated by Rheb. Triggered by the mTOR-GßL-raptor complex (called mTORC1), two downstream targets are phosphorylated: eukaryotic initiating factor 4E–binding protein 1 and S6K1/2. These steps in turn lead to protein synthesis, ribosomal biogenesis, and autophagy. The mTOR-GßL-rictor complex (also known as mTORC2) participates in actin organization [68,70] and mediates the phosphorylation and activation of Akt. Protein

phosphorylation, protein localization, and control of mTOR activity depend on the binding of auxiliary cytosolic proteins (such as raptor, rictor, and GßL). Signal perception, transduction, and downstream regulatory factors are under the control of various sensors that sense changes in nutrient availability (mainly amino acids), changes in intracellular energy levels (input from the AMPK signaling pathway), and changes in the extracellular environment (from hormone/adipokines, i.e., insulin, leptin, and adiponectin binding to cell surface receptors).

The main function of the mTOR signaling pathway is to couple energy availability to the rate of protein synthesis and cell growth. Another function is to sense amino acid availability and glucose availability and then link nutrient availability to the rate of protein synthesis and cell growth. The activation of the mTOR signaling pathway suppresses insulin sensitivity through serine phosphorylation and the inhibition of IRS1 by mTOR and its downstream effector, S6K1 [71]. TNF-α–IKKβ-mediated inactivation of TSC1 results in phosphorylation of IRS1 serine 307 and serine 636/639, impaired insulin-induced glucose uptake, tyrosine phosphorylation of IRS1, and the association between IRS1 and PI3K p85. A higher expression of pIKKβ (S181), pTSC1 (S511), and pS6 (S240/244) was found in livers obtained from both C57BL/6J mice on a high-fat diet and B6.V-Lep ob/J mice.

Clinical trials employing the mTORC1 inhibitor rapamycin to immunosuppress patients following organ transplantation have documented the development of hypertriglyceridemia and elevated serum FFAs. These data demonstrate that inhibition of mTORC1 signaling synergizes with the β-adrenergic-cAMP/protein kinase A pathway to augment phosphorylation of hormone-sensitive lipase to promote hormone-induced lipolysis. Moreover, they reveal a novel metabolic function for mTORC1 (i.e., suppression of lipolysis and increase in triglyceride storage) [72]. The effect of mTOR inhibitors is solely on the mTORC1 protein, leading to an increased activity of the kinase Akt via the inhibition of the mTORC1 negative feedback loop. A high-fat diet appears to inhibit the PI3K/protein kinase B (Akt, also known as PKB) signaling pathway, which may lead to hepatocellular injury through the activation of the mitochondrial membrane pathway of apoptosis [73].

TGF-β1 is a regulator of normal liver cell homeostasis [74]. It inhibits the proliferation of normal hepatocytes in cell culture after partial hepatectomy and induces hepatic cell death [75]. TGF-β1 signals through cytoplasmic mediators known as Smads (mothers against decapentaplegic homologs). Following TGF-β1 receptor–mediated phosphorylation, Smad2 and Smad3 associate with Smad4 and translocate into the nucleus to regulate gene expression. Smad7 competes with Smad2 and Smad3 for binding to TGF-β1 receptors and promotes ubiquitin-mediated receptor degradation, thereby suppressing TGF-β1 signaling [74]. TGF-β1 restrains growth through the induction of the cyclin-dependent kinase inhibitors $p15^{INK4B}$ and $p21^{CIP1}$ and the inhibition of genes that regulate cell cycle progression [76]. The induction of cell death by TGF-β1 has been linked to its ability to activate the JNK/transcription factor AP-1 axis [77], promoting ubiquitin-mediated degradation of TGF-β-activated kinase 1 and repression of the JNK/AP-1 axis, as described by Kaur et al. [78].

The levels of TGF-β1 have been shown to increase in hepatic fibrosis in rats and to decrease after treatment with exogenous IL-10 to suppress TGF-β1 expression [79].

As described by Chen et al. [80], serum deprivation induces apoptosis in NIH3T3 cells. This is associated with increased intracellular ceramide generation and the activation of p38 MAP kinase. Treatment of cells with TGF-β1-activated ERK1/2 inhibited the serum deprivation–induced p38 activation and the increase in intracellular ceramide formation, leading to the stimulation of cell proliferation and suppression of apoptosis. However, inhibition of p38 MAP kinase by SB203580 significantly reduced the serum deprivation–induced apoptosis. Overexpression of p38 increased cell apoptosis and reduced the antiapoptotic effect of TGF-β1.

The sirtuin (Sirt) family mediates homeostatic responses to certain physiological stresses such as nutrient restriction. Sirt1 is known to be involved in gluconeogenesis and fatty acid oxidation in the liver; it also senses nutrient availability in the hypothalamus, influences obesity-induced inflammation in macrophages, modulates the activity of the circadian clock in metabolic tissues, and regulates fat mobilization in white adipose tissue and insulin secretion in the pancreas. The activity of Sirt1 appears to be under the control of AMPK and adiponectin [81]. Wang et al. found that Sirt1 in mice positively regulated transcription of the gene encoding rictor, a component of mTORC2, triggering a cascade of phosphorylation of Akt at S473 and Foxo1 at S253, resulting in decreased transcription of the gluconeogenic genes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. Liver-specific Sirt1 deficiency caused hepatic glucose overproduction and chronic hyperglycemia and increased ROS production [82].

The expression of other growth factors promoting liver regeneration such as hepatocyte growth factor, TGF-α, epidermal growth factor, and vascular endothelial growth factor was increased in rats transplanted with endothelial progenitor cells, together with hepatocyte proliferation. There is a substantial body of evidence to suggest that oval cells are involved in liver regeneration, as they differentiate into hepatocytes and biliary cells. Bone marrow cells have been shown to be a source of stem cells with the capacity to repopulate the liver [83]. There is relatively little information regarding the cytokines that influence oval cells. Some results have indicated that oval cells are less sensitive to TGF-β1-induced growth inhibition than hepatocytes [84]. The stromal cell–derived factor 1 (SDF-1)–CXCR4 (the receptor for SDF-1α) axis may be a master regulator of trafficking of normal stem cells. In addition, oval cells express CXCR4 and migrate along the SDF-1α gradient [85]. Gp130 or IL-6 signal transducer (also called oncostatin M receptor)-mediated IL-6 signaling may play a role in oval cell proliferation in vivo. Levels of IL-6 have been shown to be elevated in the liver of mice treated with a steatogenic diet to create a NASH model, that is, a choline-deficient ethionine-supplemented diet that

induces oval cells, whereas in IL-6 knockout mice there is a reduction of oval cells. In a 2007 study, Yeoh et al. [86] determined the impact of IL-6 signaling on oval cell–mediated liver regeneration in vivo. The role of the spleen in NASH is most intriguing [1], which is generally increased in volume, a finding that has been confirmed [87]. Fresh evidence suggests that the spleen plays an important regulatory role in the fibrosis, preneoplastic lesion, and lipid metabolism of the liver [88]. Recent research has emphasized the key role played by serum concentrations of cytochrome *c* in the balance between pro- and antiapoptotic processes, that is, between cell death and growth [89].

54.6 CONCLUSION

Obesity is a known risk factor for NAFLD, type 2 diabetes, hypertension, stroke, gallbladder disease, osteoarthritis, and obstructive sleep apnea, as well as some forms of cancer (breast, colorectal, endometrial, and kidney). Plasma FFAs released through lipolysis in white adipose tissue have been shown to be a major contributor to triglyceride accumulation observed in NAFLD. Endoplasmic reticulum stress activation, mitochondrial dysfunction, hyperproduction of ROS, and increased apoptosis have been reported in most animal models of hepatic steatosis and steatohepatitis. These features are commonly observed in obese animals and in those exposed to chronic dietary fat-rich diets.

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55 Obesity, Lung Function, and Lung Disease

Nour A. Assad, Jesse H. Alvarado, and Akshay Sood

CONTENTS

55.1 INTRODUCTION

Obesity, defined by a body mass index (BMI) ≥30 kg/m^2 in adults, is the most common metabolic disease in the world. The prevalence of obesity in the United States increased during the last two decades of the twentieth century. Even though there appears to be a recent slowing of the rate of increase,[1] 35.7% of all U.S. adults during the period 2009–2010 were obese.[2] In 2008, the medical costs associated with obesity in the United States were estimated at $147 billion.[3] Physicians are therefore routinely challenged by the comorbidities associated with obesity. Although the associations between obesity and increased risk for cancer and cardiovascular,

endocrine, and rheumatologic diseases are well described, the respiratory effects of obesity, outside sleep-related disorders, are less well known. This chapter reviews the effect of obesity on pulmonary function test parameters and on asthma, chronic obstructive pulmonary disease (COPD), and influenza.

55.2 OBESITY AND PULMONARY FUNCTION TESTS

Obesity affects various resting pulmonary function parameters such as compliance, lung volumes, spirometric measures, diffusing capacity, and gas exchange. Impairment in these parameters is more clearly demonstrated in severe obesity.[4]

55.2.1 Breathing Patterns

Severely obese individuals (BMI $\geq$ 40 kg/m^2) have increased respiratory rates compared with normal-weight people (15–21 vs. 10–12 breaths per minute).[5] The higher respiratory rate among obese individuals is accompanied by smaller tidal volumes but overall higher minute ventilation rates.[5]

55.2.2 Respiratory Compliance

Respiratory compliance is defined as the change in lung volume per unit change in pressure. It combines the contributions from the chest wall and lungs, both of which are reduced in obesity.[6] While the decrease in chest wall compliance in obese individuals is due to the reduced distensibility of extrapulmonary structures from excess truncal fat,[6] the decrease in lung compliance may be secondary to increased pulmonary blood volume and increased closure of dependent airways with associated atelectasis.[7]

55.2.3 Lung Volumes

A decrease in expiratory reserve volume (ERV) is the most consistent finding in obesity (Figures 55.1 and 55.2).[8] Further, an increase in BMI is associated with an exponential decrease in ERV (Figure 55.2).[9] This is explained by the upward displacement of the diaphragm by the contents of the obese abdomen.[10]

Another consistent but less pronounced negative correlation is seen between obesity and functional residual capacity (FRC). Since the effect of BMI on residual volume is rather modest,[9] the lower FRC in obese subjects is primarily due to their lower ERV (Figure 55.1).

If obesity causes lower FRC values, one would expect a similar effect on total lung capacity (TLC). However, in reality this is not observed, except in either severely obese subjects or those with excessive central adiposity or obesity hypoventilation syndrome.[7] Since most obese individuals maintain their TLC values, they may have a slightly higher inspiratory capacity to compensate for their reduced FRC values.

55.2.4 Spirometry

Obesity is associated with low vital capacity (VC) and forced expiratory volume in 1 second (FEV_1) but normal or high FEV_1/VC ratio, creating a restrictive or nonspecific ventilatory pattern. A major explanation for the increase in ratio is peripheral airway closure, which leads to air trapping and a subsequent disproportionate reduction in VC.[11] In a 1990 study by Rubinstein et al.,[11] obesity was associated with low maximal mid-expiratory flow rate ($FEF_{25\%-75\%}$) value after adjustment for VC. Since $FEF_{25\%-75\%}$ may reflect small airway function, this finding suggests that obesity primarily affects small airways. Less often, abdominal obesity may also present with an obstructive pattern by affecting large airway function, leading to a reduction in the FEV_1/VC ratio.[12]

55.2.4.1 Effect of Obesity Pattern

Three large cohort studies demonstrate that abdominal obesity has a disproportionate effect on spirometric values regardless of BMI.[12–14] The findings of these studies contradict the previous impression that only severe obesity is associated with a reduction in VC. The effect of abdominal obesity on VC values has prompted a recommendation for measuring and reporting waist circumference during the interpretation of spirometry.[15]

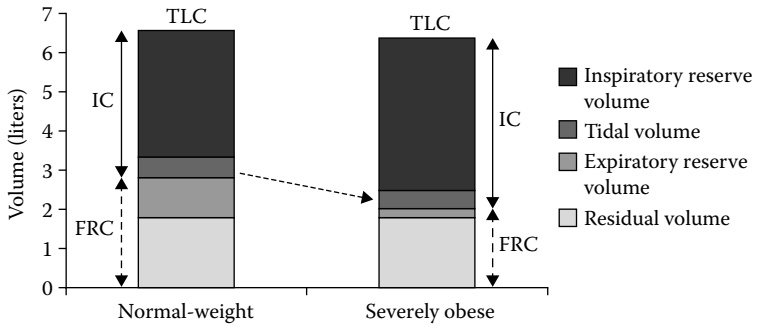

FIGURE 55.1 Effect of obesity on lung volumes: expiratory reserve volume (ERV) is decreased in obesity. Functional residual capacity (FRC), the sum of ERV and residual volume, is usually reduced as well, often approaching residual volume (see arrow). The decline in FRC in obese subjects is primarily the result of reduced ERV. Total lung capacity (TLC), the sum of FRC and inspiratory capacity or (IC), is usually preserved. Therefore, to compensate for the reduced FRC, IC, the sum of inspiratory reserve volume and tidal volume, may be increased in severe obesity. (From Sood A, *Clin. Chest Med*., 30, 445–54, vii, 2009. With permission.)

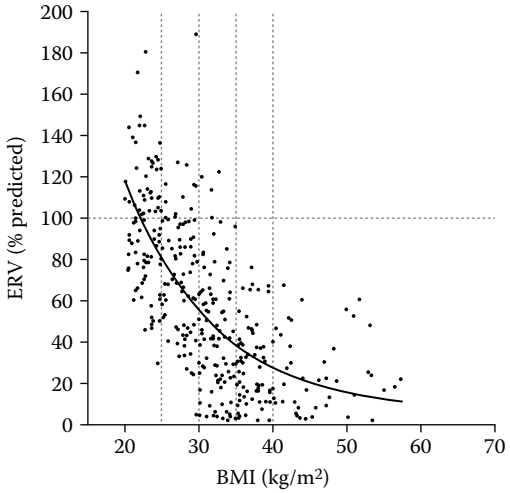

FIGURE 55.2 Expiratory reserve volume (ERV) decreases rapidly in an exponential relationship with increase in body mass index (BMI): the best-fit exponential regression equation for ERV is as follows: $ERV = 587.8 \times e^{-0.083 \times BMI} + 6.5$. The r^2 value for ERV was 0.49 ($p < .01$). (From Jones RL and MM Nzekwu, *Chest*, 130, 827–33, 2006. With permission.)

55.2.4.2 Effect of Sex

Some studies suggest that the effect of obesity on spirometric values is more pronounced among men than women possibly because of the greater abdominal obesity seen among men than women. However, because of their smaller initial spirometric values at baseline, women may suffer a greater percentage decline in lung function as a consequence of obesity.[10]

Given their lower baseline VC and FEV_1 values, obese individuals may be more susceptible to the long-term adverse effects of cigarette smoking, pulmonary infections, and environmental exposures. However, the interaction between these variables and obesity on longitudinal decline in spirometric function has not been reported in the literature.

55.2.5 Oxygenation and Ventilation-Perfusion Mismatch

Obese individuals have a greater ventilation–perfusion mismatch than normal-weight people. This mismatch results from the lung bases being relatively more perfused than ventilated in both sitting and recumbent positions in obese people.[16] Further, this is the consequence of the premature closure of small airways in dependent lung zones in obese subjects.

Interestingly, there seems to be a correlation between low FEV_1 and the presence of hypoxemia as well as increased alveolar–arterial oxygen ($A\text{-}aO_2$) gradient.[16] Once again, the pattern of obesity seems to play a role as it was recently shown that there is a linear relationship between waist to hip ratio and partial pressures of oxygen and carbon dioxide in arterial blood (PaO_2 and $PaCO_2$) and $A\text{-}aO_2$ gradient.[17] This ventilation–perfusion mismatch explains the mild widening of $A\text{-}aO_2$ gradient that is observed in obesity at rest.[17] Unlike other lung diseases, the $A\text{-}aO_2$ gradient in obese individuals decreases with exercise because of the recruitment of atelectatic units with deeper inspiration.

Despite the greater carbon dioxide production from increased tissue mass, individuals with simple obesity usually maintain eucapnia (i.e., a normal $PaCO_2$) because of their higher minute ventilation.[5] On the other hand, subjects with the obesity hypoventilation syndrome may be unable to increase their minute ventilation and may therefore develop hypercapnia.[18]

55.2.6 Diffusing Capacity

Diffusing capacity is generally preserved in obesity. However, some studies suggest an increased value in obese individuals, whereas others suggest the opposite.[4,19,20] Diffusing capacity may be increased because of the presence of greater pulmonary blood volume in obese individuals. On the other hand, structural changes in the lung interstitium from lipid deposition and/or decreased alveolar surface area may decrease diffusing capacity values in a minority of obese individuals.[20]

55.2.7 Effect of Change in Weight on Pulmonary Function

Most effects of obesity on pulmonary function are reversed with weight loss. Multiple studies have shown significant improvements in ERV with variable degrees of weight loss. A relatively large decrease in mean BMI from 47 to 39 kg/m^2 by a low-calorie diet in one study resulted in a tripling of ERV.[21]

The converse, that is, the effect of gain in weight on change in lung function, is inadequately studied. Among healthy young adults, increasing BMI in initially thin participants were associated with increasing and then stable forced vital capacity (FVC) and FEV_1. On the other hand, there were substantial lung function losses with increasing BMI among initially fat subjects.[22] Lung function losses with increasing BMI have also been described in older populations with smoking and occupational exposures.

55.2.8 Mechanisms

Obesity affects respiratory function via various mechanical and inflammatory mechanisms. Mechanical effects include reduction in respiratory compliance and lung volumes, as well as gas trapping from premature small airway closure, particularly at the lung bases. On the other hand, chronic or intermittent hypoxia in obese individuals may lead to a greater secretion of proinflammatory cytokines and a lesser secretion of anti-inflammatory cytokines by adipose tissue. This has been hypothesized to result in greater inflammation and edema of small airways, resulting in their premature closure.

55.3 OBESITY AND ASTHMA

The frequencies of asthma and obesity in the United States increased by 50% and 73%, respectively, during the period 1980–2000.[23] This contemporaneous rise of the two diseases is not coincidental—it is now increasingly apparent that obesity is a risk factor for asthma.

55.3.1 Epidemiology

Obesity is associated with an increased risk for incident and prevalent asthma, and there appears to be a dose–response gradient between asthma risk and severity of overweight/obesity status.[24] The obesity–asthma association is remarkably consistent across a wide range of populations and demonstrable among various races and ethnicities, different ages (ranging from children to the elderly), both developed and developing countries, and different socioeconomic classes.

55.3.1.1 Sex Interaction

It is currently inconclusive whether the association of obesity with asthma varies by sex. Some studies have shown than the obesity–asthma association is stronger in men than in women.[25] However, most studies, including the initial reports of this association, show that this association is stronger or exclusively seen among women than men.[26–30] One potential explanation for the stronger association among women than men may be the effect of female sex hormones, as suggested by a study that demonstrated a stronger obesity–asthma association among girls with early versus late menarche.[31]

55.3.1.2 Atopy Interaction

Atopy, defined as the genetic predisposition to develop immunoglobulin E (IgE) antibodies to allergen exposure, is a strong risk factor for asthma, particularly for the childhood-onset type. Although the issue is not settled, a few large studies have demonstrated a stronger association of nonatopic asthma with obesity.[32–34] This finding suggests that obesity-associated asthma may have a non-IgE or a non-TH2 mechanistic basis and may therefore be a different endotype of asthma (see Section 55.3.5).

55.3.2 Effect of Fat Composition and Distribution

High BMI does not always reflect excess body fat. For example, BMI is a less reliable measure of excess fat in men than in women, since it reflects their greater muscle mass. Obesity is thus believed to be a heterogeneous disorder that involves multiple related phenotypes. It is plausible that excess ectopic body fat (fat that is present in nonadipose tissues like skeletal muscles and viscera) is more strongly associated with asthma than physiological fat depots. Ectopic body fat might also be related to proinflammatory cytokines (adipokines) that are associated with asthma, as discussed later in Section 55.3.3.3.

55.3.2.1 Fat Mass, Lean Mass, and Asthma

Some studies suggest that fat mass may have differing associations with asthma between men and women. One study that analyzed percentage of total fat (using bioelectrical impedance technique) found a significant association between percentage of fat and asthma only in women and not in men. Another study using dual-energy x-ray absorptiometry (DEXA) technique interestingly suggested that excess lean mass was a stronger predictor for asthma than excess fat mass among women, whereas lean mass was protective against asthma among men.[35] The authors hypothesized that DEXA scanning accurately identifies large physiological fat depots but inaccurately identifies ectopic smaller fat deposits within skeletal muscles and viscera as lean mass. This ectopic fat is more metabolically active than physiological fat and might play a more significant role in airway inflammation. Further, the deposition of ectopic fat in skeletal muscle is more prominent in women, a process called "marbling" of the muscles (Figure 55.3). Thus, the greater marbling of muscles among women than men may explain the sex-specific associations of lean mass with asthma in this study.

FIGURE 55.3 Marbling of muscle: the term derived from a gross description of beef steak refers to intramuscular fat deposition, giving an appearance similar to marble pattern. Marbled muscle is metabolically more active. Further, leptin is involved in the marbling of muscle in beef cattle. (From Sood A, *Exerc. Sport Sci. Rev.*, 39, 48–56, 2011. With permission.)

55.3.2.2 Android versus Gynoid Body Shape and Asthma

Android body shape is characterized by an abdominal distribution of fat, whereas gynoid shape is characterized by a gluteofemoral distribution of fat (Figure 55.4). Some cross-sectional studies have shown that abdominal adiposity is a stronger predictor for prevalent asthma in women than BMI alone.[36,37] This finding may be explained by the metabolic effects of visceral fat and/or the direct mechanical effects of abdominal adiposity on the lung. The metabolic effects of abdominal adiposity on the airway are further supported by studies suggesting that insulin resistance may increase the risk for asthma, independent of BMI.[38] However, a recent longitudinal study examining the risk for incident asthma among women has challenged the belief that abdominal fat distribution is the key predictor for asthma in women.[39] Neither the metabolic syndrome nor its individual components (i.e., abdominal adiposity, systemic hypertension, hyperglycemia, high triglyceride, or high high-density lipoprotein [HDL]-cholesterol) were stronger predictors than BMI alone in predicting incident asthma risk among women in this study.[39] It is difficult to explain the contradiction of the associations of abdominal adiposity with prevalent asthma compared to incident asthma. One possible explanation is that asthma itself results in preferential abdominal fat accumulation among women.

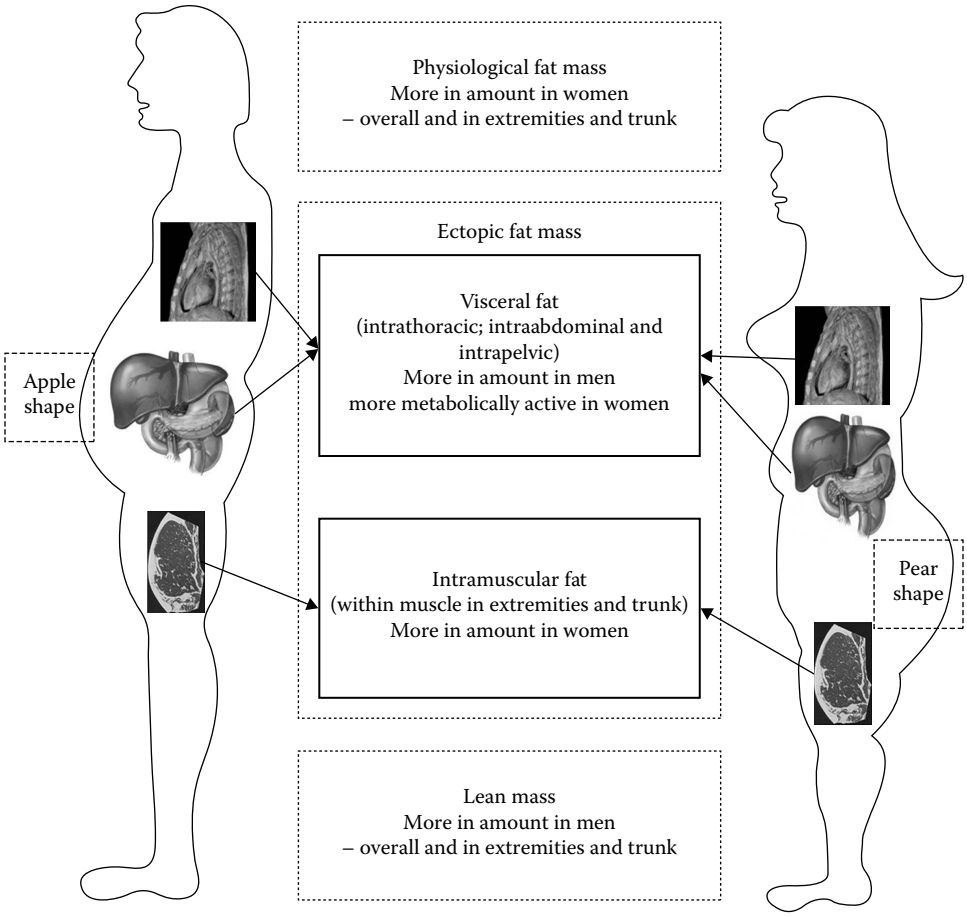

FIGURE 55.4 Sex-related differences in obesity phenotypes: typically, women manifest the gynoid pattern and men the android pattern of obesity, corresponding to the pear-shaped and apple-shaped body habitus, respectively. Interestingly, asthma risk appears to be strongly associated with the development of android pattern of obesity in women. On the other hand, the gynoid pattern of obesity is not so strongly associated with asthma. The figure also demonstrates sex-related differences in the distribution of lean and fat mass including physiological fat and ectopic fat mass (the latter term further includes hepatic, visceral, and intramuscular fat depots). Although the specific obesity phenotype that is best associated with asthma is unclear, ectopic fat in the truncal viscera and skeletal muscle may play an important role in women. (From Sood A, *Exerc. Sport Sci. Rev.*, 39, 48–56, 2011. With permission.)

On the other hand, gluteofemoral fat (of which women have a disproportionate amount) does not appear to be an important predictor for asthma among women.[30] Gluteofemoral fat is considered more "metabolically benign"[40] than visceral or skeletal muscle fat in the sense that adipocytes in this area are hyperplastic and not hypertrophic and therefore associated with the excretion of a more favorable adipokine milieu.[41]

To summarize, the specific obesity phenotype that is best associated with asthma is unclear. Ectopic fat in the truncal viscera and skeletal muscle may play an important role. To confirm this hypothesis, future studies using computed tomography and magnetic resonance imaging of visceral fat and magnetic resonance spectroscopy of skeletal muscle fat need to be performed.

55.3.3 Potential Mechanisms

Several factors support a causal association between obesity and asthma. These include data demonstrating that obesity precedes the development of asthma,[27] a dose–response gradient between obesity and asthma risk,[24] and clinical improvement in asthma following weight loss.[42] The arguments used against a causal association are related to the relatively weak strength of association (usually odds ratios [ORs] of <2.0), conflicting data on the obesity–atopy association, and inadequate understanding of the mechanisms that explain the association.

The primary mechanisms that have been proposed to explain the obesity–asthma association include the following:

1. Misclassification error
2. The mechanical effect of obesity on airway hyper-responsiveness
3. The inflammatory function of adipose tissue
4. Obesity-associated comorbidities

55.3.3.1 Misclassification Error

It was previously thought that the association between obesity and self-reported asthma was due to misclassification bias, whereby obese subjects differentially reported asthma-like

symptoms without objective evidence of airway hyperreactivity.[43] However, it was recently shown that obesity is unlikely to be an independent predictor of the misdiagnosis of asthma.[44] Therefore, misclassification error is an unlikely explanation for the obesity–asthma association.

55.3.3.2 Mechanical Effect of Obesity on Airway Hyperresponsiveness

As discussed in Section 55.2.3, obese individuals have lower FRC.[6] This leads to reduced retractive force of the lung parenchyma on the airway and shortening of the airway smooth muscle cells, which, in turn, leads to airway narrowing and airway hyper-reactivity.[45]

55.3.3.3 Inflammatory Function of Adipose Tissue

Adipose tissue is not an inert organ. It produces over 50 proteins called adipokines that regulate various body functions. These include energy-regulating adipokines such as leptin and adiponectin that play an important role in systemic inflammatory conditions such as diabetes mellitus and atherosclerosis. Recent research suggests that leptin and adiponectin may also play a role in inflammatory lung conditions such as asthma.

55.3.3.3.1 Leptin

Leptin is primarily a proinflammatory adipokine. Leptin, along with the leptin receptor, is expressed by many cells in the human lung, including bronchial epithelial cells.[46,47] The lung may therefore be a target organ for leptin signaling. Animal studies have demonstrated that obese mice have innate airway hyperresponsiveness that is independent of the cause of obesity[48] and that may at least be partly explained by excess systemic leptin levels.[49] Further, exogenous systemic leptin is associated with an increase in allergen-induced airway hyper-reactivity in sensitized lean mice.[49]

Despite the convincing murine studies, the association between systemic leptin and asthma is controversial in humans. The evidence suggests that high systemic leptin concentrations may be associated with greater asthma prevalence and severity in select populations such as prepubertal boys, peripubertal/postpubertal girls, and premenopausal women.[50–52] Even in studies that demonstrate a leptin–asthma association, systemic leptin does not appear to be the only intermediary factor that explains the obesity–asthma association. This was reported by Sood et al.,[52] in whose study the association between BMI and asthma in women was only slightly attenuated after adjustment for serum leptin concentration. This suggests that other metabolic pathways and mechanical factors may also play a role in the obesity–asthma association.

55.3.3.3.2 Adiponectin

Adiponectin is a predominantly anti-inflammatory adipokine. Under certain conditions, however, adiponectin may have proinflammatory effects as well.[53] Systemic adiponectin concentrations are reduced in obesity. The relative hypoxia present in obese individuals results in the necrosis of adipocytes and, consequently, a decreased production of adiponectin. Adiponectin and its multiple receptors are expressed on multiple cell types in the lung.[54] Adiponectin is transported from blood into the alveolar lining fluid via the T-cadherin molecule on the endothelium,[54] in addition to being produced within the lung. Adiponectin circulates in low-, medium-, and high-molecular-weight complexes that may vary in efficacy regarding their effects on target tissues. Studies suggest that the high-molecular-weight isoform is the most biologically active isoform of systemic adiponectin in regulating insulin resistance. However, it is unclear whether the same also applies to human asthma.

Mouse studies demonstrate that allergen bronchoprovocation leads to reduced serum adiponectin concentrations, as well as the reduced expression of adiponectin mRNA in adipose tissue.[55] Further, exogenous adiponectin infusion attenuates allergic airway inflammation and airway hyperresponsiveness in mice.[55]

Unlike murine studies, human data on the association between systemic adiponectin and asthma are controversial. Some studies demonstrate that low serum adiponectin concentrations are independently associated with greater asthma prevalence among premenopausal women and peripubertal girls. A recent longitudinal study suggests that low serum adiponectin concentrations predict incident asthma in women, particularly among smoking women, and that adiponectin may in fact be a stronger predictor than BMI in this regard.[56] Further, low serum adiponectin concentrations are associated with greater asthma severity among boys but, surprisingly, lesser asthma severity among men.[51,53] It is possible that proinflammatory effects of adiponectin dominate under certain physiologic conditions and anti-inflammatory effects under others. Further, the obesity–asthma association in humans does not appear to be entirely explained by serum adiponectin alone,[57] again implying the multiplicity of mechanistic pathways for the obesity–asthma association.

55.3.3.4 Obesity-Associated Comorbidities

Several diseases that coexist with obesity have also been linked to asthma prevalence or severity. These diseases include gastroesophageal reflux disease, obstructive sleep apnea, and depression. Although none of these diseases individually explain away the obesity–asthma association, it is important to control these comorbidities when considering treatment for asthma in obese patients.

55.3.4 Clinical Presentation of Asthma in Obese Patients

Asthma is manifested by recurrent episodes of variable respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough. In terms of clinical manifestations of asthma, obese asthmatics have greater symptoms, medication use, exacerbation rates, and health-care utilization than normal-weight asthmatics (Table 55.1).[36,51,58–61] Further, these relationships are stronger among women with asthma compared to men with asthma.[51,59] However, the basis for the greater clinical severity of asthma in obese individuals is not well understood.

TABLE 55.1
Comparison of Various Manifestations of Asthma between Obese and Nonobese Subjects

		Severity of Manifestation among Obese Asthmatics, Compared to Nonobese Asthmatics
Clinical manifestations of asthma	Asthma symptoms	↑↑
	Medication use	↑↑
	Health-care utilization	↑
	Absenteeism	↑
Physiological manifestations of asthma	Extent of peak expiratory flow rate variability	↑
	Extent of bronchodilator responsiveness	Not studied
	Methacholine airway hyper-reactivity	↔
Inflammatory manifestations of asthma	Sputum eosinophil count	↔/↓
	Exhaled nitric oxide	↔/↓
	Exhaled breath condensate 8-isoprostane	↑

Note: "↑↑" strong increase, "↑" indicates increase, "↔" indicates no change, and "↓" indicates decrease.

There are also some interesting differences between obese and nonobese asthmatics during an acute exacerbation in the emergency department. Although the two groups have similar symptom severity and similar response to intensive bronchodilator treatment,[58,62] obese asthmatics are more likely to be hospitalized and have longer hospitalization stays than nonobese asthmatics.[62,63] Some have explained this discrepancy on the basis of differences in symptom perceptiveness to bronchospasm between obese and nonobese asthmatics.[64] However, a careful examination of perceptiveness of dyspnea during laboratory-based bronchoprovocation has not revealed differences between the two groups.[65] Others have demonstrated a greater extent of dynamic hyperinflation during acute bronchospasm among obese asthmatics compared to nonobese asthmatics.[66] It is possible that dynamic hyperinflation takes a longer time to resolve in obese versus nonobese asthmatics with an acute exacerbation.

Unlike the clinical manifestations of asthma, the associations between obesity and inflammatory and physiological asthma manifestations are less clear (Table 55.1). Studies demonstrate either similar or possibly lower sputum eosinophil counts and exhaled nitric oxide levels among obese asthmatics compared to nonobese asthmatics.[67–70] Yet the former group has greater airway oxidative stress than the latter, as suggested by higher exhaled breath condensate 8-isoprostane concentrations.[67]

55.3.5 Is the Obesity-Associated Asthma Phenotype Unique?

Asthma is not a single disease entity but a collection of as many as five clinical phenotypes or consistent groupings of characteristics.[71] Similarly, obesity-associated asthma may not be one disease process but a collection of as many as three clinical phenotypes, with the age at disease onset as the key differentiating factor (pediatric, young adulthood, or late adulthood).[72] The childhood-onset obese asthma phenotype is almost always atopic and does not have a clear sex preponderance. On the other hand, the two adult-onset obese asthma phenotypes are female preponderant and less likely to be atopic. Between these two obese asthma phenotypes, the phenotype of young adulthood onset is more severe (as suggested by their lower prebronchodilator and postbronchodilator lung function) than the phenotype of late adulthood onset. Yet, subjects in the latter group remarkably report symptoms and health-care utilization that are "discordant" to their degree of airflow obstruction (whereas it is concordant in the former group). Although it is clear that the latter group has many clinical differences from other phenotypes of asthma, it is not well established that this group constitutes a unique endotype with a distinct pathophysiological mechanism. The lower prevalence of atopy associated with this group nevertheless suggests that there may be non-T_H2 inflammatory mechanisms for this asthma phenotype. However, little is understood about the non-T_H2 inflammatory mechanisms for asthma at this stage. One such hypothesized mechanism may include neurogenic inflammation, as has been shown in a recent murine study.[73]

55.3.6 Therapeutic Response in Obese Patients

Unfortunately, the current clinical guidelines for asthma do not specifically address the management of this disease among obese individuals. On the one hand, obese patients with asthma tend to have a greater rate of exacerbation on treatment with theophylline.[74] On the other hand, obese patients with asthma may show less beneficial clinical response to inhaled corticosteroids.[61,75] The poor clinical response to corticosteroids that has been observed in obesity-related asthma may also be due to the lack of association of this phenotype with T_H2 inflammation, which is traditionally a corticosteroid-responsive process. It is not known whether this lack of corticosteroid responsiveness results from pathways that involve interleukin-6 or tumor necrosis factor-α, either alone or in association with increased oxidative stress.

55.3.7 Effect of Weight Loss

Weight reduction, even if it is modest, leads to improved asthma prevalence, quality of life, and indicators of asthma severity including symptoms, exacerbations, use of rescue medications, and need for hospitalization.[42,76] There has been a report of significant reduction in serum markers of oxidative stress among asthmatics following weight loss secondary to dietary restrictions.[76] In the most convincing study to date, surgical weight loss in a group of people who had nonallergic, late-onset (non-T_H2) asthma was associated with improvements in bronchial hyperresponsiveness.[77] In contrast, similar weight loss in obese individuals with allergic (T_H2) asthma did not improve bronchial hyperresponsiveness and the high T_H2 cytokine production a year after bariatric surgery in these individuals suggests that weight loss may even worsen T_H2 asthma. Thus, weight loss as a therapy for obesity-associated asthma seems to be more beneficial when the asthma is not associated with T_H2 inflammation.

In summary, the obesity–asthma association is possibly causal in nature and there likely are multiple mechanistic pathways that explain this association. Asthma in obese patients is symptomatically more severe than in the nonobese. It is proposed that obesity-associated asthma is mediated by non-T_H2 mechanisms. This may also explain the inadequate clinical response to corticosteroids in the obese asthmatic population as well as the improvement in bronchial responsiveness in nonallergic but not in allergic obese asthmatics following weight loss.

55.4 OBESITY AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a chronic progressive respiratory disorder characterized by the presence of airflow limitation.[78] While chronic bronchitis is defined in clinical terms and emphysema is defined in anatomical terms, these two phenotypes of COPD are not always easily distinguishable.[79] Increased body fat is typically, although not always, seen with chronic bronchitis, whereas emphysema is typically associated with loss of fat and/or lean mass.[80–82] A recent study demonstrates that the prevalence of obesity is higher among subjects reporting COPD than in the non-COPD population.[83]

55.4.1 Risk for Chronic Obstructive Pulmonary Disease

The effect of obesity on the risk for COPD is controversial and has not been adequately studied. Most epidemiological data suggest that an overweight or obese status may protect against the risk for developing emphysema-dominant COPD phenotype in men.[84–87] This results from an increase in FEV_1/FVC ratio that accompanies weight gain. However, recent studies suggest that the protective effect of obesity on COPD may not be entirely true.[14,88] For instance, a large Chinese population-based study ($n = 7358$) carefully excluded individuals with asthma and demonstrated that abdominal obesity was independently associated with airflow obstruction (adjusted OR = 1.4; 95% confidence interval = 1.1–1.8).[14] Thus, data are still confusing regarding whether obesity both predisposes to and protects against spirometric airflow obstruction. The authors hypothesize that when obesity primarily affects small airways the FEV_1/FVC ratio increases (because of air trapping). On the other hand, the opposite happens when large airways are primarily affected. Other measures to define emphysema such as dynamic hyperinflation might yield more consistent relationships with obesity than the FEV_1/FVC ratio. Excessive reliance on the FEV_1/FVC ratio may also lead to obese subjects being wrongly classified as having no airflow obstruction.

55.4.2 Chronic Obstructive Pulmonary Disease Mortality

The effect of obesity on COPD mortality is controversial and has not been adequately studied. Surprisingly, limited epidemiological data suggest that an overweight or obese status may protect against mortality from COPD.[85–87] The large Copenhagen City Heart Study suggested such a protective effect on mortality in subjects with severe disease but not with mild or moderate disease.[86] The Korean Cancer Prevention Study similarly showed that the risk of death from respiratory causes and specifically from COPD decreased progressively with increasing BMI.[85] In most studies, obese COPD subjects were limited in number and died more frequently from nonrespiratory causes than respiratory causes.[89] Further, these study populations did not have the type and severity of obesity currently prevalent among COPD subjects in the United States. It should also be pointed out that there is no obvious reason why obesity should protect against mortality in COPD.[87] This phenomenon, well characterized in other chronic wasting conditions, is referred to as the "obesity paradox." One possible explanation is that BMI–mortality associations are J shaped or U shaped in COPD, and the results reflect bias from linear modeling. Further, lean mass, not fat mass, may better predict survival than BMI in moderate to severe COPD.[90] It is therefore possible that the high BMI in these studies of mostly men with COPD simply reflects their greater lean mass (and not excess fat mass), which may explain the survival advantage with high BMI in COPD.

55.4.3 Physiological Derangements of Chronic Obstructive Pulmonary Disease

Studies indicate that obese patients with COPD have greater symptoms, activity limitation, medication use, and healthcare utilization than normal-weight patients with COPD.[83] Compared to the subject with either obesity or COPD alone, dynamic hyperinflation during exercise is greater in the subject with both conditions.[91] Dynamic hyperinflation occurs when patients commence inhalation before full exhalation has been achieved, leading to air trapping or increased

end-expiratory lung volume. Dynamic hyperinflation explains most of the variation in dyspnea intensity in diseases with airflow limitation.[92] Dynamic hyperinflation occurring in a setting of increased ventilatory requirement (as during exercise) results in an earlier mechanical limitation of ventilation with greater dyspnea in the patient with both obesity and COPD than in the patient with either condition alone.[91]

55.4.4 Potential Mechanisms

In addition to mechanical bases, there may be inflammatory and metabolic mechanisms by which obesity may affect the airway of individuals with COPD. For instance, several studies suggest that both circulating and airway leptin, a proinflammatory adipokine, is associated with greater systemic and airway inflammation and lower lung function in stable COPD patients.[93–97] A recent longitudinal study further demonstrated that metabolic syndrome markers (such as triglycerides and HDL-cholesterol) and leptin are independent risk factors of greater susceptibility to lung function impairment in response to particulate inhalation after the World Trade Center event in New York.[98]

In summary, COPD subjects are increasingly obese and are at risk for underdiagnosis of disease. Although they are more symptomatic and have a lower quality of life than their normal-weight counterparts, obese COPD subjects may have a mortality advantage. Studies examining fat and lean masses separately may better explain this so-called obesity paradox.

55.5 OBESITY AND INFLUENZA

The number of seasonal influenza-associated deaths in the United States varies annually from 3000 to 49,000.[99] During 2009, an influenza A pandemic occurred from the H1N1 strain. During this outbreak, a pattern of greater mortality among obese cases was noted. For example, a case study of critically ill adults in California showed that of the 92 cases who died from H1N1 infection 61% were obese and 30% were severely obese (BMI $\geq$ 40 kg/m^2).[100] The mortality experience among humans was interestingly replicated in the laboratory using lean and diet-induced obese mice immunized with the 2009 H1N1 vaccine and subsequently challenged with the homologous H1N1 live virus.[101] Compared to lean mice, obese mice had a greater mortality (14% vs. 100% by day 14), as well as a more severe lung inflammation.[101] Murine studies also suggest that obesity is associated with delayed entry and impaired function of dendritic and mononuclear cells in the lung in response to H1N1 infection.[102] This, in turn, may lead to alterations in lung T-lymphocyte populations that may eventually be detrimental to the obese infected host.[102] In addition to the higher mortality, obese people mounted a less efficacious long-term immune response to the 2009 H1N1 vaccine than normal-weight people.[103] In summary, the differences in clinical outcomes between obese and normal-weight people in response to the 2009 H1N1 influenza pandemic suggest that obesity alters the immune response to lung infections.

55.6 SUMMARY

In summary, more than a third of all U.S. adults are obese.[2] Obesity has a primarily reversible effect on pulmonary function tests. In addition, obesity is a risk factor for asthma. It is proposed that obesity-associated asthma is mediated by non-T_H2 mechanisms. Similarly, COPD subjects are increasingly obese and are at risk for underdiagnosis of this disease. Although they are more symptomatic and have a lower quality of life than their normal-weight counterparts, obese COPD subjects may have a mortality advantage that is not well understood. Finally, the increased mortality experienced by obese subjects during the 2009 H1N1 influenza pandemic suggests that obesity also alters the immune response to lung infections. There is thus a great need for physicians to recognize and manage the respiratory effects of obesity.

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56 Obesity, Arthritis, and Gout

Luke Dawson, Anita E. Wluka, Yuanyuan Wang, and Flavia M. Cicuttini

CONTENTS

56.1 OBESITY AND OSTEOARTHRITIS

Osteoarthritis (OA) is the most prevalent chronic joint disease, characterized by pain and loss of function attributable to changes affecting the whole joint, including articular cartilage and subchondral bone, which result in radiological changes.[1] The knee, hip, and hand joints are most commonly affected. Treatments for OA are largely symptomatic, including paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief and total joint replacement for the treatment of end-stage symptomatic OA.[1] Therapy aimed at reducing disease progression is limited.

Of the 86 million persons aged 50–84 years in the United States, 40% have obesity or OA or both, resulting in 86 million quality-adjusted life-years lost.[2] Obesity is the most important modifiable risk factor for knee OA,[3] and there is strong evidence for a link between obesity and OA at the knee,[3] hip,[4] and hand.[5] Recently, efforts have been focused on understanding the potential mechanisms by which obesity plays a

role in the pathogenesis of OA and weight loss affects both symptoms and joint structure. This is important in terms of identifying potential preventive strategies for OA and novel approaches to treatment: the management of obesity is likely to be a key in the management of OA.

56.1.1 Obesity and Knee Symptoms and Disability in Osteoarthritis

There is strong evidence that obesity as measured by body mass index (BMI) is associated with increased knee pain.[6–8] Higher BMI is associated with a three- to fourfold increased risk of knee pain with disability.[8] Obesity and overweight are responsible for one-fifth of knee pain cases, one-third of pain with disability cases, and one-third of severe pain with disability cases.[8] A clear dose–response relationship between BMI and onset of knee pain has been shown.[7] A 5% gain in weight is associated with adverse effects on knee pain, stiffness, and function, especially in individuals who are obese or who have knee OA.[9] Although there is less data relating obesity to the severity of symptoms in those with OA, some studies have suggested a relationship between weight and OA symptoms[3] and that obesity is strongly implicated in disability once arthritis is present.[10] The link between obesity and joint pain is also present at hips, knees, ankles, and feet.[11]

56.1.2 Obesity and Knee Osteoarthritis

56.1.2.1 Data from Cross-Sectional Studies

Obesity is a well-established risk factor for knee OA. Fletcher and Lewis-Faning in 1945[12] and then Kellgren and Lawrence in 1958[13] were the earliest to describe the relationship between obesity and knee OA. The reported increased risks range from two- to sevenfold for people in the top tertile of BMI compared to those in the bottom tertile.[12–15] The risk of OA increases with degree of obesity, and it is strongly related to bilateral disease and is an important risk factor for both tibiofemoral and patellofemoral knee OA.[15–17] The proportion of OA attributable to obesity in middle-aged women is estimated at 63%.[18]

56.1.2.2 Data from Longitudinal Cohort Studies

Longitudinal studies have consistently confirmed that obese individuals are more likely to develop knee OA later in life. The Framingham Knee OA Study found a strong association between overweight and knee OA 35 years later.[3] This association was stronger in women than in men and related to both symptomatic and asymptomatic diseases and stronger for more severe, rather than mild, radiological disease.[3] Similarly, the Johns Hopkins Precursors Study found that increased BMI at young age in men predisposed to an increased risk of knee OA.[19] The Chingford Study found that the risk of developing osteophytes was increased in women with a high BMI.[18] These results suggest that higher BMI earlier in life may be a more important risk factor for the subsequent development of knee OA than heavier weight later in life.

There is a strong dose–response association between obesity and OA with obese individuals having a markedly increased risk of knee OA relative to those who are overweight.[20] Studies of twins have shown that for every 1 kg increase in weight, a twin has a 14% increased risk of developing tibiofemoral osteophytes and a 32% increased risk of patellofemoral osteophytes compared to their co-twin.[17] The risk of knee OA increases by 35% for every 5 kg of weight gain.[21]

56.1.2.3 Obesity and Knee Structure in Magnetic Resonance Imaging Studies

In the past, it has been difficult to directly assess joint structure noninvasively, which has limited the progress in understanding the pathogenesis of OA. Magnetic resonance imaging (MRI) allows noninvasive assessment of the whole joint and assessment of articular cartilage as a measure of OA severity and progression.[22] Knee cartilage volume measured from MRI is a valid and reproducible measure,[22] is sensitive to change in both normal subjects without OA and those with OA,[22] and correlates with radiographic grade of OA.[23] Other important structures such as bone marrow lesions that are associated with knee pain and progression of OA can also be measured from MRI.[24] Thus, with MRI, it is possible to examine the joints as a continuum from the normal through to the diseased joint. This has allowed more detailed investigation of the risk factors and etiologies of OA, including obesity.

In cross-sectional studies of randomly selected subjects, increased BMI is associated with lower cartilage volumes[25] and increased prevalence of cartilage defects[25] and bone marrow lesions.[26] Longitudinal studies in OA populations have supported this, showing that greater BMI is associated with increased loss of cartilage volume.[27] These findings are also observed in non-OA populations, showing associations between BMI and adverse knee structural changes including bone marrow lesions[28] and cartilage defects.[29] These findings in healthy populations suggest that obesity may occur before OA rather than the converse and support the notion that obesity is not simply related to OA as a disease, but it is independently linked to the pathogenesis of OA.

56.1.3 Obesity and Osteoarthritis at Other Joints

56.1.3.1 Obesity and Hand Osteoarthritis

A recent systematic review addressed the association between BMI and hand OA.[5] Of the 25 studies deemed eligible, 15 were considered of high quality; 10 of the high-quality studies found a positive association between weight or BMI and hand OA, with an odds ratio of 1.9.[5] Sixty-four percent of the included studies showed a positive association between obesity and hand OA.[5] The Rotterdam Study is the largest cross-sectional study addressing this question.[30] It reported a positive association between BMI and hand OA after accounting for metabolic factors, for the distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints but not for the carpometacarpal joint. The study also found that when subjects were overweight as well as hypertensive and diabetic,

these factors had an additive effect on hand OA, suggesting that OA has a metabolic component in its etiology.[30]

56.1.3.2 Obesity and Hip Osteoarthritis

Although there is less data for the hip compared to the knee in relation to obesity, a recent systematic review and meta-analysis have confirmed a moderate association between obesity and hip OA.[4] For a 5-unit increase in BMI, the risk of hip OA increased by 11%. This risk was slightly higher in females than in males. The relationship between obesity and hip OA is less pronounced than the relationship at the knee joint (risk increased by 33% per 5-unit increase in BMI).[4] Obesity increased the risk of total hip replacement due to OA with BMI at early adulthood showing a stronger association compared with BMI at middle age.[31]

56.1.3.3 Obesity and Lumbar Spine Osteoarthritis

Very few studies have examined the association between obesity and OA of the lumbar spine. Obesity was associated with facet joint OA of the lumbar spine with a clear dose–response relationship.[32] A recent cross-sectional study found that obesity was associated with increased lower back pain in a community-based population, but rather than being due to increased weight per se, this relationship was largely attributable to fat mass.[33]

56.1.3.4 Obesity and Foot and Ankle Osteoarthritis

There are very few studies examining the association between obesity and OA at the foot or ankle. One study found a correlation between BMI and foot OA.[34] Although significant, this association was relatively small.[34] Similar to lower back pain (above), while foot pain has been linked to obesity, this is largely attributable to fat mass, in particular, the android distribution of fat rather than the gynoid.[35] This suggests a metabolic role of fat in foot pain.

56.1.4 Obesity and the Progression of Osteoarthritis

It is important to clarify whether obesity accelerates disease progression once OA is established or whether it just acts as a risk factor for incident OA. Obesity was associated with the progression of OA over 12 years[36] and with progressive joint space narrowing.[37] before symptomatic disease, BMI was associated with the progression of cartilage defects[38] and cartilage volume loss[27] over 2 years. One study found that obesity predicted OA progression in those with neutral or valgus knee alignment.[39] Some studies found no association between BMI and cartilage volume loss over time.[40,41] These differences may be partly due to the populations being examined, particularly the level of obesity within the populations.

56.1.5 Body Composition and Osteoarthritis

BMI is the most commonly used measure of obesity. However, a limitation of this measure is that it does not capture differences in body composition. For example, the body composition of two individuals with the same high BMI may vary significantly, with one having high fat mass and low muscle mass while the other having low fat mass and high muscle mass: two very different body types that BMI cannot differentiate. There is emerging evidence that fat mass and muscle mass behave differently in OA process. The investigation of this proposal has been facilitated by the ability of MRI for joint structural assessment.

56.1.5.1 Muscle Mass and Knee Osteoarthritis

Loss of muscle mass may be the primary event for the onset of OA.[42] It is proposed that muscle loss leads to decreased physical activity and increased fat mass, in turn leading to further muscle loss due to the decreased physical activity, which perpetuates the cycle.[42] A number of studies have supported this proposal, showing that reduced lower limb muscle mass correlates with knee OA. Muscle mass is protective against knee OA where increased muscle mass was associated with greater tibial cartilage volume[29] and reduced tibial cartilage loss over 2 years[43] and is inversely associated with joint space narrowing.[44] A more recent study found that although people with knee OA had larger thigh muscles, the muscles were of significantly poorer quality, as measured by strength per muscle unit.[45] This may relate to the finding that those with OA had greater intermuscular fat compared to those without OA.[45]

56.1.5.2 Fat Mass and Knee Osteoarthritis

There are less data for the association between fat mass and the development of OA. In asymptomatic adults, increased fat mass was associated with reduced tibial cartilage volume and increased cartilage defects.[29] Fat mass is also a predictor for the risk of total knee replacement for OA.[46] These studies suggest that body composition plays a role in the pathogenesis of OA from an early stage of disease. It is likely that fat mass contributes to OA through both mechanical and metabolic mechanisms. The relationship between BMI and reduced cartilage volume could be explained by leptin.[25]

56.1.5.3 Fat Distribution and Knee Osteoarthritis

Another interesting question is whether the location of body fat affects OA, especially android (abdominal or central obesity) versus gynoid (lower body obesity) distribution. Measures of fat distribution such as waist circumference and waist-to-hip ratio are better predictors of major public health problems such as diabetes and cardiovascular diseases than BMI.[47] However, less is known about whether this is also the case in OA. Several studies have found no links between OA and trunk-to-lower limb fat ratio[48] or body fat distribution.[49] There is no established difference in knee medial compartment loading between centrally obese and lower body obese individuals, and it is suggested that obesity distribution is not the mechanism by which obesity increases the risk of knee OA.[50]

56.1.5.4 Body Composition and Osteoarthritis at Other Joints

Body composition is associated with OA at other joints. Risk of total hip replacement for OA was associated with

percentage body fat, waist circumference, and waist-to-hip ratio.[46,51] However, the relationships were less strong than those for knee OA.[46,51] Fat mass, but not lean body mass, was associated with increased levels of lower back pain.[33] Android fat distribution had a slightly stronger association with disability from low back pain than gynoid fat distribution, suggesting that central obesity associated with metabolic disease may play a part in low back pain.[33]

56.1.6 Mechanisms for Obesity and Pathogenesis of Osteoarthritis

The mechanisms by which obesity may lead to OA are unclear. A number of potential mechanisms have been proposed: (1) obesity increases the load across the joint resulting in increased or abnormal stress and subsequent deterioration of joint structures; (2) obesity acts indirectly by metabolic changes associated with increased fatness such as glucose intolerance, hyperlipidemia, hyperestrogenemia, or changes in bone density; and (3) elements of the diet that result in obesity, such as high fat content, adversely affect bone, cartilage, or other joint structures. It is most likely that the effect of obesity on OA is due to a combination of both biomechanical and metabolic factors, as discussed in the following.

56.1.6.1 Loading, Alignment, and Joint Biomechanics in Obesity

56.1.6.1.1 Loading and the Obesity–Osteoarthritis Link

There is evidence that increased loading is associated with adverse effects on the knee joint. This may explain in part the effect of obesity on OA. Obese individuals have higher ground reaction forces, which is an estimate of joint load, than nonobese individuals.[52] Higher stress on the joint from loading is associated with younger age at total hip replacement surgery.[53] Thus, obesity is likely to result in increased load and detrimental effect on the joint. Increased loading due to obesity leads to activation of chondrocyte mechanoreceptors, which in turn activates cytokines, growth factors, and metalloproteinases.[54] These factors trigger inhibition of matrix synthesis, which can lead to cartilage degradation and OA. Moderate exercise is beneficial for cartilage constitution; however, excessive stress or static stress disrupts the homeostasis of anabolism and catabolism within the cartilage.[55]

56.1.6.1.2 Knee Alignment and the Obesity–Osteoarthritis Link

Knee alignment has been connected to the obesity–OA link, where one study found that obesity only affected OA progression in moderately misaligned limbs.[56] In varus knee alignment, the load-bearing mechanical axis passes medial to the knee (i.e., bowlegged when it is extreme), which further increases force across the medial compartment, whereas in valgus alignment, the load-bearing mechanical axis passes lateral to the knee (i.e., knock-knees when it is extreme), which increases force across the lateral compartment.[57] Varus alignment increased the progression in the medial compartment by 4-fold in mild OA and 10-fold in severe OA, whereas valgus alignment increased the progression in the lateral compartment by 2-fold in mild OA and 10-fold in severe OA.[58] Obesity is associated with OA severity in subjects with varus alignment but not those with valgus alignment,[59] while associated with disease progression in those with valgus or neutral knees, but not those with varus knees.[39] Although a little conflicting, these findings suggest that knee alignment plays a role in obesity-related OA.

56.1.6.1.3 Altered Biomechanics and the Obesity–Osteoarthritis Link

Altered biomechanics in obese individuals has been implicated as a possible mechanism leading to the obesity–OA relationship. A recent systematic review concluded that obese subjects walk more slowly, have a smaller stride length and a greater step width, and walk with a greater toe-out angle compared with normal-weight subjects.[60] These daily alterations due to obesity could be associated with cartilage degeneration leading to OA,[60] and altered gait patterns may cause shifts in load-bearing contact location initiating OA in the cartilaginous region not conditioned to the new loading.[61]

Medial compartment OA is more common than lateral compartment OA, which may be due to the medial compartment bearing the majority of the load during weight bearing (60%–70%).[57] Adduction moments of the knee (reflecting dynamic loading of the medial compartment) predict OA progression.[62] Adduction moments are an estimation of the load through the knee compartment during each step due to normal force transmission through the leg and with the magnitude being approximately 3.3% body weight multiplied by height.[57] Therefore, it makes sense that obese people have a greater peak external knee adduction moment compared with healthy individuals,[52] and greater maximum adduction moments are related to higher disease progression and severity.[57] Although this suggests a pathway for loading leading to OA, it may be that gait is altered in obesity to protect against medial compartment loading, nullifying this effect. Knee loads can be reduced in obese patients to approximately normal levels if they walk at slower speeds.[52]

56.1.6.2 A Metabolic Component in Osteoarthritis

A number of factors suggest a metabolic and/or systemic component in OA. These include the female preponderance, menopausal onset of generalized OA, and the inverse relationship with osteoporosis. Furthermore, obesity is also linked to OA of the hand and fingers, an association that cannot be explained by increased loading. The increased adipose tissue in obesity cannot be considered simply as excess mass, as it has significant endocrine activity, which is relevant in OA.[63] Adipocytes release cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) as well as adipokines such as leptin, adiponectin, resistin, and visfatin.[64] In obesity, the increased adipose tissue leads to increased production of these factors, which leads to a chronic inflammatory state.[64]

56.1.6.2.1 Inflammation

Obesity is considered as a low-grade inflammatory state, with increased C-reactive protein (CRP) and pro-inflammatory cytokines including IL-1, IL-6, IL-8, IL-18, and TNF-α.[64] All of these are associated with synovitis and the pathogenesis of OA.[65] IL-6 and TNF-α are associated with knee cartilage volume loss,[66] and IL-6 is associated with the prevalence and progression of radiographic knee OA.[67] IL-10, which is decreased in obesity, has chondroprotective effects by counteracting the effects of other cytokines.[64]

56.1.6.2.2 Adipokines

56.1.6.2.2.1 Leptin Leptin is secreted by adipose tissue and its levels are directly correlated with white adipose tissue mass.[68] Leptin plays a role in decreasing food intake and stimulating energy expenditure to regulate body weight as well as regulating physiological processes such as infection, inflammation, and autoimmune diseases.[68] Leptin binds to the leptin receptor (Ob-R), which is present in cultured human articular chondrocytes and native human cartilage, as well as osteoblasts, stromal cells, and disc cells in the musculoskeletal system. Obesity directly correlates with high circulating levels of leptin and leptin's expression in OA cartilage, which in turn correlates with the grade of cartilage destruction.[69] Leptin receptor expression and leptin levels in severely osteoarthritic cartilage are elevated compared with minimally affected cartilage.[69] Leptin is associated with both anabolic and catabolic actions in chondrocytes; however, most studies have pointed to a catabolic mechanism. This occurs by inactivation of nitric oxide synthase causing loss of chondrocyte phenotype, induced apoptosis, and activation of matrix metalloproteinases (MMP-9 and MMP-13), which all damage articular cartilage.[69] Knee OA susceptibility is associated with leptin gene single-nucleotide polymorphisms.[70] Leptin levels are higher in women, which may be a possible explanation for the higher prevalence of OA in women. Leptin was associated with decreased cartilage volume and explained the associations of BMI and sex (female) with decreased cartilage volume,[25] indicating that leptin may be the pathway by which obesity and female gender lead to OA. In obese mice lacking leptin or leptin receptors, there was no development of OA,[71] whereas in obese normal mice, OA did develop,[72] suggesting that leptin is critical in the obesity–OA link.

56.1.6.2.2.2 Adiponectin Adiponectin levels are decreased in obesity.[68] Adiponectin downregulates MMP-13 and upregulates tissue inhibitor of metalloproteinases-2 : both actions protect cartilage from degradation.[69] Adiponectin levels in OA synovial fluid are 100-fold less than in the plasma from the same subjects.[64] However, adiponectin levels were elevated in patients with erosive hand OA compared with patients with nonerosive disease.[64]

56.1.6.2.2.3 Resistin Resistin is primarily produced by adipocytes, also expressed by neutrophils, lung, heart, and synovial tissue.[68] Resistin levels increased in OA patients.[64] Following knee trauma, resistin levels quickly rise in the synovial fluid and serum,[64] leading to matrix degradation and inflammatory cytokine release from articular cartilage.[73]

56.1.6.2.2.4 Visfatin Visfatin is expressed by adipocytes, muscle, liver, and bone marrow and is correlated with regulation of insulin secretion; lung injury; sepsis; atherosclerotic lesions; and IL-1, IL-6, IL-10, and TNF-α production.[68] Visfatin may have catabolic effects on cartilage as it stimulates MMP production and is expressed in osteoarthritic chondrocytes.[64]

56.1.7 Weight Loss and Osteoarthritis

56.1.7.1 Weight Loss and Symptoms

Weight loss has consistently shown a modest but significant beneficial effect on the symptoms of OA. A recent meta-analysis showed that a 10% loss of weight has a moderate to large clinical effect, and a loss of at least 5% within 20 weeks achieved some symptomatic relief.[74] Weight loss also improves function. An 8-week low-energy diet resulting in 10% weight loss gave a 28% improvement in function in OA patients.[75] Modest weight loss plus modest exercise is more effective than either intervention alone.[76] Pain decreased by 30% in the diet plus exercise group, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function measures improved by 24% in the diet and exercise group but only 18% in the diet-only group.[76]

Bariatric surgery produces significantly greater weight loss in obese individuals compared to solely dietary measures.[77] Weight loss following lap band surgery results in improved pain and function scores at the knee.[77] Following bariatric surgery, an average weight loss of 20% has been recorded in OA patients, which was associated with improved pain and function.[78]

There are a number of mechanisms by which weight loss improves symptoms and function. Weight loss is associated with improved biomechanics, whereby 13.5% weight loss results in 7% reduction in knee loading, 13% lower axial impulse, and 12% reduction in knee abductor moment.[79] There may also be a metabolic effect, with weight loss being associated with reduced serum levels of leptin, IL-6, and CRP, which are associated with improved physical function.[78,80]

56.1.7.2 Weight Loss and Knee Structural Changes

One study in non-OA subjects showed that joint space width increased from 4.6 to 5.25 mm with BMI reducing from 43.4 to 36.9 kg/m^2 3 months after bariatric surgery,[81] suggesting that surgically induced weight loss is an effective and rapid method of reversing radiological signs of OA. However, it was also noted that the changes may be due to reduced loading. Weight loss of 20% reduced cartilage degradation and improved cartilage collagen synthesis by around 30%.[78] A recent study

found that weight loss was associated with improved quality (increased proteoglycan content) and quantity (reduced cartilage thickness losses) of medial articular cartilage, with no improvement in the lateral compartment.[82] This is the first study to have shown disease-modifying effects of weight loss.

56.1.7.3 Prevention of OA through Weight Loss

Weight loss significantly reduces the risk of the development of knee OA. The Framingham cohort study demonstrated that a decrease in BMI of 2 units or more in the previous 10 years reduced the risk of developing OA by over 50%.[3] Among women with a high risk for OA due to elevated BMI ($\geq$25 kg/m^2), weight loss decreased the risk by 60%.[3] It is estimated that one-third of knee OA cases could be prevented if people maintained a BMI of 25 kg/m^2 or less.[83]

56.1.8 Key Points

Obesity is a significant risk factor for knee OA and to a lesser extent, hip, hand, spine, and foot OA. Obesity may contribute to OA processes through loading, altered biomechanics, and metabolic factors. Weight loss and exercise, to maintain muscle but lose fat, are modest but effective methods of treating OA and reducing its risk in asymptomatic individuals.

56.2 OBESITY AND GOUT

Gout is the most common inflammatory arthritis in males and affects more than 1% of adults in the United States.[84] It is characterized by the intra-articular deposition of monosodium urate crystals following chronic hyperuricemia, which causes severe pain, swelling, and tenderness.[85] Gout is commonly treated with NSAIDs or colchicine for acute attacks and is prevented with urate-lowering therapy, such as allopurinol, between attacks.[85] Gout is associated with hypertension, diabetes, metabolic syndrome, renal and cardiovascular diseases, as well as obesity.[85]

56.2.1 Association between Obesity and Gout

56.2.1.1 Data from Cross-Sectional Studies

A large body of evidence supports an association between gout and obesity. The New Haven Survey showed that hyperuricemia was associated with obesity.[86] In healthy adults aged 65–79 years, serum uric acid level was positively associated with body weight, BMI, body fatness, and lean body mass in men but not women.[87] In a study of middle-aged men, a positive association was observed between BMI and gout.[88] Some data have suggested that body fat and the distribution[15] pattern of fat may be more important than total weight as a risk factor for gout.[89] After adjustment of age and BMI, a high waist-to-thigh circumference ratio was a risk factor for gout, particularly in women, and the association of waist-to-hip ratio with gout was less pronounced in men.[89] Visceral fat (estimated from abdominal CT scans) was independently related to serum uric acid concentration, uric acid clearance, uric acid/creatinine ratio, while BMI and subcutaneous fat were not.[90]

56.2.1.2 Data from Longitudinal Cohort Studies

The association between obesity and gout has been confirmed in large longitudinal studies. The Johns Hopkins Precursors Study found that BMI at age 35 years and excessive weight gain between cohort entry (median age 22 years) and age 35 years were significant risk factors for gout.[91] The Harvard Growth Study reported that the risk of gout was increased among men who were overweight in adolescence and those currently overweight; moreover, being overweight in adolescence was a stronger predictor of this risk than being overweight in adulthood.[92] The Health Professionals Follow-up Study showed a clear dose–response relationship between BMI and the risk of gout,[93] with waist-to-hip ratio demonstrating a similar increase in the risk.[93] Forty-one percent of gout cases were attributable to a BMI of >23 kg/m^2. Weight gain since young adulthood was associated with increased risk of gout while a reduction in 10 lb (4.5 kg) of weight reduced the risk.[93] The Third National Health and Nutrition Examination Survey further confirmed this link, where abdominal obesity increased the risk of gout.[94] The prevalence of abdominal obesity was 62.9% among those with gout compared to 35.3% in those without gout.[94] There is also data for a similar association between obesity and hyperuricemia.[95]

56.2.2 Gout and the Metabolic Syndrome

Data from the Third National Health and Nutrition Survey have confirmed that gout is strongly associated with the metabolic syndrome, including obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension, hyperglycemia, and diabetes.[94] The prevalence of metabolic syndrome was 62.8% in those with gout, but only 25.4% in those without gout.[94] In terms of individual components of the metabolic syndrome, patients with gout were at higher risk of abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and hyperglycemia.[94]

These findings also extend to obesity and hyperuricemia, where the prevalence of individual metabolic syndrome components increases substantially with rising uric acid levels.[95] The prevalence of the metabolic syndrome is 18.9% for patients with uric acid levels of <6 mg/dL, compared to 70.9% for patients with uric acid levels of >10 mg/dL.[95] Serum uric acid levels are associated with hyperinsulinemia in a number of studies.[96,97]

56.2.3 Mechanism for Metabolic Risk of Gout

The mechanism by which obesity increases the risk of gout is poorly understood. Several theories have been proposed. Obesity may increase the risk of gout by raising uric acid levels through decreased renal excretion as well as increased production.[93] Insulin resistance syndrome is also believed to increase systemic adenosine concentrations (a precursor to uric acid), which may lead to hyperuricemia through increased production.[98] Furthermore, insulin itself may enhance renal uric acid reabsorption through the proximal tubule.[98] Visceral fat area and level of insulin resistance have

an inverse correlation with renal excretion of uric acid.[93] Increases in serum leptin are associated with a proportional increase in serum uric acid, suggesting that leptin may play a role in the link between obesity and gout.[98] Other mechanisms proposed include chronic joint trauma, due to abnormal joint loading from excess weight, facilitating crystal deposition.[93]

Another possible mechanism by which obesity and the metabolic syndrome increase the risk of gout is through medications prescribed for patients with cardiovascular disease. Diuretics, low-dose (but not high-dose) aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blockers (except losartan) are all associated with an increased risk of hyperuricemia or gout, while losartan and calcium channel blockers reduce the risk of gout.[84,99]

56.2.4 Lifestyle Modification of Gout

As outlined in Section 56.2, gout significantly increases the risk of metabolic disease. These complications need to be considered when prescribing lifestyle measures for gout. Interventions that decrease the risk of gout as well as that of other health complications would be very beneficial.[100] Therefore, current lifestyle recommendations are targeted at reducing the risk of gout as well as that of metabolic disease, thus increasing the overall benefit for the patients.[100] It is probably best to tailor lifestyle measures to the individual patient, by reducing dietary risk factors (outside the scope of this chapter), while bearing in mind that there may be concurrent metabolic or cardiac disease. Dietary risk factors for hyperuricemia and gout include red meat, seafood, beer, spirits, sugar, and sugar-sweetened drinks, while vegetable-protein, dairy, coffee, and vitamin C seem to be protective.[100]

56.2.5 Key Points

Obesity is a significant risk factor for hyperuricemia and gout, and weight loss is effective in lowering this risk. Obesity probably contributes to gout risk by increasing production and decreasing excretion of uric acid. Metabolic disease and some drugs used in cardiovascular disease are also strongly associated with hyperuricemia and gout.

56.3 SUMMARY

Obesity is an important modifiable risk factor for OA and gout, the two common chronic joint diseases associated with significant morbidity and cost to the community. Preventive efforts to reduce obesity in the population are likely to have a major impact on the two conditions.

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57 Obesity and Mental Health

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CONTENTS

57.1 INTRODUCTION

The relationship between obesity and mental health has been a topic of interest to both researchers and the media for many years. Obesity used to be perceived as a mental illness, but was removed from the *Diagnostic and Statistical Manual of Mental Disorders* during development of the third edition because there was no consistent associated psychopathology; it is now considered a medical disorder, much like type 2 diabetes. However, obesity is still recognized as both a precipitant and a consequence of psychopathology. For obese persons, the psychosocial consequences of living with excess weight are only too familiar and may in some instances be more distressing than the many medical comorbidities associated with obesity. There is also good evidence to suggest that mental health problems (e.g., depression) or their treatments (e.g., psychiatric medications) can lead to obesity. Thus, a bidirectional relationship exists between obesity and some mental health problems. Historically, there has been concern that dieting and weight loss, as well as some weight loss medications, can cause or exacerbate depression. As such, most individuals who meet criteria for anxiety or depression are routinely screened out of weight loss trials, so the field knows little about how best to treat obese persons with comorbid mental health issues.

This chapter reviews the relationships (both cross-sectional and longitudinal) between obesity and various mental health problems, including depression, substance abuse, anxiety, and bipolar disorder. Data are presented on numbers of people seeking weight loss treatment who also have psychopathology. The chapter also reviews how psychopathology changes in response to intentional weight loss, and it covers preliminary data addressing how depression affects the outcome of weight loss treatment.

57.2 RELATIONSHIP BETWEEN OBESITY AND DEPRESSION: CROSS-SECTIONAL ANALYSES

Depression is one of the better studied mental health issues associated with obesity. Overall, the data support a consistent relationship between depression and obesity. A 2010 meta-analysis identified 17 epidemiological studies in 204,507 adults that examined the cross-sectional relationship between depression and obesity.[1] Obesity was either measured objectively (3 studies) or self-reported (14 studies), and depression was assessed using diagnostic interviews (6 studies) or symptom checklists (11 studies). The 17 studies yielded 28 comparisons of obese vs. nonobese individuals who were included in the meta-analysis. Half of the comparisons (14) yielded significant positive associations between obesity and depression, whereas negative associations were found in 2 comparisons, and no association was found in the remaining 12 comparisons. The pooled odds ratio (OR) of 1.18 (95% confidence interval [CI]: 1.01–1.37) led the authors to conclude that, overall, the odds of being depressed were 18% higher in obese vs. nonobese persons.

This meta-analysis also addressed the question of whether participant characteristics, or differences between the studies,

moderated the relationship between obesity and depression. Gender emerged as the only significant moderator of the relationship: obese and nonobese men had the same risk of depression (OR = 1.00, 95% CI: 0.76–1.31), but obese women had a 32% increased risk of depression compared to their nonobese counterparts (OR = 1.32, 95% CI: 1.23–1.40). No other characteristics, including participant age, publication date of the study, or methods of assessing depression (diagnostic interview vs. symptom checklist) or of assessing obesity (objective vs. self-report) appeared to significantly affect the relationship.

In addition to gender, the severity of obesity has been repeatedly shown to influence the strength of the relationship. For example, Petry et al.[2] found that obese individuals had a 50% greater likelihood than nonobese individuals of being depressed (OR = 1.53, 95% CI: 1.41–1.67), but the odds were more than 100% greater among those with Class III (body mass index [BMI] >40 kg/m^2) obesity (OR = 2.02, 95% CI: 1.74–2.35).[2] These data are supported by those of Onyike et al.,[3] who found that neither Class I (BMI 30–34.9) nor Class II (BMI 35–39.9) obesity was significantly related to past-month, past-year, or lifetime depression, but that Class III obesity was associated with significantly greater odds of depression in each time frame (past-month OR = 4.98, 95% CI: 2.07–11.99; past-year OR = 2.92, 95% CI: 1.28–6.67; lifetime OR = 2.60, 95% CI: 1.38–4.91).

While these studies establish that obesity and depression are related, they are not able to determine whether obesity predicts depression or vice versa. Longitudinal analyses, covered in the following section, address the temporal relationship between depression and obesity.

57.3 RELATIONSHIP BETWEEN OBESITY AND DEPRESSION: LONGITUDINAL ANALYSES

Many researchers have wondered whether depression develops as a *consequence* of being obese. It is easy to imagine how obesity, with its associated social stigma and prejudice, as well as impairments in physical functioning, could lead a person to become depressed. Conversely, it is possible that depression causes weight gain and eventual obesity. Cardinal symptoms of depression include anhedonia (a loss of interest or pleasure in activities previously enjoyed), increased fatigue, and negative thoughts regarding the self, which might interfere with efforts toward weight control, resulting in decreased physical activity and consumption of more high-calorie foods. Prospective examinations of the relationship between obesity and depression have been conducted in a variety of age groups and over a range of follow-up periods. A recent meta-analysis[4] and systematic review[5] have shed light on this question and broadly concluded that there is evidence to support both potential temporal pathways.

57.3.1 Obesity to Depression

The meta-analysis conducted by Luppino et al.[4] found that the adjusted pooled OR of developing depression among those who were obese at baseline was 1.57 (95% CI: 1.23–2.01), indicating a significantly increased risk of developing depression. Contrary to the moderating effects found with gender in the cross-sectional analyses (summarized earlier), subgroup analyses found no differences in the ORs for pooled analyses of women (OR = 1.67, 95% CI: 1.11–2.51) vs. men (OR = 1.31, 95% CI: 1.13–1.51; $p = .81$ for difference). The analyses did show, however, that effects were stronger in studies conducted in the United States (OR = 2.12, 95% CI: 1.48–3.03) vs. Europe (OR = 1.33, 95% CI: 0.98–1.81; $p = .05$ for difference) and when the presence of depressive disorder was the outcome (OR = 2.15, 95% CI: 1.48–3.12), rather than depressive symptoms (OR = 1.36, 95% CI: 1.03–1.80; $p = .05$ for difference). Mean age at baseline (<20, 20–59, ≥60 years old), follow-up duration (<10, ≥10 years), and study quality (high, low) did not significantly moderate the obesity-to-depression temporal relationship.

A systematic review of the literature set out to evaluate the strength of evidence for prospective associations among depression and obesity.[5] Researchers examined 25 studies, 10 of which tested "obesity-to-depression" pathways and 15 of which tested "depression-to-obesity" pathways. A significant majority (80%) of the studies supported a significant obesity-to-depression association, with covariate adjusted ORs within the range of 1.0–2.0. Seven of the 10 studies examined gender as a moderator of the relationship between obesity and depression, but only 2 reported significant findings.[6,7] Two studies examined race/ethnicity as a moderator,[8,9] but only one found a significant effect: the relationship between BMI and subsequent depression was greater for African-American than Caucasian participants.

In contrast to these findings, a 2010 study by Gariepy et al.[10] found no increased risk for depression in individuals who were obese at baseline. They assessed obesity and depression 7 times over a 12-year period in more than 10,500 Canadian adults. A noteworthy strength of this study was that major depression was assessed by structured clinical interview. The unadjusted hazard ratio for past-year depression in obese women was 1.03 (95% CI: 0.78–1.36), and adjusting for potential confounders did not alter the ratio. In obese men, the unadjusted hazard ratio was 0.70 (95% CI: 0.49–0.99), which remained stable after adjustment (0.71, 95% CI: 0.51–0.98). Thus, in this sample, obesity was found to be unrelated to the development of depression in women and protective against the development of depression in men.

Clearly, more research is required to elucidate whether obesity is a risk factor for depression. It is possible that excess weight confers a risk for incident depression only in certain subpopulations, such as women with class III obesity, and these subgroups need to be identified. Not all obese individuals go on to develop depression, and future research should focus on identifying those obese individuals most at risk, as well as factors that protect against incident depression. Given the potential for these disorders to perpetuate each other, early intervention targeting each disorder would be prudent.

57.3.2 Depression to Obesity

Evidence to support the depression-to-obesity relationship appears to be less consistent than that for the obesity-to-depression relationship. Of the 15 studies addressing depression-to-obesity relationships examined in the recent review conducted by Faith et al.,[5] only 8 (53%) reported significant depression-to-obesity ORs, and 3 of these studies indicated that individuals had a *lower* risk of obesity if they had a history of depression. That said, the strength of the associations in those studies which found a positive relationship were notable, with ORs in the range of 2.0–3.0. In Luppino et al.'s investigation,[4] while the pooled depression-to-obesity relationship was significant in both unadjusted (OR = 1.58, 95% CI: 1.33–1.87) and adjusted (OR = 1.40, 95% CI: 1.15–1.71) analyses, the ORs were smaller than those found for obesity-to-depression relationships and were smaller than those in the Faith et al. review. None of the potential moderators tested (sex, age, follow-up, method of assessing depression, study quality, or study location) significantly altered the relationship.

Thus, the factors that mediate the relationship between depression and obesity have yet to be empirically established. Potential mediators include hyperphagia and hypersomnia seen in atypical presentations of depression. Even in the more typical cases of depression, where loss of appetite and decreased need for sleep are common, other symptoms such as loss of motivation, fatigue, and decreased ability to concentrate (and therefore stick to a diet) could all contribute to weight gain over the long term. Additionally, negative thoughts characteristic of depressive disorders could sabotage weight loss efforts, such as "It's no use, I'll never be able to lose weight, I may as well stop trying," or "I haven't got the willpower to keep going." Finally, physiological alterations observed in depressed or stressed individuals may contribute to hyperphagia,[11] preference for carbohydrates,[12,13] and increases in fat deposition.[14,15]

57.4 OBESITY AND OTHER PSYCHIATRIC DISORDERS: CROSS-SECTIONAL ANALYSES

57.4.1 Obesity and Substance Abuse

The relationship between obesity and substance abuse behaviors has attracted significant attention recently because of the possibility of a shared neural vulnerability to obesity and addictive behaviors. MRI studies have revealed activity in the mesolimbic dopamine pathways in the brains of obese individuals upon exposure to food-related stimuli, the same pathway that underlies processing of pleasure and reward.[16,17] Moreover, studies of obese individuals compared to substance-dependent populations have shown similar reductions in striatal dopamine D_2 receptors, suggesting the potential for deficits in reward system circuitry.[18]

Most epidemiological studies have shown that obese persons tend to have a lower risk of substance use problems than those of average weight, although the evidence is inconsistent, with some researchers finding an increased risk of obesity with a history of such problems (see Table 57.1).[2,19–22] For example, Petry et al.[2] found that obese persons were more likely to have a lifetime history of an alcohol-use disorder than those of average weight. Furthermore, in an investigation of nearly 40,000 U.S. adults, the risk of obesity was found to be 49% higher among women and 26% higher among men, with a family history of alcoholism or alcohol problems than their counterparts without this family history.[23] These elevations in risk became somewhat attenuated yet remained significant (OR = 1.30, 95% CI: 1.19–1.43 in women; OR = 1.11, 95% CI: 1.01–1.23 in men) after adjustment for race, age, education, income, personal alcohol use, smoking status, and major depression. It is possible that individuals with a vulnerability to addictive behaviors "transfer" their addictive tendencies toward food when they give up their preferred substances, resulting in obesity. However, the notion that obesity results from an addiction to food is highly controversial (see Ziauddeen et al.[24] for an excellent review). Conversely, several reports in the media have identified an increase in addictive behaviors (include drug and alcohol abuse) following bariatric surgery, leading to the concept of "addiction transfer," although robust empirical evidence for this phenomenon is lacking.[25–27]

57.4.2 Obesity and Anxiety and Bipolar Disorder

A significant body of data now exists to suggest that obese persons are more likely to have an anxiety disorder or bipolar disorder than nonobese individuals.[2,19–22] Similar to the case with depression, the relationships are stronger in obese women vs. men (see Table 57.1)[21,71] and for persons with Class III obesity as compared with obese persons in general.[2,22]

The study by Petry et al. assessed the relationship between obesity and six separate anxiety disorders and found significant relationships with five of them. Obesity and extreme obesity were associated most strongly with generalized anxiety, panic disorder without agoraphobia, and specific phobias. Using the World Mental Health Survey Initiative, Scott et al.[22] examined the relationship between obesity and anxiety in more than 62,000 participants around the world in both developing and developed countries. They reported a significant pooled OR of 1.2 for total obesity and 1.5 for severe obesity with anxiety disorders, and the relationships were stronger in women than men and in younger (18–34 years) and older (65+ years) participants than those in middle-aged groups (35–49 and 50–64 years). It is not clear why women or people within these age categories would have stronger associations. Little is known about causal factors underlying the relationship between obesity and anxiety, but researchers have hypothesized that poor body image, teasing, and repeated failed weight loss attempts could fuel anxiety in obese individuals, while comfort eating in an anxious person may lead to weight gain.

Barry et al.[21] reported significant associations between obesity and bipolar I and bipolar II disorder in obese women but not in men, with ORs ranging from 1.56 to 2.24.

TABLE 57.1
Odds Ratios of Lifetime and Current Psychiatric Disorders in Obese Persons (Both Sexes), Obese Women, and Obese Men, Compared with Average-Weight Individuals, Found in Large Epidemiological Studies

	Simon et al. (2006)			Mather et al. (2009)			Barry et al. (2008)	
Disorder or Category	**Obese**	**Obese Men**	**Obese Women**	**Obese**	**Obese Men**	**Obese Women**	**Obese Men**	**Obese Women**
				Lifetime				
Any mood disorder	1.27 (1.15–1.41)	1.21 (0.99–1.46)	1.29 (1.11–1.50)	1.29 (1.12–1.49)	1.17 (0.91–1.50)	1.38 (1.16–1.64)	1.39 (1.21–1.60)	1.79 (1.63–1.28)
Major depressive disorder	1.21 (1.09–1.35)			1.41 (1.22–1.64)	1.38 (1.05–1.81)	1.43 (1.21–1.68)	1.35 (1.14–1.59)	1.58 (1.43–1.75)
Bipolar disorder/mania	1.47 † (1.12–1.93)			1.53 (1.17–2.00)	1.39 (0.88–2.18)	1.67 (1.23–2.28)	1.20 (0.93–1.55)	2.24 (1.80–2.78)
Any anxiety disorder	1.28 (1.05–1.57)	1.17 (0.82–1.67)	1.34 (1.09–1.64)	1.22 (1.10–1.36)	1.25 (1.06–1.46)	1.20 (1.05–1.38)	1.35 (1.18–1.53)	1.76 (1.58–1.96)
Any substance use disorder	0.78 (0.65–0.93)	0.75 (0.60–0.93)	0.88 (0.65–1.18)					
Alcohol use disorder								
Drug use disorder								
				Past Year				
Any mood disorder	1.19 (1.00–1.42)			1.20 (0.98–1.46)	1.05 (0.73–1.52)	1.30 (1.04–1.63)	1.33 (1.20–1.59)	1.75 (1.52–2.01)
Major depressive disorder	1.09 (0.89–1.34)			1.24 (1.02–1.52)	1.21 (0.82–1.80)	1.27 (1.02–1.58)	1.31 (1.03–1.67)	1.49 (1.25–1.76)
Bipolar disorder/mania	1.61† (1.07–2.43)			1.91 (1.33–2.73)	1.45 (0.82–2.56)	2.44 (1.52–3.91)	1.15 (0.80–1.64)	2.41 (1.84–3.17)
Any anxiety disorder	1.34 (1.07–1.66)			1.29 (1.11–1.48)	1.45 (1.14–1.84)	1.19 (1.00–1.42)	1.36 (1.16–1.61)	1.79 (1.58–1.96)
Any substance use disorder	0.65 (0.40–1.06)			0.88 (0.66–1.16)	0.87 (0.62–1.24)	0.88 (0.55–1.41)		
Alcohol use disorder				1.05 (0.80–1.39)				
Drug use disorder				0.53 (0.31–0.89)				

Sources: Table reproduced from *Psychiatrics Clinics of North America*, 34, Berkowitz RI and Fabricatore AN, Obesity, psychiatric status, and psychiatric medications, 747–764, 2011, with permission from Elsevier; Data from Simon GE et al., *Arch. Gen. Psychiatry*, 63, 824–830, 2006. With permission; Mather AA et al., *J. Psychosom. Res*., 66, 277–85, 2009. With permission; Barry D et al., *Ann. Epidemiol.*, 18, 458–466, 2008. With permission.

† indicates bipolar I and bipolar II disorder

The mechanisms underlying the relationship between obesity and bipolar disorder are not yet clearly defined. Some have revealed a potential neural substrate—reduced brain volume—that may increase the likelihood of developing bipolar disorder in obese individuals.[28] Using MRI, Bond et al.[28] found that otherwise normal persons with higher BMI had lower gray matter and total brain volumes than normal weight individuals. In those with bipolar disorder, however, there was a correlation between BMI and decreased white matter and temporal lobe volume, which had been previously found to be vulnerabilities for bipolar disorder.[28] Interestingly, other evidence has shown that patients already diagnosed with bipolar disorder and who are obese tend to have more frequent manic and depressive episodes and are more likely to attempt suicide than those at normal weight.[29,30]

57.5 RATES OF PSYCHOPATHOLOGY IN CLINICAL SAMPLES OF OBESE PATIENTS

Prevalence rates of psychopathology among obese individuals seeking weight reduction treatments are higher than those in the general population. Carpiniello et al.[31] compared 293 obese people seeking treatment with matched nonobese controls from the general population and found ORs of 3.5 (95% CI: 2.5–4.9) for Axis I mental disorders and 4.3 (95% CI: 2.7–6.9) for Axis II disorders. The prevalence of mood disorders (31.4% vs. 12.3%), anxiety disorders (30.0% vs. 12.3%), and eating disorders (15.7% vs. 1.0%) was significantly higher in cases vs. controls, but there were no differences in the prevalence of psychotic (1.0% vs. 0.3%), substance use (2.1% vs. 0.7%), or other disorders (1.7% vs. 0.6%).

Psychopathology in clinical samples appears to be more common in severely obese (Class III) treatment seekers vs. those with Class I and II obesity. A study comparing 146 extremely obese women with 90 mildly to moderately obese women seeking bariatric surgery and lifestyle modification, respectively, found that the extremely obese women reported significantly higher scores on the Beck Depression Inventory®-II[32] (indicating greater symptoms of depression) than the mildly–moderately obese women (13.2 vs. 8.1).[33] In addition, women with extreme obesity were more likely (than less obese women) to report a history of clinically significant psychological problems (45.9% vs. 29.2%), physical abuse (24.3% vs. 6.6%), and sexual abuse (19.9% vs. 8.9%).

Rates of psychopathology in persons seeking bariatric surgery are of interest to the field, in part because of reports of increased suicidal ideation following surgery.[34] Most bariatric surgery centers require a psychological assessment as part of the screening process for surgery, which has led to concern that patients may minimize their level of distress to make sure that they are cleared for surgery.[35] To alleviate this concern, research has been conducted independently of clinical appointments for obesity surgery (i.e., whether they can go forward to have surgery). For example, Kalarchian et al.[36] assessed 288 bariatric surgery candidates who were evaluated using structured clinical interviews for Axis I and Axis II disorders, independently of the preoperative screening process. These researchers found that 66% of candidates (mean BMI = 52.2 kg/m^2) had at least one lifetime Axis I disorder and 38% met criteria for an Axis I disorder at the time of the evaluation. Using similar methods, Mauri et al.[37] found that a smaller percentage of patients (21%) had at least one current Axis I disorder, albeit in a less obese sample (mean BMI = 43.5 kg/m^2). In both studies, the most common current Axis I conditions were binge eating disorder and major depressive disorder, and the most common diagnoses on Axis II were avoidant and obsessive-compulsive personality disorders. While these findings suggest high rates of psychopathology in bariatric surgery candidates, the lack of a control group precludes comparisons with nonobese, less obese, or nontreatment-seeking individuals.

57.6 DOES INTENTIONAL WEIGHT LOSS CAUSE DEPRESSION?

For more than half a century, clinicians have been concerned that dieting and intentional weight loss caused (or exacerbated) symptoms of depression. These concerns stemmed from two studies published in the 1950s. The first reported that lean men who lost 25% of their initial weight following a very-low-calorie diet displayed adverse psychological symptoms that included depression, anxiety, and kleptomania.[38] Following this, Stunkard[39] described a "dieting depression" that included symptoms of nervousness and weakness in a group of obese women with psychiatric diagnoses attempting to lose weight. While neither of these studies is applicable to the majority of obese individuals without serious psychiatric diagnoses who lose more modest amounts of weight, clinicians today still question whether depressed individuals should be encouraged to lose weight, even if medically indicated. As such, most weight loss studies tend to screen out depressed individuals,[40–43] making it difficult to know whether depressed individuals experience an improvement, no change, or worsening in their mood.

In 2007, a clinical trial published in *The Lancet*[44] concluded that there were adverse emotional reactions associated with the weight loss medication rimonabant, which included depression and anxiety. This drug never received approval from the U.S. Food and Drug Administration and was removed from the European market in January 2009. In 2008, Merck abandoned development of its weight loss drug taranabant because of reports of similar side effects. The Food and Drug Administration now requires that weight loss medications are evaluated for their effects on depression and suicidality.[45] Thus, the relationship between dieting and depression is under the spotlight again.

Most studies of weight loss achieved with behavioral treatments have revealed reductions, rather than increases, in symptoms of depression,[46–48] although the majority of participants in these studies were not depressed at baseline. Faulconbridge et al.[49] examined changes in self-reported symptoms of depression in individuals treated with the weight loss drug sibutramine, lifestyle modification, or a combination of the two. The majority of individuals showed small

but significant improvements in their symptoms of depression as they lost weight, with no differences across treatment groups. A significant minority of the sample (13.9%), however, reported potentially significant worsening in symptoms of depression after 52 weeks of treatment. These individuals did not differ significantly at baseline from the other participants in initial BMI, education, gender, ethnicity, or initial Beck Depression Inventory®-II score. However, almost half (44.4%) of these participants had a psychiatric history, compared with only 26.9% (i.e., 45 of 167) of the rest of the sample ($p < .05$). In addition, they lost significantly less weight than the rest of the sample (5.4 ± 7.8% vs. 9.0 ± 7.8% of their initial weight, respectively; $p < .03$).

A larger study[50] recently investigated changes in symptoms of depression in more than 5000 overweight/obese participants with type 2 diabetes in the Look AHEAD (Action for Health in Diabetes) trial assigned to either an intensive lifestyle intervention (ILI) or a usual-care control group. At 1 year, participants in the ILI group (who lost a mean of 8.6% ± 6.9% of their initial weight) reported significantly greater reductions in their symptoms of depression than participants in the control group (who lost a mean of 0.7% ± 4.8% of their initial weight). Moreover, the incidence of potentially significant symptoms of depression in those not reporting depression at baseline (risk ratio = 0.66, 95% CI: 0.5–0.8; $p < .001$) was significantly lower in the ILI group than in the control group (6.3% vs. 9.6%).

Most studies evaluating psychological changes in bariatric surgery patients have shown improvements in symptoms of depression and anxiety, as well as significant improvements in quality of life.[51] However, Adams et al.[34] reported an increased risk of nondisease-related mortality, including accidents and suicide, in bariatric surgery patients when compared with nonsurgery-seeking obese controls. Further work is required to elucidate the characteristics of those most at risk for depression and suicidality when losing weight.

A recent meta-analysis examining changes in symptoms of depression with weight loss supports the conclusion that, in most cases, positive changes in mood are observed with weight loss. The authors compared seven categories of weight loss interventions in 7937 participants across 31 studies and found significant reductions in symptoms of depression with nearly all interventions.[52] The authors found that lifestyle modification treatments (diet and exercise combined with behavior therapy) were superior to control (standard mean difference [SMD] = 0.28, 95% CI: 0.17–0.40) and nondieting interventions (SMD = 0.31, 95% CI: 0.08–0.54) in reducing symptoms of depression and were marginally better than dietary counseling (SMD = 0.40, 95% CI: −0.01 to 0.81) and exercise-alone programs (SMD = 0.31, 95% CI: −0.01 to 0.62). Despite the positive associations between weight loss and improvements in mood within groups, meta-regression analyses found no relationship between change in weight and change in depressive symptoms among groups treated with lifestyle modification, suggesting that other aspects of treatment (e.g., social support) may be responsible for the beneficial effect on mood.

57.7 EFFECT OF PSYCHOPATHOLOGY ON OUTCOMES OF WEIGHT LOSS INTERVENTIONS

Two questions of interest arise when considering whether preexisting psychopathology negatively affects outcomes in weight loss trials. First, researchers have considered whether those with mental health problems at baseline can achieve the same magnitude of weight loss as those without such problems. In addition, it has been suggested that those with depression will experience worsening symptoms when subjected to the rigorous requirements of diet and exercise. The majority of research in this area has been conducted in depressed individuals, and the literature is briefly reviewed here.

Given the lack of motivation and fatigue experienced by some patients with psychiatric diagnoses, there is concern that those with depression or anxiety will not be able to adhere to the requirements of a weight loss trial. Typical weight loss trials that include a lifestyle intervention require regular (often weekly) participation in group meetings and strongly encourage completion of food diaries and adherence to calorie goals and exercise prescriptions.[53] Thus, some question whether depressed individuals will be able to achieve the same magnitude of weight loss as those without a psychiatric history. Studies of whether pretreatment symptoms of depression impede weight loss have yielded mixed results. Several investigations found no relationship between these two variables,[49,54,55] whereas others observed smaller weight losses in patients with greater symptoms of depression,[56–58] and still others showed more favorable outcomes among those with baseline psychopathology.[51,59,60] All of these studies were limited by small sample sizes and by relatively low levels of baseline psychopathology.

Studies examining whether obese individuals with major depressive disorder can lose weight safely (i.e., without an exacerbation of mood symptoms) are lacking. Faulconbridge et al.[61] recently conducted a pilot study with 12 obese individuals diagnosed with major depressive disorder who received a combination of lifestyle modification for their obesity and cognitive behavioral therapy for their depression. Results were very encouraging: the mean weight loss among those who completed the study was 11.4% of initial weight, comparable to the magnitude of weight loss observed in nondepressed participants undergoing lifestyle modification interventions.[53] In addition, depression scores (as assessed by the Hamilton Depression Rating Scale[62]) declined from 20.4 at baseline to 9.3 at the end of treatment, indicating significant improvements in symptoms of depression. All but one of the study's completers showed significant improvements in their symptoms of depression, and 67% met standards for complete remission.[63] One participant, however, did show worsening symptoms of depression and required extra psychiatric care, despite losing >8% of her initial weight. Another small study[64] recruited 14 obese individuals with comorbid major depressive disorder and provided behavioral activation for depression combined with nutritional counseling for weight loss.

Participants achieved a mean weight loss of 2.5 kg (5.5 lbs) over 12 weeks, and the mean Hamilton Depression Rating Scale score declined from 16.0 at baseline to 5.8 at the end of treatment. Both of these studies were limited by small sample sizes and lack of an appropriate control group, but each provided encouragement for larger randomized controlled trials investigating this question, which are now under way.

Overall, the data do not appear to justify the exclusion of persons with psychopathology from treatment for obesity based on the rationale that they will not lose weight. Careful monitoring of individuals who undertake weight reduction, however, appears prudent, given the small minority of patients who do experience adverse psychological events. Reliable psychosocial predictors of treatment failure, to our knowledge, have yet to be identified, although some studies have suggested that higher self-reported symptoms of depression at baseline are a predictor of attrition from weight loss trials.[55,65,66]

57.8 OBESITY AND PSYCHIATRIC MEDICATIONS

A growing area of research is the relationship between psychiatric medications and weight gain leading to the development of obesity. Antipsychotic drugs, certain classes of antidepressant medications (selective serotonin reuptake inhibitors and tricyclic antidepressants), and mood stabilizers (such as lithium) are among the medications known to cause weight gain (see Volume 2, Chapter 17). While a summary of this literature is beyond the scope of this chapter, the reader is referred to several excellent reviews[67–70] and to other chapters in the *Handbook of Obesity.* Any recommendations to patients to take these drugs (or not) should consider the risks of uncontrolled psychiatric symptoms alongside the risk of weight gain for that particular patient.

57.9 SUMMARY

The chronic stress that can be associated with excess adiposity—attributable to social stigma, medical comorbidities, or quality-of-life impairments—may predispose obese persons to psychopathology. Conversely, psychopathology may predispose a normal weight person to emotional eating and decreased physical activity, resulting in the development of obesity. Strong evidence from epidemiological and clinical studies now exists to support a relationship between obesity and several mental health problems, including depression, substance abuse, anxiety, and bipolar disorder. Historically, most studies have focused on the relationship between obesity and depression, and longitudinal research has provided evidence to support a bidirectional relationship between these two disorders. For the majority of obese individuals undertaking modest weight reduction, weight loss has favorable effects on mood, with a small minority of patients reporting worsening symptoms. Preliminary data examining weight loss in patients with major depressive disorder (formally diagnosed by a trained clinician) suggests that depressed individuals can lose clinically significant amounts of weight and can undertake weight reduction safely (i.e., without an exacerbation of mood symptoms). We conclude that there is not sufficient evidence to justify their exclusion from weight loss trials, but we recommend careful monitoring of obese individuals who undertake weight reduction by any means. Finally, further research efforts to develop weight loss treatments for those obese persons with mental health problems are encouraged.

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58 Obesity and Health-Related Quality of Life

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CONTENTS

58.1 INTRODUCTION

Over the past two decades, there has been a dramatic increase in research on obesity and quality of life. The reason for this growth of interest is that obesity has negative consequences that go far beyond morbidity and mortality. Indeed, obesity is a vexing health problem that has pervasive social implications. Whereas in mainstream psychology quality of life is defined as a global, conscious, and cognitive judgment of satisfaction with one's life,[1] within the medical literature the term has been redefined as a health outcome commonly known as health-related quality of life (HRQOL) that broadly encompasses two major domains of functioning: mental and physical.[2] Moreover, these two domains have subcomponents, and outcome measures can be defined as either generic or condition/disease specific.

The most widely used generic measure of HRQOL in adults is the Medical Outcomes Study's 36-item Short-Form Health Survey (SF-36).[3] The SF-36 has two composite scores, physical composite score (PCS) and mental composite score (MCS), and eight subscales,[4] four that are conceptually linked to the physical domain (physical functioning, role physical, body pain, and general health) and four to the mental domain (vitality, social functioning, role emotional, and mental health). A condition-specific measure of HRQOL in the adult obesity literature is the Impact of Weight on Quality of Life (IWQOL) questionnaire that assesses the degree to which obesity negatively affects functioning in eight areas: health, social/interpersonal, work, mobility, self-esteem, sexual life, activities of daily living, and comfort with food.[5,6] The original IWQOL measure has 74 items, although a shorter version is now available.[7]

The advantage of using a generic measure such as SF-36 is that it allows for comparisons across different diseased populations; however, a related weakness is that it ignores important outcomes such as the interpersonal consequences of being obese. For this reason, obesity researchers interested in adults often use well-validated and norm-referenced measures related to specific outcomes (e.g., depression, anxiety, and psychosocial problems).

In children and adolescents, HRQOL can be measured from the perspective of either the child/adolescent or the parent. Many different assessment approaches have been developed to measure HRQOL in these populations.[8] As with adults, these include both generic measures and condition-specific measures.[9] The most commonly used generic measure of HRQOL is the Pediatric Quality of Life Inventory (PedsQL),[10] which covers a wide age range (2–18 years) and has four scales: physical functioning, emotional functioning, social functioning, and school functioning. The PedsQL is administered by interview for young children (aged

5–7 years). An alternative generic measure of HRQOL is the Child Health Questionnaire, which can be used with children and adolescents ranging from 5 to 18 years old[11] or with parents as proxies providing HRQOL information about their children.[12] Also, a semistructured interview to assess generic HRQOL in adolescents, named the Youth Quality of Life Instrument, has been developed.[13] The reliability and validity of all three measures have been established.[8]

The most commonly used obesity-specific measure of child and adolescent HRQOL is Impact of Weight on Quality of Life–Kids, which has good reliability and validity for a total score and four subscales: physical comfort, body esteem, social life, and family relations. This assessment can be used with children and adolescents between the ages of 11 and 19 years.[14,15] An alternative obesity-specific measure is Sizing Me Up, which was developed for children aged 5–13 years[16] and for parents as proxies.[17]

This chapter reviews the literature on the relationship between obesity and HRQOL. It is an update of the review by Williamson and O'Neil in the 2004 edition of *The Handbook of Obesity*. Considerable research on obesity and HRQOL has been conducted since the 2004 chapter was written. In particular, research on HRQOL in obese children and adolescents has greatly expanded, and there are now several studies specific to older adults. In addition, cross-sectional studies of HRQOL have begun to use similar assessment methods, allowing the comparison of results across studies. In 2004, there were very few published randomized controlled trials (RCTs) of weight loss and changes in HRQOL. More recently, a number of very well-controlled studies in both adult and adolescent populations have been published. Also, much has been learned about how moderators such as gender and psychosocial variables affect the relationship between obesity and HRQOL.

The chapter is organized so that the earlier (pre-2003) literature is reviewed first to provide context for the more recent findings. The review of research since 2003 covers findings related to adults, children, and adolescents. The studies are classified as either cross sectional or longitudinal, which include uncontrolled studies and RCTs.

58.2 EARLY RESEARCH ON OBESITY AND HEALTH-RELATED QUALITY OF LIFE

58.2.1 Cross-Sectional Studies

Studies conducted in the 1980s and 1990s established that obesity in adolescence and/or early adulthood predicted lower rates of marriage in adulthood and, for women, lower educational achievement and income and higher rates of poverty.[18] Relative to thinner women, heavier women were more likely to marry men of lower socioeconomic status.[19]

Fontaine and colleagues[20] reported that obese patients seeking weight loss treatment functioned worse in all eight domains of SF-36 compared to population norms. Physical and social functioning was worse among the most severely obese in the sample. Subsequently, Fontaine et al.[21] reported more impairment in HRQOL, especially on physical functioning, among a group of treatment-seeking obese patients compared to a group of obese respondents not trying to lose weight. In 2000, using SF-36 Brown et al.[22] evaluated the effects of obesity on HRQOL in a large population-based sample of Australian women 18–23 years of age. They found that even among this young group HRQOL was lower among overweight and obese groups on subscales measuring general health, physical functioning, and vitality. Using a mail survey of nearly 9000 adults in the Oxford region of England, Doll and coworkers[23] assessed the association of obesity with quality of life as measured by SF-36. Increasing degrees of obesity were associated with decreasing physical well-being, regardless of the presence or absence of other chronic medical conditions. Emotional well-being was adversely affected only for those obese patients with chronic medical conditions, and their emotional functioning was not significantly different from that of nonobese patients with equal degrees of chronic illness. In a review of this early literature, Kushner and Foster[24] concluded that obesity adversely impacted HRQOL related to physical functioning to a greater extent than mental functioning.

Additional evidence regarding the perceived effect of obesity on quality of life may be inferred from the value that obese people place on weight loss. Rand and MacGregor[25] reported that gastric bypass patients who had lost at least 45 kg (100 lb) indicated that they would prefer to be blind, deaf, dyslexic, diabetic, or an amputee rather than return to severe obesity and stated unanimously that they would forego the opportunity to be a millionaire if it required them to be obese again. It is apparent from these earlier studies that obesity is a status that is loathed by those who have developed excess adiposity.

58.2.2 Psychological Functioning

Obesity is not a psychiatric diagnosis.[26] Nevertheless, many early studies that assessed psychological functioning among obese persons relied on standard measures of psychiatric conditions rather than mental health subscales from generic or disease-specific measures of HRQOL. These studies reported that among nonclinical samples of obese people rates of diagnosable psychopathology were no greater than those among nonobese groups[27,28]; in addition, the extent of psychological distress among treatment-seeking obese groups was similar to that observed among other groups of medical or surgical patients.[29] These observations suggest that the higher rates of distress among obese subjects observed in clinical studies, compared to population-based studies, may reflect a selection bias in which those who are more distressed seek treatment. Indeed, when treatment-seeking obese samples have been compared with nonclinical obese samples, higher rates of psychological disturbance or distress have often been found among the treatment-seeking patients. For example, among obese females those seeking treatment were more depressed and histrionic than those from a nonclinical sample.[30] Another study[31] reported that

treatment-seeking obese adolescents and young adults had higher prevalence rates of mood, anxiety, somatoform, and eating disorders than either a less obese population or the general population of similarly aged individuals.

There have been a few reports of impaired self-esteem among adult obese patients,[5] but most of the early research in this area focused on children and adolescents. Early studies of the impact of obesity on self-esteem among preteen children produced inconsistent results[32]; however, the deleterious effects of obesity on self-esteem were found to be more consistent among adolescents and young adults.[33,34] Strauss[33] reported that in white and Hispanic females obesity in the preteen years predicted impaired self-esteem in early adolescence. These studies suggested that obesity, especially in adolescence, adversely impacts self-esteem and that childhood obesity may lead to lower self-esteem in some adolescent girls.

58.2.3 Interpersonal Correlates of Obesity

In the United States and other Western societies, obese people inhabit a world that is poised to treat them adversely.[29,35–37] Negative attitudes toward obese people have been demonstrated among adults and children, even preschoolers.[38] These same negative attitudes have been reported among health-care professionals.[39–42] Negative attitudes are frequently reflected in prejudicial behavior against obese people. Extreme discrimination in employment and educational settings has frequently been documented.[37,43,44] Obese adults often report perceived mistreatment due to their weight at the hands of strangers and loved ones alike; the frequency of such reports is related to degree of obesity.[45]

One result of repeatedly interacting with a world that is often flinty and at worst hostile may be a reduction in opportunities to develop certain social skills. For example, in a study in which obese and nonobese women conversed on the telephone with anonymous partners who were unaware of their weight status, the obese women were rated by both the partners and the reviewers of the taped conversations as being less friendly, less likable, less attractive, and less socially skilled.[46] However, the same research team later found no differences between obese and nonobese women in the rated quality of their actual relationships or social behavior, based on ratings by both participants and their friends and coworkers.[47] Interestingly, a study of 9-year-old British schoolgirls found that although overweight and obese girls were less likely than nonoverweight girls to be rated as pretty by peers, they were just as popular as measured by peer nomination questions.[48]

58.2.4 Conclusions

Early (pre-2003) research established an inverse relationship between obesity and HRQOL, especially with physical functioning. This research also found that obesity was associated with a variety of social and economic conditions, including stigmatization, lower rates of marriage, lower educational achievement, and increased poverty. These early findings provide the context for understanding the findings of studies that have been conducted over the past decade, which are reviewed in Sections 58.3 and 58.4.

58.3 RECENT CROSS-SECTIONAL STUDIES

58.3.1 Adults

58.3.1.1 Association of Obesity with Health-Related Quality of Life

Cross-sectional research on obesity and HRQOL has expanded considerably over the past decade. SF-36 and its abbreviated form (SF-12)[49] have been used most frequently in these studies, but other measures of generic and obesity-specific measures of HRQOL have also been increasingly employed.[50–53] Table 58.1 summarizes the findings from seven recent studies that all used SF-36 or SF-12 to measure

TABLE 58.1
Recent Cross-Sectional Studies of Obesity and HRQOL in Adults

Author, Year, Country	Population	Overweight/Obese	Obesity Associated with MCS	Obesity Associated with PCS
Jia and Lubetkin, 2005, United States	General population	Mixed weight status	Yes	Yes
Rejeski et al., 2006, United States	Type 2 diabetics	Overweight and obese	No	Yes
Tsai et al., 2008, United States	Metabolic syndrome	Overweight and obese	Yes	Yes
Mond and Baune, 2009, Australia	General population	Mixed weight status	No	Yes
Wee et al., 2010, Asia (mixed)	General population	Mixed weight status	No	Yes
Vetter et al., 2011, United States	Metabolic syndrome and controls	Overweight and obese	No	Yes
Bentley et al., 2011, United States	General population	Mixed weight status	No	Yes

HRQOL in adults. These studies were conducted on a variety of subject populations in the United States, Australia, and Asia. We elected to report the association of obesity with the two composite scores (PCS and MCS) of SF-36 and SF-12. An association was reported if overweight/obese participants differed from lean controls with a significantly lower score on a composite scale or if a significant negative correlation between body mass index (BMI) and the composite score was reported. As can be seen in Table 58.1, PCS was found to be associated with obesity in all seven studies. In contrast, only two of the seven studies reported an association between obesity and MCS. These findings are consistent with early studies that used SF-36[24]: impaired physical health related to HRQOL is more strongly associated with obesity than is impaired mental health. Studies using HRQOL measures other than SF-36 and SF-12 have consistently reported that obesity is associated with impaired HRQOL that is both generic and specific to features of obesity.[50,51,53–55]

58.3.1.2 Moderators of Health-Related Quality of Life and Obesity

Table 58.2 summarizes the results of studies pertaining to factors that moderate the association between obesity and HRQOL. One of the most consistent findings of these studies is that women share a disproportionate burden of being overweight compared to men.[50,56–59] This effect is clearly strongest for measures of physical functioning. A recent study from Germany is of interest, which reported that social support buffered the effects of obesity on physical health for men but not women.[58] Also, in a large-scale study by Bentley and colleagues[50] poorer mental health was related to obesity in women but not men. This phenomenon is generally believed to stem from a lower social pressure for thinness among men and is reflected in a higher self-esteem, a higher quality of life, and better marriage prospects among obese males.[5,19]

As presented in Table 58.2, there is also evidence that race/ethnicity may moderate the effects that obesity has on HRQOL. Early research[60–63] reported that minority adults (especially black women) tended to be less concerned about overweight status and were less motivated to lose body weight than white men and women. More recently, Bentley and colleagues[50] reported that overweight black adults had a higher HRQOL than black adults in other BMI categories. In addition, African–American men and women have shown lower levels of body size dissatisfaction.[64] Therefore, although black adults may be at lower risk for developing mood or self-esteem problems associated with obesity, they may also be less motivated to lose weight. With respect to obesity and

TABLE 58.2
Moderators of the Obesity-HRQOL Relationship

Author, Year, Country	Sample	Overweight/Obese	Moderators	Primary Conclusions of Relevance to this Review
Bentley et al., 2011, United States	31,710 Adults	Heterogeneous on BMI	Sex, race	Consistent indirect relationship was found between BMI status with multiple global measures of HRQOL and measures of physical health; effects observed for mental health, but for women only; overweight blacks had higher HRQOL than blacks in other BMI categories.
Fallon et al., 2005, United States	110 Obese and 34 normal-weight adolescents and their parents	Heterogeneous on BMI	Race	Obese white adolescents had poorer scores on social/interpersonal, self-esteem, and physical appearance as assessed by the IWQOL measure than their normal-weight counterparts; obese black adolescents showed greater impairment on their general health score than blacks with normal BMI; these effects were corroborated by parents' perceptions; the authors concluded that obesity led to greater impairment on HRQOL among white than black adolescents.
Kortt and Dollery, 2011, Australia	16,488 Men and women; aged 18–79 years	Heterogeneous on BMI	Sex, medical conditions	Based on the SF-36, obese women and men (BMI > 30) had lower scores than those with BMI < 25; no effect found for being overweight; the relationship between obesity and SF-36 scores was attenuated but not negated by arthritis and depression/anxiety.
Messier et al., 2004, United States	316 Older overweight and obese adults with knee osteoarthritis	Heterogeneous on BMI of 26 and above	Exercise	An exercise group experienced greater improvement in functional status, 6-minute walking time, and stair climbing performance than a control group.
Mond and Baune, 2009, Germany	4181 Men and women; aged 18–65 years	Heterogeneous on BMI status	Sex	Controlling for age, social status, and medical conditions, mild obesity in women was associated with impaired physical function (SF-36 PCS), whereas the effect for men was dependent on moderate obesity; no effect on MCS for women was found, whereas overweight men actually had better MCS scores than those of normal weight; women shared a disproportionate amount of the burden of being overweight, an effect that was not due solely to medical comorbidity.

TABLE 58.2 (*Continued*)
Moderators of the Obesity-HRQOL Relationship

Author, Year, Country	Sample	Overweight/Obese	Moderators	Primary Conclusions of Relevance to this Review
Smith and McFall, 2005, United States	25,794 Men and women; adults with diabetes and 25,794 matched controls	Heterogeneous on BMI status (not considered in analyses)	Exercise and weight control	Researchers examined the number of days limited in last 30 days with poor physical health, poor mental health, limited activity, depression, pain, stress, and poor sleep; those with diabetes were more limited in all areas compared to controls; among those with diabetes, weight control was not a burden on outcomes, and exercise was associated with less limitations in all areas assessed.
Vetter et al., 2011, United States	390 Obese adults; 269 had metabolic syndrome and 121 did not	Heterogeneous on obesity status	Metabolic syndrome	There was no evidence across three HRQOL measures that the presence or absence of metabolic syndrome affected HRQOL; BMI and disease burden were independently related to PCS scores in multivariate analyses.
Wee et al., 2010, Singapore	5027 Men and women (Chinese, Malay, and Indian)	Heterogeneous on BMI status	Race/ethnicity, sex	Using SF-36, it was found that increasing BMI status was associated with poorer PCS scores on SF-36; this effect was moderated by gender but not race/ethnicity.
Wiczinski et al., 2009, Germany	2732 Men and women, aged 35–74 years	Heterogeneous on BMI status	Social support, sex	For both men and women, BMI status was indirectly associated with the SF-12 PCS but not MCS; social support buffered the effect of obesity on HRQOL for men but not women.

TABLE 58.3
Recent Cross-Sectional Studies of Obesity and HRQOL in Children and Adolescents

Author, Year, Country	Population	Overweight/Obese	Obesity Associated with Total PedsQL	Obesity Associated with Physical Functioning	Obesity Associated with Social Functioning	Obesity Associated with Emotional Functioning	Obesity Associated with School Functioning
Modi et al., 2008, United States	Adolescents	Overweight or obese	Yes	Yes	Yes	Yes	Yes
Riazi et al., 2010, United Kingdom	Children and adolescents	Mixed weight status	Yes	Yes	Yes	Yes	Yes
Boyle et al., 2010, United Kingdom	Children and adolescents	Mixed weight status	Yes	Yes	Yes	Yes	No

race/ethnicity, it is important not to overgeneralize findings, that is, most studies have made comparisons between white and black adults and not other racial/ethnic groups. In a large Asian study from Singapore studying Chinese, Malay, and Indian men and women, Wee and colleagues[57] reported the typical sex effect for the SF-36 PCS score, but failed to observe any effect for race/ethnicity (see Table 58.2).

Early research reported that obese binge eaters experience more psychological disturbances than obese people who do not frequently engage in binge eating.[65,66] There has been considerable controversy about the distinction between a psychiatric syndrome called binge-eating disorder and binge eating as a behavioral correlate of obesity.[67] Studies that have used very strict definitions and structured interview methods for assessing binge-eating disorder have found that the syndrome as defined by the American Psychiatric Association[26] is actually quite rare (1%–3%) even in obese people seeking treatment.[68] However, binge eating as a symptom of obesity is much more common; significant binge eating is observed in 7%–15% of obese adults.[67] Men are slightly less likely to report binge eating than women, and most ethnic groups report comparable rates of binge eating. Womble et al.[69] found that binge eating was highly correlated with obesity and that the combined influences of negative affect and dietary restraint accounted for much of the variability in binge eating among obese people. These findings suggest that binge eating is associated with increased adiposity[70] and thereby lower HRQOL. Since higher levels of obesity are negatively correlated with HRQOL, the presence of binge eating moderates the association of obesity with HRQOL.

Finally, given the volume of data suggesting that obesity has a greater effect on physical compared to mental aspects of HRQOL, one might expect that levels of physical activity attenuate the effect that obesity has on HRQOL and that markers of physical functioning would be important moderating variables of this relationship as well. In the literature on aging, Villareal and colleagues[71] reported that a physical activity intervention among prefrail, older obese adults did improve PCS scores on SF-36 compared to a control group (see Table 58.3), and a similar result was reported by Messier et al.[72] using objective measures of physical function. In fact, in a large population study by Smith and McFall[73] exercising

adults with diabetes who had various levels of adiposity as assessed by BMI reported fewer limitations in physical health, mental health, depression, pain, stress, and sleep than those who did not exercise.

To our knowledge, the only study that has examined whether baseline levels of physical functioning may moderate relationships between obesity and HRQOL comes from a recent RCT (see the study by Williamson et al.[74]) (Table 58.4). In this study, participants with poorer baseline levels of physical function experienced greater improvement on their PCS scores of SF-36 as a result of weight loss than those with higher levels of baseline HRQOL.

58.3.2 Children and Adolescents

58.3.2.1 Association of Obesity with Health-Related Quality of Life

In a review of cross-sectional studies of the association of child and adolescent obesity with HRQOL, Tsiros et al.[9] concluded that overall HRQOL was negatively correlated with

TABLE 58.4
RCTs of Weight Loss and Studies of Weight Regain in Adults

Author, Year, Country	Sample	Design	Primary Conclusions of Relevance to this Review
Engel et al., 2003, United States	106 Women and 16 men; mean age 46.5 years; mean BMI 40.7	Participants were part of a weight reduction program and lost ≥5%, then regained at least 5% from 10–41 months of follow-up; IWQOL completed at 3-month intervals	The effect of weight regain on HRQOL mirrored the effect of weight loss; the initial severity of HRQOL impairment had a greater impact on change in HRQOL than changes in weight.
Kaukua et al., 2003, Finland	100 Patients (61% women); mean age 48.2 years; mean BMI 42.8	2-Year observational weight maintenance/regain study following a short-term very-low-calorie diet	Since the pattern of change in HRQOL (worsening) during weight regain did not follow the percentage of weight gained, authors assumed that other factors such as involvement in weight loss or physical activity may have played a role in HRQOL during weight regain.
Kiernan et al., 2001, United States	264 Overweight adults (BMI 28–34 for men and 24–30 for women); age 25–49 years; 132 men and 132 women	Randomized to WL or WL + E for 1 year; measures taken at baseline and 1 year	Both groups had better restraint, less disinhibition, and less hunger at 1 year; men in WL + E had even better dietary restraint and lower perceived hunger than WL only at 1 year; no added benefit seen for women in WL + E group.
Rejeski et al., 2002, United States	316 Older adults with knee osteoarthritis; age 68.5 years; 78% women; BMI 34.54	18-Month RCT with four groups: C, WL only, E only, and WL + E	Across the 18 months, only the WL + E differed from C on the PCS of SF-36; those in WL, E, or WL + E had improved body satisfaction scores relative to controls; only E and WL + E differed from C on satisfaction with function.
Villareal et al., 2011, United States	93 Obese, prefrail older adult; age 69 years; BMI 37.3	1-Year RCT with four groups: C, WL, E, and WL + E; SF-36 and FSQ assessed at baseline, 6 months, and 1 year.	The PCS of the SF-36 increased by 15% from baseline in WL + E, 14% in WL, and 10% in E, and all three differed from C (experienced a four-unit decline); for the FSQ, WL, E, and WL + E improved more than C; WL + E was better than WL only.
Williamson et al., 2009, United States	5145 Men and women with diabetes; mean age 58.7 years; BMI 36; 59% women	Randomized to ILI for weight loss or DSE control; SF-36 and BDI-II assessed at baseline and 1 year	ILI improved more across 1 year than DSE on SF-36 PCS and BDI-II; greatest improvement for PCS seen in those with the lowest PCS scores at baseline; improved fitness and improved physical symptoms partially mediated treatment effects for both PCS and BDI-II at 1 year.
Yankura et al., 2008, United States	248 Postmenopausal women who lost ≥5 lb in the first 6 months of treatment; 52–62 years old; BMI ~31	Diet and physical activity weight loss study; based on weight change status from 6–18 months; participants were divided into 3 groups: WL ≥ 5 lb (21%); WS < ±5 lb (51%); WR > 5 lb gain (28%)	Between 0 and 6 months, the WR group had a decrease in the mental health and social functioning subscales on SF-36; the other two groups improved in these areas during the same period; between 0 and 18 months, energy scores improved most in the WL group.
Yancy et al., 2009, United States	545 Men and women (76%); mean age 45 years; mean BMI 34	Randomized to LCKD or LFD; told to exercise 30 minutes at least three times per week; SF-36 assessed at 4, 6, 8, 12, 16, 20, and 24 weeks	At 24 weeks, physical function, role physical, general health, vitality, social functioning, and PCS improved in both groups; body pain improved in LFD only, but role emotional, mental health, and MCS improved in LCKD only; LCKD improved more on MCS than LFD.

Note: C = control, DSE = diabetes support and education, FSQ = functional status questionnaire, ILI = intensive lifestyle intervention, LCKD = low-carbohydrate ketogenic diet, and LFD = low-fat diet, WL = weight loss, E = exercise.

obesity as reported using the child self-report ($r = -0.70$) or parent-proxy ($r = -0.77$) versions of PedsQL. This inverse relationship was found for three of the four subscales of PedsQL: physical functioning, social functioning, and emotional functioning. No association between BMI and school functioning was observed. The correlation between child self-reported HRQOL and parent proxy–reported HRQOL using PedsQL was very high (r values ranged from 0.87 to 0.93); however, relative to the child self-reports, parent-proxy reports were biased such that when youth scores were low parent scores were even lower, and when youth scores were high parent scores were even higher. In an earlier review, Floodmark[75] had concluded that treatment-seeking obese children/adolescents reported more impaired HRQOL in comparison with community samples.

Since the publication of the Tsiros et al.[9] review, several new studies have been published. The three studies that used PedsQL to assess HRQOL are summarized in Table 58.3, which reports only the results of child self-reported HRQOL. All three studies reported an inverse relationship between obesity and both the PedsQL total score and all four subscales, with one exception: Boyle and colleagues[76] did not report a significant association between BMI and school functioning. Modi et al.[77] and Wille et al.[78] reported similar findings using obesity-specific measures of HRQOL (i.e., obesity was associated with impaired HRQOL).

58.3.2.2 Moderators of the Association between Obesity and Health-Related Quality of Life

Modi and colleagues[77] reported no association of sex and age with HRQOL, but they did report less severe impairment of HRQOL in black (compared with white) adolescents with extreme obesity. Fallon et al.[79] also reported that obesity was associated with greater impairment in white adolescents in comparison with black adolescents. Tsiros et al.[9] reported mixed results for comparisons of treatment versus nontreatment participants, boys and girls, and different age groups.

In conclusion, cross-sectional studies of the association between child/adolescent obesity and HRQOL have consistently found that HRQOL is impaired across all domains except school functioning and that this impairment affects boys and girls and younger and older youth more or less equally. Results from two studies suggest that the race of adolescents may moderate this relationship such that obese black adolescents report higher HRQOL in comparison with obese white adolescents.

58.4 WEIGHT LOSS AND REGAIN AND CHANGES IN HEALTH-RELATED QUALITY OF LIFE

The process and outcome of weight loss would both be expected to affect HRQOL. For most obese and overweight people, losing weight and maintaining the weight loss involve restriction of dietary intake, physiological readjustment, major lifestyle changes, and effort. An important question is as follows: for better or worse, is intentional weight loss associated with changes in HRQOL? Sections 58.4.1 and 58.4.2 summarize research on this question.

58.4.1 Adults

Table 58.4 summarizes the results of eight studies that involved RCTs of behavioral weight loss and HRQOL.[71,74,80–82] Four of these investigations involved standard lifestyle interventions consisting of calorie reduction and/or exercise therapy,[71,74,80,81] whereas the study by Yancy and colleagues[82] compared a low-carbohydrate ketogenic diet to a low-fat diet. The study by Yancy et al.[82] is interesting in that although SF-36 improved for both dietary treatments, the MCS composite score and the role-emotional and mental health subscales of SF-36 improved only in the low-carbohydrate ketogenic diet relative to the low-fat diet. The authors suggest that the content of the diet might be important in understanding the effects of weight loss on mental health.

In the largest study of lifestyle interventions to date, Williamson and colleagues[74] found that, after 1 year of treatment, adults with type 2 diabetes randomized to a lifestyle intervention made greater improvements on the PCS of SF-36 and the Beck Depression Inventory (BDI) than those in a control group (see Table 58.4). Furthermore, improvements in fitness and a reduction in physical symptoms mediated the effects of treatment on both SF-36 and BDI.

Other studies by Villareal and colleagues,[71] studying prefrail older adults, and Rejeski and colleagues,[81] in a study of older adults with knee osteoarthritis, involved more complex designs to tease out the effects of exercise (E) from weight loss (WL) (see Table 58.4). Although both studies found treatment effects for the PCS but not the MCS of SF-36, Villareal[71] found that WL alone, E alone, or WL + E improved PCSs relative to a control group, whereas in the study by Rejeski et al.[81] the only group that differed from the control arm on PCS was WL + E (see Table 58.4 for details of study designs). Also of interest is the finding by Rejeski and colleagues[81] that satisfaction with body appearance improved with WL, E, or WL + E relative to the control group but that satisfaction with function improved only in E or WL + E. Similarly, in the Villareal study[71] participants in the WL + E group had better improvement on a measure of functional status than those in WL only. In the study by Kiernan et al.,[80] although participants in WL or WL + E experienced improved dietary restraint and reductions in hunger after 1 year of treatment, men in WL + E experienced even greater improvements for dietary restraint and perceived hunger than the WL group. Thus, it appears that there are functional benefits conferred by adding exercise to caloric restriction in studies of weight loss. Moreover, one might expect that physical activity habits would moderate the effects of obesity on HRQOL, a point made earlier in this chapter.

Finally, there are a few published studies that have evaluated the effects of weight regain on HRQOL. Although researchers generally agree that weight regain leads to a deterioration of HRQOL, early investigations in both the United States[83] and Finland[84] are conflicting. Engel and colleagues[83]

reported that the effects of weight loss and weight regain on HRQOL mirror one another, whereas Kaukua and colleagues[84] reported that the effects of weight regain on reductions in HRQOL are less severe than the improvements that initial weight loss had on HRQOL. They suggested that the perceived benefits of being involved in treatment or other factors such as changes in physical activity may have confounded comparisons of weight loss with weight regain. A more recent study identified postmenopausal women who had lost 5 lb during 6 months of treatment and then followed them for another year.[85] Three groups of women were created at follow-up: WL, weight stable (WS), and weight regain (WR; see Table 58.4 for details). An important finding was that those in the WR group experienced a decrease in social functioning and mental health during the first 6 months of treatment, whereas the WL and WS groups improved on the same subscales during this period of time. In addition, from baseline to the end of the study the most notable difference in HRQOL between WL and either the WS or the WR group was that those in the WL group experienced greater improvement in perceived energy.

58.4.2 Children and Adolescents

In a review of published papers concerning weight loss and changes in HRQOL in children or adolescents, Tsiros and colleagues[9] identified two RCTs and five non-RCTs with pre–post testing for changes in HRQOL. A wide range of interventions were utilized, including lap-band surgery, pharmacotherapy, diet and exercise, and cognitive-behavior therapy. The duration of treatment in these studies was generally very short (12 weeks or less) or unspecified. Also, most of the participants were adolescents. Because of the limitations of these studies, Tsiros et al.[9] were unable to reach strong conclusions about changes in HRQOL associated with weight loss, but the limited data suggested that the HRQOL of adolescents generally improved with weight loss.

Since the publication of the Tsiros et al.[9] review, six relevant studies have been published. The participants in these studies were all adolescents. Yackobovitch-Gavan et al.[86] reported the results of the only new RCT. In a 12-week intervention, they compared three macronutrient diets: low-carbohydrate low-fat, high-carbohydrate high-fat, and high-carbohydrate low-fat diets. They found improved HRQOL only in the two low-fat treatment arms. Silberhumer and coworkers[87] reported an uncontrolled study of gastric banding, which was associated with improved HRQOL after a 5-year follow-up. Loux et al.[88] reported an uncontrolled study of gastric bypass surgery on 16 adolescents; HRQOL improved in the 9 participants who were tested after varying time periods. Patrick et al.[89] tested the impact of 4 weeks of weight loss camp in an uncontrolled study. They reported improved HRQOL with pre–post testing.

Williams et al.[90] conducted an observational study that spanned 5 years, covering the period from childhood to adolescence. They reported significant negative correlations between BMI and HRQOL for each of the two cross-sectional analyses (2000 and 2005), which indicates that this relationship was stable across time. However, they failed to find that a higher BMI in late childhood was predictive of a lower HRQOL during adolescence. The authors concluded that preschool overweight/obesity may predict low HRQOL in elementary school, which persists throughout childhood and adolescence. If this conclusion is correct, then correction of childhood obesity at an early age may be important not only for the remediation of excess adiposity but also for the negative psychosocial effects of obesity.

Finally, Kozak et al.[91] investigated the impact of being overweight or obese during young adulthood on HRQOL 20 years later. Using SF-36, they found that obesity during young adulthood was predictive of lower PCSs but not MCSs 20 years later. We found no published papers on the effects of weight regain on HRQOL in children or adolescents.

In summary, research on the effects of intentional or surgically induced weight loss in children and adolescents remains underdeveloped and research on weight regain is nonexistent. Clearly, more research effort is needed in this area.

58.5 CONCLUSIONS

Research has found that obesity is generally associated with lower overall HRQOL and especially HRQOL related to physical functioning. However, it is important not to lose sight of the negative impact that obesity has on social and psychological functioning, particularly for women and those who are morbidly obese. The impact of obesity on HRQOL is moderated by a variety of personal characteristics, including severity of obesity, sex, race/ethnicity, and the presence of behavioral characteristics such as binge eating. Weight loss generally results in improved HRQOL in adults and adolescents. Furthermore, in the adult literature, studies that have teased out the effects of combining physical activity with weight loss suggest that the effects of this combined treatment on HRQOL are greater than those of weight loss alone. Clearly, more research is needed on weight loss in older adults given the ambivalence that the medical community continues to have on this topic. Preliminary research suggests that weight regain is associated with worsening HRQOL, but more research is needed before offering strong conclusions. In summary, research on HRQOL and obesity has been very active over the past decade, leading to a much better understanding of how obesity and weight loss are related to personal well-being. It is recommended that measures of HRQOL be routinely included in obesity treatment outcome studies of children, adolescents, and adults as important indicators of treatment effectiveness.

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59 Obesity and Pregnancy Outcomes

Raul Artal and Sarah Hopkins

CONTENTS

59.1 INTRODUCTION

The global epidemic of obesity continues to accelerate at an alarming rate. Nearly three in every five U.S. women of reproductive age (20–44 years) are now classified as overweight or obese.[1] Excessive weight gain in pregnancy is a significant contributor to rising obesity rates in women and the obesity-associated public health-care burden in the United States.[2] Obesity and excessive gestational weight gain (GWG) have been recognized as independent risk factors for maternal and fetal complications, including diabetes, hypertension, operative deliveries, macrosomia, and neonatal complications (Box 59.1).[3] More recently, we have begun to understand that maternal obesity is associated with significant lifelong consequences for the next generation as well.[4] This chapter is a review of the current knowledge regarding maternal, fetal, and neonatal pregnancy outcomes in obese women.

59.2 OBSTETRIC CONSEQUENCES OF OBESITY

59.2.1 Early Pregnancy

59.2.1.1 Early Pregnancy Loss

Obesity has a negative impact on ovulation, conception, implantation, and early fetal development.[5,6] It has been shown that obese women experience longer times to conception and that many receive treatment for infertility.[7] The most common etiologies are polycystic ovarian syndrome and hyperandrogenism, with both conditions characterized by insulin resistance. Obese women are more likely to experience pregnancy loss once pregnant, and increased miscarriage rates are seen following natural conception, ovulation induction, and assisted conception (Table 59.1). A meta-analysis[8] of studies published before September 2006 concluded that, when all methods of conception were considered together, overweight and obese women had an

BOX 59.1 SUMMARY OF COMMON COMPLICATIONS OF OBESITY IN PREGNANCY

Spontaneous abortion
Congenital anomalies
Hypertensive diseases, both preexisting and gestational
Gestational diabetes, both preexisting and gestational
Anesthetic complications
Vaginal birth after cesarean failure
Operative vaginal deliveries
Cesarean delivery
Increased complications from cesarean deliveries, including venous thromboembolism, surgical site infections, and greater blood loss
Shoulder dystocia
Maternal mortality
Antepartum hospitalization
Increased length of stay in hospital
Postpartum maternal rehospitalization
Neonatal macrosomia
Fetal death
Neonatal acidosis
Neonatal intensive care unit admission
Neonatal respiratory complications

TABLE 59.1
Adverse Early Pregnancy Outcomes and Congenital Anomalies in Obese vs. Normal-Weight Women

Outcome	OR	95% CI	Reference	Type of Study	Sample Population (Obese/Normal Weight)
			Miscarriage		
Spontaneous and assisted conception	1.67	1.25–2.25	Metwally et al.[8]	Meta-analysis	5545/11,151
Spontaneous conception only	1.31	1.18–1.46	Boots and Stephenson[9]	Meta-analysis	3800/17,146
			Congenital Anomalies		
Neural tube defects	1.70	1.34–2.15	Rasmussen et al.[14]	Meta-analysis	>1 million
	1.87	1.62–2.15	Stothard et al.[13]	Meta-analysis	33,935/497,615
	2.04	1.53–2.71	Blomberg and Kallen[15]	Single cohort	>1 million
Cardiac malformations	1.30	1.12–1.15	Stothard et al.[13]	Meta-analysis	88,070/638,983
	1.17	1.10–1.24	Blomberg and Kallen[15]	Single cohort	>1 million

Notes: CI, confidence interval; OR, odds ratio.

increased risk of miscarriage compared to women entering pregnancy with a body mass index (BMI) <25 kg/m^2. A 2011 systematic review, including 28,538 women who conceived without the use of fertility drugs or in vitro fertilization (IVF), provided further evidence of higher miscarriage rates in obese women.[9] In this pooled analysis, the miscarriage rate in obese women was 13.6% compared to 10.7% in women with a normal BMI.

The evidence is less conclusive in women who undergo assisted reproductive techniques. Subgroup analyses within the review by Metwally et al. found no increased risk of miscarriage following IVF-intracytoplasmic sperm injection in 2969 women with a high BMI compared to 5434 women with a normal BMI (odds ratio [OR] = 1.52, 95% confidence interval [CI]: 0.88–2.61).[8] However, most of the studies examining IVF outcomes have been retrospective and have suffered from an inability to adequately account for potential confounding factors, such as maternal age and the inclusion of patients with polycystic ovarian syndrome or uterine abnormalities.

The precise mechanisms by which obesity confers additional risk for miscarriage are unknown. Obesity has well-documented effects on the oocyte and embryo, which could lead to impaired or abnormal implantation and affect the ability of the embryo to develop in early pregnancy.[6] In contrast, others have suggested a role for endometrial

disturbances.[10] Examining pregnancy outcomes following oocyte donation provides a unique opportunity to separate the potential effects of obesity on the ovary and endometrium. In this model, good-quality oocytes are selected for embryo transfer, most often from young, nonobese, donor women. Therefore, any observed influence of obesity on the miscarriage rate would suggest a role for the endometrium or its environment. Pooled analysis of the small number of studies currently published suggested a significant increase in miscarriage risk in women who underwent embryo transfer using donor oocytes (OR = 1.52, 95% CI: 1.10–2.09).[8] Therefore, it is likely that both the ovary and endometrium play a role in adverse early pregnancy outcomes in obese women.

59.2.1.2 Congenital Anomalies

Congenital malformations, deformations, and chromosomal abnormalities are the leading causes of stillbirth and infant mortality in the United States.[11] More than 20 years ago, Naeye reported a positive relationship between maternal weight and the overall prevalence of birth defects.[12] Since then, a number of studies have indicated an association between pregravid weight and the risk of congenital anomalies (Table 59.1). The most consistent evidence is for neural tube defects (NTDs), in which neural tubes fail to close 3–4 weeks after conception. Obese mothers have been shown to have significantly increased odds of a pregnancy affected by an NTD.[13–15] The risk increases with the degree of obesity; there is evidence that severely obese mothers have at least a threefold higher risk of NTDs compared to women with a normal BMI.[14,15] When examined separately, the risk for spina bifida (OR = 2.24, 95% CI: 1.86–2.69) appears to be elevated to a greater degree in obese women than the risk for anencephaly (OR = 1.39, 95% CI: 1.03–1.87).[13]

Studies have shown that children of obese women also have an increased risk of cardiac malformations, particularly septal anomalies.[13,15] In addition, a 2010 study of more than 1 million infants indicated greater than normal risks for a range of malformations in those with obese mothers, including orofacial clefts, diaphragmatic hernia, hydrocephaly, hypospadias, cystic kidney, and omphalocele.[15] Many of these elevated risks were amplified by increasing obesity class.

The exact mechanisms responsible for the associations between obesity and birth defects remain unclear, but several possible explanations have been proposed. The increase in congenital cardiac malformations could be related to the higher incidence of diabetes among obese pregnant women. Many of the congenital anomalies seen in obese women are often noted in those with pregestational diabetes. Studies have indicated that the associations between obesity and birth defects remained even when women known to have diabetes were excluded. However, obesity and diabetes mellitus are known to share similar metabolic abnormalities. The early embryo is not thought to have pancreatic function until the development of beta cells, sometime after the 7th gestational week. Thus, during the time of embryonic development when the neural tube, heart, lip, and palate are developing, embryos could be theoretically receiving excess glucose from the mother and be unable to regulate the excess. Animal studies have provided evidence that hyperglycemia is teratogenic to the developing embryo.[16] Evidence also suggests that oxidative stress, a metabolic state well recognized in obese pregnant women, may be the etiology for congenital anomalies through alterations in gene expression and apoptosis during cell differentiation and growth.[17] In addition, maternal obesity has been associated with nutritional deficiencies. Obese women have been shown to have reduced serum folate concentrations, even after controlling for the intake of folic acid from food and nutritional supplements.[18] Furthermore, there is evidence that the protective effect of supplemental folic acid in reducing the risk of NTDs may not be observed in obese women.[19] While these observations may suggest that higher doses of folate are required for obese women, there have been concerns raised regarding the potential risks of high-dose folic acid supplementation. With regard to specific fetal risks, there is evidence that higher folic acid levels (4 mg/day) may mask the symptoms of anemia caused by vitamin B_{12} deficiency but still permit fetal neurological damage to occur.[20]

Another challenge is that obesity itself reduces the effectiveness of ultrasound in prenatal detection of birth defects. Ultrasonography is commonly used at 18–20-week gestation to screen for congenital malformations. Hendler and colleagues reported on ultrasound examinations in over 11,000 pregnancies, of which 39% were carried out in obese patients.[21] The rate of suboptimal visualization of fetal anomalies was 37.3% in obese women compared with 18.7% in nonobese women ($p < .001$), suggesting that the ability of ultrasound to detect fetal cardiac and craniospinal abnormalities was significantly impaired in obese women.

59.2.2 Metabolic Consequences of Obesity in Pregnancy

59.2.2.1 Metabolic Alterations

Obesity in pregnancy is associated with an exaggerated metabolic adaptation and presents with features of intermediate metabolism common to the pregnancy disorders preeclampsia and gestational diabetes mellitus (GDM). These metabolic changes may be associated with differences in fat deposition during pregnancy in obese women. It has been shown that lean and obese women tend to gain similar fat mass in pregnancy, but lean women store fat in the lower body compartment while obese women tend to gain more fat in central depots.[22] In the nonpregnant individual, central obesity is associated with metabolic dysregulation.[23] Some authors have hypothesized that central fat storage in obese pregnant women may be associated with lipotoxicity, with implications for placental function and the intrauterine nutritional environment for fetal growth.[24,25] Excess fatty acids and oxidative stress may lead to endothelial dysfunction, influence placental development, alter lipid metabolism and availability for fetal growth, and have implications for placental and fetal gene expression.[24] These metabolic alterations have profound implications for fetal and postnatal growth and development and are likely to be involved in the increased incidence of maternal complications in obese women.

59.2.2.2 Gestational Hypertension and Preeclampsia

Preeclampsia is a multiorgan, pregnancy-specific disorder that affects between 3% and 5% of all pregnancies and is associated with high perinatal morbidity and mortality for both mother and infant.[26] It is characterized by reduced placental perfusion as well as systemic inflammation and maternal endothelial dysfunction. Most observational studies have demonstrated a strong positive association between prepregnancy BMI and the risk for preeclampsia (Table 59.2). This association remained after the exclusion of women with obesity-related risk factors such as pregestational diabetes and chronic hypertension. In a large review of data from over 1.4 million women, the risk for preeclampsia doubled with each 5–7 kg/m^2 increase in prepregnancy BMI, approximating each increase in BMI category.[27]

The relative contributions of proposed mechanisms underlying the association of obesity and preeclampsia are still being investigated. Chronic hypertriglyceridemia, endothelial dysfunction, and oxidative stress, factors now recognized in obese pregnant women, are thought to be central to the pathogenesis of preeclampsia.[26] Insulin resistance, hyperlipidemia, and reduced immune function have also been implicated in the development of preeclampsia in obese women. In addition, excessive GWG has been recognized as an important risk factor for preeclampsia in women with a high prepregnancy BMI.[28]

Given the well-known association of obesity with essential hypertension outside of pregnancy, it is often difficult to estimate the prevalence of pregnancy-associated hypertension, independent of preexisting conditions. The diagnostic criteria used to differentiate these diagnoses often vary between studies, leading to substantial variation in the estimated prevalence of hypertension in obese pregnant women. In one cohort, the incidence of gestational hypertension increased from 4.8% in the normal-weight group to 10.2% in the obese group, with a further increase to 12.3% in morbidly obese women.[29]

59.2.2.3 Glucose Metabolism and Gestational Diabetes Mellitus

GDM is defined as diabetes first recognized in pregnancy. Impaired glucose metabolism usually resolves after delivery; however, GDM is associated with greater risk of subsequent type 2 diabetes mellitus and therefore may represent early presentation of overt diabetes. Studies have shown that GDM is more common than type 2 diabetes and is more prevalent in obese women than normal-weight women, occurring in up to 10% of severely obese pregnant women.[29,30] There is evidence that obesity increases the risk of developing GDM by 2.6–3.6 times compared to normal-weight women[29–32] (Table 59.2). Prepregnancy weight loss has been shown to be protective against the development of GDM, emphasizing the importance of pregravid weight on the risk for GDM. In a population-based cohort, weight loss of at least 10 lb (4.5 kg) between pregnancies decreased the risk of developing GDM in a subsequent pregnancy (RR = 0.63, 95% CI: 0.38–1.02), while weight gain of at least 10 lb (4.5 kg) was associated with significantly increased GDM risk (RR = 1.47, 95% CI: 1.05–2.04).[33]

59.2.3 Impact of Gestational Weight Gain and Fat Deposition

GWG has been correlated with fetal macrosomia, operative vaginal and cesarean section deliveries, and neonatal consequences, such as low Apgar scores and admission to the neonatal intensive care unit.[34] In recognition of the adverse effects of excessive GWG, the Institute of Medicine (IOM) recommends that obese women (BMI > 30 kg/m^2) restrict weight gain during pregnancy to 11–20 lb (5–9 kg)[35] (Table 59.3). Despite these guidelines, current indications are that as many as 50%–60% of pregnant women gain more weight than recommended during pregnancy.[36]

TABLE 59.2
Adverse Maternal Pregnancy Complications in Obese (BMI 30.0–34.9 kg/m^2) and Morbidly Obese (BMI ≥ 35 kg/m^2) Compared to Normal-Weight (BMI 18.0–24.9 kg/m^2) Women

	Obese (BMI 30.0–34.9 kg/m^2)		Morbidly Obese (BMI ≥ 35 kg/m^2)				
Outcome	**OR**	**95% CI**	**OR**	**95% CI**	**Reference**	**Type of Study**	**Sample Population**
Preeclampsia	1.6	1.10–2.25	3.3	2.40–4.50	Weiss et al.[29]	Single cohort—prospective	16,102
	2.14	1.85–2.47[a]			Sebire et al.[30]	Single cohort—retrospective	208,199
Gestational hypertension	2.5	2.10–3.00	3.2	2.60–4.00	Weiss et al.[29]	Single cohort—prospective	16,102
Gestational diabetes	3.6	3.25–3.98[a]			Sebire et al.[30]	Single cohort—retrospective	208,199
	2.6	2.10–3.40	4.0	2.60–4.00	Weiss et al.[29]	Single cohort—prospective	16,102
	3.56	3.05–4.21	8.56	5.07–16.04	Chu et al.[31]	Meta-analysis	<1 million
	3.01	2.34–3.87	5.55	4.27–7.21	Torloni et al.[32]	Meta-analysis	671,945

Note: CI, confidence interval; OR, odds ratio.
[a] 99% CI.

TABLE 59.3
Institute of Medicine/National Research Council Guidelines for Weight Gain and Rate of Weight Gain During Pregnancy for Women with Singleton Fetuses

		Total Weight Gain		Rates of Weight Gain per Week in the Second and Third Trimesters, Mean (Range)	
Category	Prepregnancy BMI (kg/m²)	(lb)	(kg)	(lb/week)	(kg/week)
Underweight	<18.5	28–40	12.5–18	1.0 (1.0–1.3)	0.51 (0.44–0.58)
Normal weight	18.5–24.9	25–35	11.5–16	1.0 (0.8–1.0)	0.42 (0.35–0.50)
Overweight	25.0–29.9	15–25	7.0–11.5	0.6 (0.5–0.7)	0.28 (0.23–0.33)
Obese	≥30.0	11–20	5–9	0.5 (0.4–0.6)	0.22 (0.17–0.27)

Source: Adapted from Institute of Medicine et al., *Weight Gain During Pregnancy: Reexamining the Guidelines*, National Academy of Sciences, 2009.

Some experts advocate for GWG less than the IOM lower limit, particularly for higher classes of obesity.[3] In support of this suggestion, there is some evidence that adverse maternal outcomes (preeclampsia, rate of cesarean delivery, and associated postoperative concerns for the mother, including postpartum hemorrhage, wound infection, venous thromboembolism, and endometriosis) are lowest when GWG is less than 10 lb.[37] Furthermore, accumulating data suggest that, particularly for class II and III obese women, optimal neonatal outcomes occur in response to significantly less weight gain than currently recommended.[38] A large meta-analysis published in 2011 concluded that prenatal dietary interventions resulting in restricted weight gain in obese pregnant women had no effect on newborn birth weight.[39] However, more comprehensive maternal and offspring data, collected from well-designed randomized controlled studies, are required to provide sufficient evidence on which to base updated weight gain recommendations.

59.2.4 Peripartum Complications

59.2.4.1 Failed Induction and Slow Labor Progression

Obese women are more likely to have medical, surgical, and obstetric complications that include higher rates of induction, dysfunctional labor patterns, increased cesarean section delivery, and a greater incidence of postoperative complications of surgery (Table 59.4).

Obesity in pregnancy has been associated with longer gestation and elevated risk for post-term delivery.[40,41] This risk is even higher with increasing degrees of obesity, as Arrowsmith et al. found that morbidly obese women had a more than twofold risk of prolonged pregnancy compared to normal-weight women (adjusted OR = 2.27, 95% CI: 1.78–2.89).[40] The association of obesity with prolonged pregnancy is thought to be related to a reduction in myometrial contractility that has been demonstrated in obese women by both clinical and laboratory markers.[42] Evidence has shown that in addition to increased obstetric risks, such as preeclampsia and perinatal morbidity and mortality, postdates pregnancies contribute to higher rates of labor induction in obese women.[28,30,40] Population-based studies suggest that approximately a third of obese women require induction of labor compared with up to a quarter of normal-weight women.[28,40,43]

Even when labor occurs spontaneously, dysfunctional labor has been observed for the obese patient. In one study, the median duration of labor from 4 to 10 cm cervical dilation increased from 6.2 hours for normal-weight to 7.9 hours for obese women, after adjustment for a number of confounding factors including labor induction, membrane rupture, oxytocin use, epidural analgesia, GWG, and fetal size.[41] Both term and post-term obese women have an increased risk for failed labor induction, leading to operative vaginal or cesarean delivery. Obese women are twice as likely to experience failed induction of labor compared with normal-weight women; however, fetal weight and parity are important additional considerations that impact pregnancy outcome.[44,45]

59.2.4.2 Mode of Delivery/Cesarean Section

Obese pregnant women face a greater likelihood of undergoing either an elective or emergent cesarean delivery, according to multiple studies.[29,30,45–47] A meta-analysis of 11 studies published between 1976 and 2005 reported that the risk of cesarean delivery in nulliparous women with singleton pregnancies was 1.5 times higher in overweight, 2.25 times higher in obese, and 3.4 times higher in morbidly obese women, compared to women with a normal BMI.[46] This risk relationship appears to have a positive correlation with both prepregnancy BMI and excessive GWG.[30,45] In addition, this risk is likely augmented by obesity-related pregnancy complications including fetal macrosomia, pregnancy-induced hypertension, and diabetes. However, elevated risk for cesarean delivery remains after controlling for hypertensive disorders, diabetes, and fetal growth,[46,47] suggesting that obesity conveys independent risk for operative deliveries.

The biological pathways associated with dysfunctional labor and increased cesarean risks in obese women have been proposed to include increased deposition of pelvic fat, which narrows the diameter of the birth canal and causes obstruction

TABLE 59.4
Odds Ratios for Adverse Labor Outcomes in Obese Compared to Normal-Weight Women

Outcome	OR	95% CI	Reference	Type of Study	Sample Population (Obese/Normal Weight)
Labor and Delivery Complications					
Prolonged pregnancy (≥42 weeks gestation)	1.72	1.23–2.42	Sebire et al.[30]	Single cohort—retrospective	31,276/176,923
Prolonged pregnancy (≥290 days gestation)	1.52	1.37–1.70	Arrowsmith et al.[40]	Single cohort—retrospective	2051/9530
Induction of labor	1.70	1.64–1.76	Sebire et al.[30]	Single cohort—retrospective	31,276/176,923
Failed induction of labor	2.16	2.07–2.27	Wolfe et al.[44]	Single cohort—retrospective	19,559/38,110
Cesarean delivery	1.7	1.40–2.20	Weiss et al.[29]	Single cohort—prospective	386/4560
	2.05	1.86–2.27	Chu et al.[31]	Meta-analysis	NA
	2.36	2.15–2.59	Poobalan et al.[46]	Meta-analysis	22,293/143,875
Maternal Complications					
Postpartum hemorrhage	1.39	1.32–1.46	Sebire et al.[30]	Single cohort—retrospective	31,276/176,923
	1.24	1.24–1.28	Heslehurst et al.[43]	Meta-analysis	>1 million
Wound infection	2.24	1.91–2.64	Sebire et al.[30]	Single cohort—retrospective	31,276/176,923
	3.34	2.74–4.06	Heslehurst et al.[43]	Meta-analysis	>1 million
Perinatal Complications					
Stillbirth	2.6	1.7–3.8	Cnattingius et al.[54]	Single cohort—prospective	10,412/123,900
	3.4	2.1–5.5	Nohr et al.[55]	Single cohort—prospective	100,066/835,863
	3.1	1.6–5.9	Kristensen et al.[56]	Single cohort—prospective	951/19,169
Small for gestational age (<10th percentile)	0.84	0.78–0.91	Heslehurst et al.[43]	Meta-analysis	>1 million
Large for gestational age (>90th percentile)	2.36	2.2–2.5	Sebire et al.[30]	Single cohort—retrospective	31,276/176,923
Birth weight >4000 g	1.7	1.4–2.0	Weiss et al.[29]	Single cohort—prospective	1473/13,752
Birth weight >4500 g	2.0	1.4–3.0	Weiss et al.[29]	Single cohort—prospective	1473/13,752
Meconium	1.57	1.42–1.73	Heslehurst et al.[43]	Meta-analysis	>1 million
Shoulder dystocia	1.04	0.97–1.12	Heslehurst et al.[43]	Meta-analysis	>1 million
Admission to neonatal intensive care unit	1.35	1.22–1.49	Heslehurst et al.[43]	Meta-analysis	>1 million

Note: CI, confidence interval; OR, odds ratio.

to the birth passage.[45] Obese patients may therefore have difficulty completing the second stage of labor because of soft tissue dystocia, increasing the need for operative vaginal delivery in this population. Given the rapid increase in obesity prevalence during the past two decades, the independent effect of obesity on risk for cesarean delivery has undoubtedly contributed to the increasing overall rates of operative and cesarean deliveries, both in the United States and worldwide.

59.2.4.3 Postoperative Complications

The increased cesarean delivery rate for obese patients has implications for their intraoperative and postoperative care, as the inherent risks of surgical complications are magnified by obesity. Studies have found that operative risks in obese patients include increased operative time, excessive blood loss (>1000 mL),[48] and increased postoperative complications such as wound infection and dehiscence.[49] A course of perioperative antibiotics has been shown to reduce postoperative infection and endometritis rates by up to 75% and is recommended for obese women undergoing cesarean delivery.[50] There is also evidence that the risk for postpartum deep vein thrombophlebitis is increased with higher BMI.[30,51,52] Venous thromboembolism is one of the leading causes of maternal death in the United States and occurs more often in obese pregnant women.

Furthermore, primary cesarean delivery has implications for clinical management of subsequent deliveries. Of prime concern, the success of vaginal birth after cesarean (VBAC) in future pregnancies is inversely related to BMI. In a prospective multicenter trial including over 4000 VBAC attempts, nonobese women had a VBAC failure rate of 15% compared to 30% and 39% for obese and morbidly obese women, respectively.[53] In addition to lower likelihood of VBAC success, the increased operative risks associated with cesarean delivery after failed VBAC (e.g., infection, uterine rupture and hemorrhage, and the

need for blood transfusion) must be considered in subsequent pregnancies. Furthermore, extreme obesity may impede adequate monitoring of uterine activity and fetal heart rate, which may further compromise the safety of VBAC in obese women.

59.2.5 Fetal and Perinatal Complications

59.2.5.1 Stillbirth

Stillbirth occurs in 2–5 per 1000 births and constitutes more than half of all perinatal deaths in the United States.[11] Pregravid obesity is associated with an increased risk of perinatal mortality, particularly in association with obesity-related disease and prolonged pregnancy (Table 59.4).

The Swedish Medical Birth Register is a large population-based register that contains virtually all births in Sweden and includes prospectively collected data on maternal characteristics and complications during pregnancy, delivery, and the neonatal period. This database has been used to investigate the relationship between prepregnancy body weight and antepartum stillbirth. Among both nulliparous and parous obese women, the risk for late fetal death (stillbirth occurring at 28 or more completed weeks of gestation) was more than twice that of normal-weight women.[54] Within the Danish National Birth Cohort, the risk of stillbirth was three times higher in obese women compared to women with a normal prepregnancy BMI.[55] This risk was elevated after exclusion of women with obesity-related disease, suggesting that obesity confers independent risk for stillbirth.[56]

The biological pathways underlying these pathophysiological associations remain conjectural. Metabolic and vascular abnormalities associated with GDM and hypertensive disorders are common in obese pregnant women without clinical disease. Maternal obesity has been associated with hyperlipidemia and endothelial dysfunction, both of which are linked to failure of normal placental implantation in early pregnancy and elevated risk of infarction or abruption of the placenta in late pregnancy.[57] In support of this hypothesis, data from The Danish National Birth Cohort suggest that obese women have a fivefold increased risk of stillbirth associated with placental dysfunction.[55]

59.2.5.2 Fetal Overgrowth/Macrosomia

Maternal adiposity is strongly linked to weight[58,59] and fat mass at birth.[60,61] Hence, maternal obesity has been shown to significantly increase the risk of delivering large for gestational age (LGA) offspring,[62,63] bringing both immediate and long-term consequences for mother and child. Studies have found that infants weighing greater than 4500 g at birth have an elevated risk of infant mortality,[64] shoulder dystocia, and birth trauma, including clavicle and humerus fractures and brachial or facial paralysis.[65] Increased odds for delivering a large birth weight baby persist after adjustment for obesity-related disease. Even after adjustment for GDM, there is evidence that obese pregnant women have a 1.5- to 2-fold risk for a macrosomic fetus.[62]

Excessive GWG is also associated with increased neonatal birth weight. However, a progressively stronger relationship is observed between GWG and birth weight as pregravid weight decreases, suggesting that GWG has less impact on birth weight in obese women. In women who were at least 135% of their ideal prepregnancy weight for height, no correlation was observed between GWG and birth weight.[66] Nevertheless, GWG in overweight and obese women also has been shown to correlate with neonatal fat mass,[60] which may be a better indicator of fetal overgrowth.

There are a number of hypothesized mechanisms to explain the relationship between maternal size and fetal and neonatal size. It is conceivable that the influence of maternal size may not be necessarily due to prenatal factors but may relate to the inheritance of genes that confer susceptibility to obesity.[67] However, the classical equine crossbreeding experiments of Walton and Hammond emphasized the role of maternal constraint in determining offspring size at birth.[68] Shire horses (large draught or cart horses) produce considerably larger offspring than Shetland ponies. But if a Shire stallion is mated with a Shetland mare, the offspring is born small (appropriate size for a Shetland foal). In contrast, if the mother is a Shire, the offspring is born large but hardly grows as it matures. More recently, the development of ovum donation for infertility treatment has supported the role of the maternal environment in determining birth size. Brooks et al. found that the recipient's weight at the time of egg donation had a greater influence on birth weight than the weight of the donor, suggesting that genetic inheritance is not the primary determinant of fetal growth.[69] Nevertheless, these findings do not preclude a role for epigenetic effects in the determination of offspring size.

The concept that intrauterine overnutrition may affect fetal growth and the lifelong risk of obesity is now well supported,[70] but is by no means a new suggestion. Pedersen's original model, presented almost 60 years ago, proposed a "hyperglycemic-hyperinsulinism" pathway to explain fetal overgrowth in response to maternal diabetes.[71] Freinkel refined this hypothesis in the 1980s with the concept of fuel-mediated teratogenesis.[72] This hypothesis suggests that increased availability of maternal fuels, including glucose, free fatty acids, ketone bodies, and amino acids, leads to fetal hyperinsulinemia[73–75] and increased leptin concentrations.[76] Elevated umbilical cord insulin and leptin levels (reflecting fetal concentrations) have been associated with increased birth weight and fat mass at birth[77,78] and appear to assume a primary role in the stimulation of fetal growth.

59.3 LONG-TERM POSTNATAL CONSEQUENCES OF OBESITY IN PREGNANCY

59.3.1 Maternal Obesity after Pregnancy

Obesity and excessive GWG both have been shown to carry an increased risk for postpartum weight retention, which not only imparts higher risk in future pregnancies but also carries lifelong cardiovascular and metabolic consequences for women.[79] Postpartum weight retention has been reported to occur in all BMI categories.[2] The current obesity epidemic, in women, could certainly be linked to GWG.[3]

59.3.2 Obesity and Health Consequences in Childhood

There is increasing evidence to suggest that maternal obesity has an important influence on the risk of obesity in offspring. Fisch et al. were among the first to suggest a link between maternal and offspring size. Over 30 years ago, they published findings from a prospective study of almost 1800 children in the United States in which maternal prepregnancy weight was higher in mothers of the most obese 7-year-old children (top 5% of weight for height) compared to the mothers of the leanest 7-year-olds.[80]

A number of subsequent studies have provided evidence that maternal obesity independently predicts offspring obesity, particularly in childhood. In 2004, Whitaker and colleagues reported findings from a sample of almost 8500 preschool children born in the United States.[81] They examined the prevalence of obesity (BMI ≥ 95th percentile) at 2, 3, and 4 years of age in relation to the presence of maternal obesity in early pregnancy. Within each age group, infants who were LGA (≥90th percentile for birth weight) had an increased prevalence of obesity compared with appropriate for gestational age (AGA) (10th–89th percentile) or small for gestational age infants (SGA) (<10th percentile) ($p < .001$ at each age group). The risk of obesity for LGA neonates remained elevated in a multivariate model containing maternal fatness, but maternal obesity in early pregnancy was the risk factor with the greatest OR for subsequent offspring obesity. After controlling for birth weight, children whose mothers were obese in early pregnancy were more than twice as likely to be obese preschoolers. These results suggest that, regardless of maternal size, being a large baby incurs an increased risk of obesity in early postnatal life. However, being large at birth is not the only described pathway contributing to postnatal obesity, as a number of studies have also linked low birth weight to the later development of central adiposity.[82] A more detailed description of fetal life and early postnatal determinants of adiposity can be found in Chapter 11.

The children of women who gain excessive weight during pregnancy have also been shown to be at increased risk for obesity in postnatal life[83,84] and to demonstrate increased cardiovascular risk profiles at 9 years of age.[85] Furthermore, female children of mothers with excessive GWG are more likely to themselves become overweight mothers and may be perpetuating a cycle of obesity that is significantly contributing to the epidemic of obesity and associated comorbidities in the developed world.[86]

59.4 INTERVENTIONAL STRATEGIES IN OBESE PREGNANT WOMEN

59.4.1 Preconception and Interpregnancy Care

Many of the adverse effects of obesity may occur in the periconceptual period in early pregnancy. Consequently, weight loss during the prepregnancy or interpregnancy period may provide protection against obesity-related pregnancy complications. In one large prospective study, weight gain between pregnancies, resulting in a significant increase in prepregnancy weight, was associated with a threefold elevated risk for preeclampsia in the latter pregnancy (OR = 3.2, 95% CI: 2.5–4.2). In contrast, a reduction in pregravid weight between the first and second pregnancies resulted in a significant reduction in cesarean delivery rate and reduced risk of delivering a LGA baby.[87,88] Medical professionals who see women of reproductive age and recognize obesity should counsel and discuss the risks they would face during pregnancies complicated by obesity.[89]

59.4.2 Pregnancy after Bariatric Surgery

An estimated 150,000 bariatric surgeries are performed in the United States each year. Bariatric surgery is considered appropriate for very obese women (BMI ≥ 40 kg/m^2) or women with a BMI ≥ 35 kg/m^2 when comorbid conditions (diabetes mellitus, coronary artery disease, and severe sleep apnea) are present.[90] Patients who achieve even modest weight loss following bariatric surgery have shown a reduction in adverse obesity-related pregnancy outcomes, such as decreased incidence of GDM and pregnancy hypertensive disorders[91] and a reduction in fetal overgrowth.[92] A reduction in pregestational diabetes in this population may also be associated with improved pregnancy outcomes.[93] In general, patients are advised to avoid pregnancy for at least 8 months following surgery because of higher risks for surgical complications and the desire to avoid fetal exposure to rapid weight loss and possible fetal malnutrition. However, recent evidence suggests that pregnancy outcomes may be comparable even when pregnancy occurs within a year of surgery.[94] Other complications that have been documented in pregnant women following bariatric surgery include internal hernia formation and bowel ischemia; band slippage and excessive nausea; bowel obstructions; staple lines strictures; vitamins A and B_{12} and folate deficiency; and chronic diarrhea.[95]

In 2011, the Swedish Medical Birth Register was used to examine pregnancy outcomes in a cohort of 494,692 women, including 681 who had bariatric procedure during the study period.[96] Despite weight-loss surgery, more than half of women postsurgery were still obese at the start of their pregnancy. Compared to the control group of women who did not undergo bariatric surgery, postsurgery women delivered slightly earlier, had significantly lighter infants, and had an increased incidence of SGA infants. The mechanisms responsible for the modest increase in SGA infants are unknown; however, protein malnutrition associated with fetal growth restriction has been postulated in connection with malabsorptive bariatric surgery.[97] In another analysis, women who had bariatric surgery before the birth of their first child were compared to those who had bariatric surgery after their first pregnancy. Both groups contained a similarly low proportion of normal-weight women, but the women who had the surgery before pregnancy had a lower proportion of morbid obesity, suggesting an overall reduction in the degree of obesity. Compared to the presurgery mothers, postsurgery women had

a significantly lower incidence of LGA infants. Thus, despite only a modest reduction in obesity, women who underwent bariatric surgery before pregnancy had a lower risk for LGA infants that may confer long-term benefits for their children.

59.4.3 Lifestyle Interventions in Obese Pregnant Women

Pregnancy is an ideal time to encourage women to make healthy lifestyle changes and should no longer be considered a state of confinement. Many women are concerned about the health of their babies and are in frequent contact with their health-care provider. Lifestyle interventions promoting behavioral change through dietary modification and increased physical activity may provide women with a better awareness of the impact of body weight on maternal and neonatal health. The increasing global prevalence of obesity in women of reproductive age is a significant risk factor for adverse maternal and neonatal outcomes. Excessive GWG compounds these risks and is also associated with increased postpartum weight retention.[2,3] Interventions to reduce excessive GWG may therefore reduce the short- and long-term consequences of obesity on maternal and fetal complications in pregnancy.

Over the past decades, interventions designed to promote the adoption of healthy lifestyle behaviors, such as a nutrient-dense diet and regular physical activity, have reported only modest success in preventing excessive GWG.[98,99] Furthermore, most interventions have not been shown to improve overall adherence to the IOM's recommendations for appropriate GWG. In contrast, more recent lifestyle interventions including a combination of intensive dietary management, structured physical activity, cognitive or behavioral management, and more restrictive GWG goals have been associated with significant reductions in GWG.[100–103] Interestingly, these studies have aimed to restrict GWG to levels below the current IOM recommendations for obese pregnant women and have reported no indications of adverse pregnancy outcomes such as restricted fetal growth. These findings are in agreement with previous suggestions that optimal pregnancy outcomes for obese women may occur at GWG less than the current IOM guidelines.[38] For the overweight pregnant woman who is gaining less than the recommended amount but has an appropriately growing fetus, no evidence exists that encouraging increased weight gain to conform with the current IOM guidelines will improve maternal or fetal outcomes.[104]

59.5 SUMMARY

The increasing global prevalence of obesity in women and the continuing trend of excessive GWG are associated with several adverse perinatal outcomes. The maternal consequences of obesity include an increased risk of GDM and preeclampsia and increased anesthetic, perioperative, and postoperative complications. Maternal obesity also conveys significant risks to the fetus, including early pregnancy demise, congenital anomalies, and increased risk of macrosomia. Many of the adverse effects of obesity occur early in the prenatal period. Therefore, medical professionals who counsel women of reproductive age should recommend significant weight-loss efforts before conception. In addition, pregnancy is an opportune time to encourage women to make healthy lifestyle changes and should no longer be considered a state of confinement. Pregnancy is a motivating time for women, as positive outcomes may benefit both the mother and her child. The frequency of prenatal care provides regular opportunities for education on the benefits of lifestyle change for long-term weight control. In addition, the unique period of frequent medical contact associated with prenatal care provides a supervised environment in which lifestyle modifications can be carried out in a controlled and supportive manner.

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60 Obesity, an Inactive Lifestyle, and Low Fitness

The Most Unhealthy Combination

Paul A. McAuley and Steven N. Blair

CONTENTS

60.1 BACKGROUND

The word obesity derives from the Latin *obesus*, which means "to devour." While excess caloric intake certainly contributes to obesity, physical activity plays an equally important role. Obesity, or more precisely, excess adiposity, results from a prolonged imbalance between caloric intake and expenditure. It is difficult to know how much of the increased prevalence of obesity in recent decades is due to overeating, how much is the result of decreased physical activity, and how much is a combination of both. Whereas much of the media attention has focused on eating behavior, declining levels of energy expenditure have received comparatively less notice despite increasing evidence that they may play as important a role. For example, Church and colleagues[1] recently examined trends in occupational activity over the past five decades and found that the occupational-related decline in energy expenditure explained a significant portion of the obesity epidemic.

There is little doubt that an inactive lifestyle is a major contributor to obesity. Data from cross-sectional studies have demonstrated that obesity prevalence is inversely associated with physical activity,[2] and in a 20-year longitudinal study of 459 Canadian men and women, higher cardiorespiratory fitness (hereafter fitness) was associated with lower odds of obesity.[3] More direct evidence for the independent contribution of physical activity comes from intervention trials in which diet-plus-exercise interventions provided significantly greater weight loss than diet-only interventions.[4] Regular physical activity, and especially aerobic exercise training, can also increase or preserve fitness.[5] Therefore, the link between obesity and adverse health outcomes may be mediated in part by habitual low levels of physical activity and low fitness. Thus, associations among obesity, physical activity, fitness, and health outcomes are complex and require further elucidation.

Previous work in the area of fitness versus fatness and health outcomes has been primarily concerned with the extent to which fitness or physical activity counterbalances the morbidity/mortality risks associated with obesity.[6–11] While the bulk of the evidence suggests that higher fitness and physical activity reduce obesity-related health hazards, obese individuals are more likely to be inactive and have poor fitness. For example, using data from the National Health and Nutrition Examination Survey and defining "fit" using sex- and age-specific criteria from the Aerobics Center Longitudinal Study (ACLS), Duncan[12] reported in 2010 that a mere 16.5% of U.S. adults aged 20–49 years were defined as both obese and fit (medium or high fitness levels) versus 42.9% in this population defined as normal-weight and fit.

However, since 20.4% of this population was obese, this also means that approximately 80% of obese individuals in the 20- to 49-year-old age group are fit using these criteria and therefore are not at high risk for morbidity and mortality.

This chapter focuses on the negative effect of obesity on health outcomes when combined with an inactive lifestyle and/or low fitness. Specifically, we address the following two questions: (1) Does obesity exacerbate the increased health risk associated with poor fitness or inactivity? (2) What is the relative importance of obesity, low fitness, and an inactive lifestyle as predictors of mortality and cardiometabolic morbidity?

60.2 DEFINITIONS

60.2.1 Low Fitness

Maximal exercise testing on a treadmill or cycle ergometer is the widely accepted gold standard for measuring fitness. While peak metabolic equivalents (METs) or the maximum volume of oxygen uptake (VO_2max) in milliliters of oxygen per kilogram of body weight per minute (1 MET = 3.5 mL/kg/min) are the standard units that quantify fitness, there is no widely accepted definition for *low fitness*. In the first study of fitness and mortality from the ACLS, participants were assigned to a fitness category based on age and sex norms of treadmill time rather than an absolute METs value.[13] The low fitness group comprised individuals with treadmill times in the first quintile. In subsequent ACLS reports, in which joint associations of fitness and fatness were examined,[14–18] fitness was grouped into a binary variable with the first quintile being designated as "unfit" and the second through fifth quintiles as "fit." A similar approach was adopted in the two fitness, fatness, and mortality reports from the Lipid Research Clinics (LRC) study.[19,20] While a few ACLS reports used the lowest third of exercise duration to define "unfit" and the upper two-thirds as "fit" according to sex and age groups,[21,22] a three-category classification system of low (bottom quintile), moderate (second and third quintiles), and high (fourth and fifth quintiles) is more commonly used. In the Veterans Exercise Testing Study, a longitudinal study of male veterans referred to exercise testing for clinical reasons, absolute cut points of <5 METs and ≥5 METs (estimated from final treadmill speed and grade) defined unfit and fit, respectively.[23] This method of classification is based on the disability evaluation used by the U.S. Social Security Administration,[24] which defines disability as failure to achieve 5 METs. Common methods used to classify fitness into "unfit" and "fit" categories in representative epidemiological studies are summarized in Table 60.1.

To avoid expenses required for specialized laboratory equipment and trained personal, some studies estimate fitness from less expensive and easier to administer submaximal exercise tests. Whereas standardized protocols for many such tests have been employed in several studies, correlations between fitness predicted from submaximal exercise testing and maximal exercise testing are typically in the range of 0.7–0.85.[25] While submaximal exercise testing may be of practical value as a field test, it can result in misclassification of fitness. For this reason, this chapter includes only studies of fitness determined from maximal exercise testing.

60.2.2 Physical Activity

Because of the technical challenges and higher expense involved in measuring fitness, validated physical activity questionnaires are often used as proxies in epidemiological studies. However, a review of the validation reports shows that the correlations between self-reported physical activity and a gold standard are typically in the range of 0.3–0.5, and thus self-reports account for approximately 10%–25% of the variance in the exposure.[26,27] Consequently, physical activity

TABLE 60.1
Definitions for Fitness Categories from Maximal Exercise Testing in Representative Epidemiological Studies

Study	Reference	Measure Used to Calculate CRF in METs	Unfit and Fit Categories
ACLS	Blair et al.[13]	Time (minutes) on modified Balke treadmill exercise test	Age and sex norms: Unfit—quintile 1 Fit—quintiles 2–5
LRC	Stevens et al.[19]	Time to produce a predicted maximal heart rate, based on age and training, during a Bruce treadmill exercise test	Sex norms: Unfit—quintile 1 Fit—quintiles 2–5
ACLS	Sui et al.[21]	Time (minutes) on modified Balke treadmill exercise test	Age and sex norms: Unfit—tertile 1 Fit—tertiles 2 and 3
ACLS	McAuley et al.[22]	Time (minutes) on modified Balke treadmill exercise test	Age and sex norms: Unfit—tertile 1 Fit—tertiles 2 and 3
VETS	McAuley et al.[23]	Final speed (mph) and grade (%) on ramp treadmill exercise test and maximal oxygen uptake (VO_2max)	Unfit—<5 METs Fit—≥5 METs

Notes: ACLS, Aerobics Center Longitudinal Study; CRF, cardiorespiratory fitness; LRC, Lipid Research Clinics Study; MET, metabolic equivalent; VETS, Veterans Exercise Testing Study.

measures are less consistent and do not translate as well as fitness across studies. Nevertheless, self-report of physical activity is the most common method employed in large-scale epidemiological studies. Since we were not able to identify any studies meeting our selection criteria that specifically examined combined associations of objectively measured physical activity and adiposity level with health outcomes, this chapter includes studies with only self-reported physical activity. However, it is important to recognize that because of the inaccuracy of self-reported physical activity, use of these data results in substantial misclassification. This leads to a dramatic underestimate of the importance of physical activity when trying to isolate the individual components of fitness and fatness and their effects on health outcomes.

60.2.3 Adiposity

All but two studies[15,33] reviewed in this chapter used BMI as the primary adiposity exposure measure. Some of these studies also included waist circumference and percentage body fat using subcutaneous skinfold techniques and hydrostatic weighing (densitometry). While many studies used the standard BMI cut points of 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m^2 to define categories of normal-weight, overweight, and obese, some studies used quintiles or quartiles. Similarly, for waist circumference, while standard cut points of >102 cm for men and >88 cm for women were used to define central obesity in some studies, other studies used tertiles. Agreed-upon criteria for defining obesity from percentage body fat do not exist. In studies with percentage body fat measurements, obesity was defined as ≥30% for women and ≥25% for men or in tertiles.

60.3 LITERATURE SELECTION

Our goal was to include all published studies from prospective investigations that included either objectively measured cardiorespiratory fitness or self-reported physical activity and at least one standard adiposity measure. In addition, participants had to be grouped into at least four fitness or physical activity and fatness categories, and the data analysis had to include Cox proportional hazards models with a reference group identified. Since our aim was to answer specific questions related to comparisons between groups, we were interested only in well-collected data on large sample sizes (>1000 subjects) with long follow-up (at least 5 years), as well as studies that reported relative risks adjusted for age and multiple health risk factors. Finally, since our focus was on mortality and cardiometabolic morbidities, we confined our review to four outcomes: (1) all-cause mortality, (2) cardiovascular disease (CVD) mortality, (3) coronary heart disease (CHD), and (4) type 2 diabetes. The literature search was performed using the PubMed database with the following search terms: fitness, physical activity, fatness, adiposity, body mass index, obesity, mortality, CHD, and diabetes. This search identified more than 700 articles. However, the vast majority of these studies did not have data on the variables of interest. After exclusions, 16 articles met the inclusion criteria.

60.4 ANALYSIS OF SELECTED STUDIES

60.4.1 All-Cause Mortality

Studies with all-cause mortality as an outcome are summarized in Table 60.2. Six studies[14–16,18–20] used fitness and three studies[28–30] used physical activity as the exposure. BMI was the adiposity exposure variable in eight studies[14,16,18–20,28–30] (two of which[16,18] also included waist circumference and percentage body fat), and only waist circumference and percentage body fat were used in one study.[15] Four studies[14,15,20,30] included only men, two studies[18,28] included only women, and three studies[16,19,29] included men and women. Altogether, these nine studies included approximately 237,000 subjects with a mean follow-up ranging from 8 to 24 years.

In all of the fitness studies, all-cause mortality was significantly higher for unfit participants who were normal-weight or obese, had a normal or high waist circumference, and had normal or high percentage body fat, compared with their respective fit and normal reference groups. Four studies[15,16,19,20] indicated that the all-cause mortality related to unfit-normal-weight and unfit-obese individuals was similar, while two studies[14,18] revealed higher relative risks for unfit-obese than for unfit-normal-weight groups, in ACLS men (3.1 for obese vs. 2.2 for normal-weight) and in ACLS women (2.5 for obese vs. 1.5 for normal-weight). Similar results were observed for waist circumference and percentage body fat with one exception. Lee et al.[15] found higher relative risks for unfit-low waist circumference (4.9) than for unfit-high waist circumference (2.4) in ACLS men.

Similarly, in the studies of physical activity, inactive persons who were normal-weight or obese had higher all-cause mortality risks compared with their active and normal-weight counterparts. None of the physical activity studies included data on waist circumference or percentage body fat. While two studies[28,29] showed higher all-cause mortality risks for inactive-obese than for inactive-normal-weight groups, one study found equal results for these groups.[30]

60.4.2 Cardiovascular Disease Mortality

Studies with CVD mortality as an outcome are summarized in Table 60.3. Four studies[14,15,19,20] used fitness and three studies[28–30] used physical activity as the exposure. BMI was the adiposity exposure variable in six studies,[14,19,20,28–30] and only percentage body fat was used in one study.[15] Four studies[14,15,20,30] included only men, one study[28] included only women, and two studies[19,29] included men and women. Altogether, these seven studies included approximately 223,000 subjects with a mean follow-up ranging from 8 to 24 years.

In all of the fitness studies, CVD mortality was significantly higher for unfit participants who were normal-weight or obese and had normal or high percentage body fat, compared with their respective fit and normal reference groups. One exception was noted for unfit-normal-weight men from the LRC study[19] who did not differ significantly from the reference group. Four studies[14,15,19,20] indicated that the CVD

TABLE 60.2
All-Cause Mortality Risk for Combined Fitness- or Activity-Fatness Groups

Reference	Participants	Adiposity Classification	Fitness or Activity Classification	Mean Follow-up (years)	Fitness- or Activity-Fatness Groups	Adjusted RR (95% CI)
		Fitness				
Wei et al.[14]	25,714 men, mean age 43.8 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0)	Age and sex group quintiles Fit: quintiles 2–5 Unfit: quintile 1	10	Fit-normal Fit-overweight Fit-obese Unfit-normal Unfit-overweight Unfit-obese	1.0 1.1 (1.0–1.3) 1.1 (0.8–1.5) 2.2 (1.8–2.8) 2.5 (2.1–3.0) 3.1 (2.5–3.8)
Lee et al.[15]	21,925 men, aged 30–83 years, United States	BF: Lean (quartile 1, <16.7%) Normal (quartiles 2 and 3, 16.7%–<25.0%) Obese (quartile 4, ≥25.0%) WC: Low (quartile 1, <87 cm) Moderate (quartiles 2 and 3, 87–99 cm) High (quartile 4, ≥99 cm)	Age and sex group quintiles Fit: quintiles 2–5 Unfit: quintile 1	8	Fit-lean Fit-normal Fit-obese Unfit-lean Unfit-normal Unfit-obese Fit-low WC Fit-moderate WC Fit-high WC Unfit-low WC Unfit-moderate WC Unfit-high WC	1.0 0.8 (0.6–1.1) 0.9 (0.7–1.3) 2.1 (1.2–3.7) 1.6 (1.2–2.3) 1.9 (1.4–2.6) 1.0 1.1 (0.7–1.7) 1.0 (0.5–1.7) 4.9 (2.2–10.8) 2.1 (1.1–3.9) 2.4 (1.4–4.1)
Sui et al.[16]	2087 men and 516 women, aged 60–100 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese I (30.0–34.9) Obese II/III (≥35.0) WC: Normal (<88 cm, women; <102 cm, men) Obese (≥88 cm, women; ≥102 cm, men) BF: Normal (<30%, women; <25%, men) Obese (≥30%, women; ≥25%, men)	Sex group quintiles Fit: quintiles 2–5 Unfit: quintile 1	12	Fit-normal Fit-overweight Fit-obese I Fit-obese II/III Unfit-normal Unfit-overweight Unfit-obese I Unfit-obese II/III Fit-normal WC Fit-high WC Unfit-normal WC Unfit-high WC Fit-normal BF Fit-high BF Unfit-normal BF Unfit-high BF	1.0 0.9 (0.7–1.1) 1.1 (0.8–1.7) 0.9 (0.2–3.5) 3.6 (2.5–5.3) 1.7 (1.2–2.5) 1.7 (1.0–2.8) 3.4 (1.7–6.4) 1.0 1.2 (0.9–1.6) 2.8 (2.2–3.8) 2.7 (1.9–3.6) 1.0 1.0 (0.8–1.2) 2.9 (2.0–4.4) 2.4 (1.8–3.2)

Farrell et al.[18]	11,335 women, mean age 45 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0) WC: Normal (<88 cm) High (≥88 cm) BF: Normal (<30%) High (≥30%)	Age and sex group quintiles Fit: quintiles 2–5 Unfit: quintile 1	12.3	Fit-normal Fit-overweight Fit-obese Unfit-normal Unfit-overweight Unfit-obese Fit-normal WC Fit-high WC Unfit-normal WC Unfit-high WC Fit-normal BF Fit-high BF Unfit-normal BF Unfit-high BF	1.0 1.1 0.5 1.5* 1.9* 2.5* 1.0 0.9 1.7* 2.0* 1.0 1.0 1.4 2.0*
Stevens et al.[19]	2506 women, mean age 46.6 years; 2860 men, mean age 45.1 years; United States	BMI: Not fat (sex-specific quintiles 1–4; 18.7–27.6, women; 19.5–28.6, men) Fat (sex-specific quintile 5; 27.7–42.6, women; 28.7–39.4, men)	Sex group quintiles Fit: quintiles 2–5 Unfit: quintile 1	24	Women: Fit-not fat Fit-fat Unfit-not fat Unfit-fat Men: Fit-not fat Fit-fat Unfit-not fat Unfit-fat	 1.0 1.3* 1.3* 1.6* 1.0 1.3* 1.4* 1.5*
Stevens et al.[20]	1359 men, aged 40–59 years, Russia 1716 men, aged 40–59 years, United States	BMI: Not fat (country-specific quintiles 1–4) Fat (country-specific quintile 5)	Country group quintiles Fit: quintiles 2–5 Unfit: quintile 1	17.6	Russia: Fit-not fat Fit-fat Unfit-not fat Unfit-fat United States: Fit-not fat Fit-fat Unfit-not fat Unfit-fat	 1.0 0.9 1.9* 1.7* 1.0 1.4* 1.4* 1.5*

(*Continued*)

TABLE 60.2 (*Continued*)
All-Cause Mortality Risk for Combined Fitness- or Activity-Fatness Groups

Reference	Participants	Adiposity Classification	Fitness or Activity Classification	Mean Follow-up (years)	Fitness- or Activity-Fatness Groups	Adjusted RR (95% CI)
			Physical Activity			
Hu et al.[28]	116,564 women, aged 30–55 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0)	Self-reported leisure PA: High PA (≥3.5 hours/week) Moderate (Mod) PA (1.0–3.4 hours/week) Low PA (<1.0 hour/week)	24	High PA-normal High PA-overweight High PA-obese Mod PA-normal Mod PA-overweight Mod PA-obese Low PA-normal Low PA-overweight Low PA-obese	1.0 1.3 (1.1–1.5) 1.9 (1.6–2.3) 1.2 (1.1–1.3) 1.3 (1.2–1.5) 2.1 (1.8–2.3) 1.6 (1.4–1.7) 1.6 (1.5–1.8) 2.4 (2.1–2.7)
Hu et al.[29]	24,684 women and 22,528 men, aged 25–64 years, Finland	BMI: Nonobese (<30.0) Obese (≥30.0)	Self-reported occupational and leisure PA: Inactive (low) Active (moderate or high)	17.7	Women: Active-nonobese Active-obese Inactive-nonobese Inactive-obese Men: Active-nonobese Active-obese Inactive-nonobese Inactive-obese	 1.0 1.1* 1.6* 2.1* 1.0 1.2* 1.5* 1.8*
Orsini et al.[30]	37,633 men, aged 45–79 years, Sweden	BMI: Normal (<25.0) Overweight (25.0–29.9) Obese (≥30.0)	Usual PA during past year: Low (tertile 1) Moderate (Mod) (tertile 2) High (tertile 3)	9.7	High PA-normal High PA-overweight High PA-obese Mod PA-normal Mod PA-overweight Mod PA-obese Low PA-normal Low PA-overweight Low PA-obese	1.0 1.6 (1.2–2.3) 1.9 (0.9–4.1) 1.6 (1.2–2.2) 1.7 (1.3–2.3) 2.1 (1.2–3.6) 2.2 (1.6–2.9) 2.0 (1.5–2.7) 2.2 (1.4–3.6)

Notes: BF, body fat; PA, physical activity; WC, waist circumference.
*$P < .05$

TABLE 60.3
Cardiovascular Disease Mortality Risk for Combined Fitness- or Activity-Fatness Groups

Reference	Participants	Adiposity Classification	Fitness or Activity Classification	Mean Follow-up (years)	Fitness- or Activity-Fatness Groups	Adjusted RR (95% CI)
			Fitness			
Wei et al.[14]	25,714 men, mean age 43.8 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0)	Age and sex group quintiles Fit: age-decade quintiles 2–5 Unfit: age-decade quintile 1	10	Fit-normal Fit-overweight Fit-obese Unfit-normal Unfit-overweight Unfit-obese	1.0 1.5 (1.1–2.0) 1.6 (1.0–2.8) 3.1 (2.2–4.5) 4.5 (3.4–6.0) 5.0 (3.6–7.0)
Lee et al.[15]	21,925 men, aged 30–83 years, United States	BF: Lean (quartile 1, <16.7%) Normal (quartiles 2 and 3, 16.7–<25.0%) Obese (quartile 4, ≥25.0%)	Age and sex group quintiles Fit: quintiles 2–5 Unfit: quintile 1	8	Fit-lean Fit-normal Fit-obese Unfit-lean Unfit-normal Unfit-obese	1.0 1.4 (0.8–2.7) 1.4 (0.7–2.8) 3.2 (1.1–8.9) 2.9 (1.5–5.8) 4.1 (2.2–7.7)
Stevens et al.[19]	2506 women, mean age 46.6 years, 2860 men, mean age 45.1 years; United States	BMI: Not fat (sex-specific quintiles 1–4; 18.7–27.6, women; 19.5–28.6, men) Fat (sex-specific quintile 5; 27.7–42.6, women; 28.7–39.4, men)	Sex group quintiles Fit: quintiles 2–5 Unfit: quintile 1	24	Women: Fit-not fat Fit-fat Unfit-not fat Unfit-fat Men: Fit-not fat Fit-fat Unfit-not fat Unfit-fat	 1.0 1.4 1.5* 2.0* 1.0 1.4 1.6 1.7*
Stevens et al.[20]	1359 men, aged 40–59 years, Russia 1716 men, aged 40–59 years, United States	BMI: Not fat (country-specific quintiles 1–4) Fat (country-specific quintile 5)	Country group quintiles Fit: quintiles 2–5 Unfit: quintile 1	17.6	Russia: Fit-not fat Fit-fat Unfit-not fat Unfit-fat United States: Fit-not fat Fit-fat Unfit-not fat Unfit-fat	 1.0 0.9 1.9* 3.1* 1.0 1.3 1.6* 1.6*
			Physical Activity			
Hu et al.[28]	116,564 women, aged 30–55 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0)	Self-reported leisure PA: High PA (≥3.5 hours/week) Moderate (Mod) PA (1.0–3.4 hours/week) Low PA (<1.0 hour/week)	24	High PA-normal High PA-overweight High PA-obese Mod PA-normal Mod PA-overweight Mod PA-obese Low PA-normal Low PA-overweight Low PA-obese	1.0 1.6 (1.2–2.1) 2.9 (1.9–4.2) 1.5 (1.2–1.9) 2.1 (1.6–2.6) 4.3 (3.3–5.4) 1.9 (1.5–2.4) 2.5 (2.0–3.2) 4.7 (3.7–6.1)
Hu et al.[29]	24,684 women and 22,528 men, aged 25–64 years, Finland	BMI: Nonobese (<30.0) Obese (≥30.0)	Self-reported occupational and leisure PA: Inactive (low) Active (moderate or high)	17.7	Women: Active-nonobese Active-obese Inactive-nonobese Inactive-obese Men: Active-nonobese Active-obese Inactive-nonobese Inactive-obese	 1.0 1.2* 1.7* 2.2* 1.0 1.4* 1.4* 2.1*
Orsini et al.[30]	37,633 men, aged 45–79 years, Sweden	BMI: Normal (<25.0) Overweight to obese (≥25.0)	Usual PA during past year: Low (tertile 1) Moderate (Mod) (tertile 2) High (tertile 3)	9.7	High PA-BMI < 25.0 High PA-BMI ≥ 25.0 Mod PA-BMI < 25.0 Mod PA-BMI ≥ 25.0 Low PA-BMI < 25.0 Low PA-BMI ≥ 25.0	1.0 1.5 (0.8–2.8) 1.1 (0.6–2.1) 1.5 (0.8–2.7) 1.6 (0.9–3.1) 1.7 (0.9–3.2)

*$P < .05$

mortality risks for unfit-obese were higher than for unfit-normal-weight individuals. One exception was noted for U.S. men from LRC,[20] where equal results were observed for the two unfit groups. In one study[15] of percentage body fat, higher relative risks were observed for unfit-obese (4.1) than for unfit-lean ACLS men (3.2).

Similarly, in the physical activity studies, inactive persons who were normal-weight or obese had higher CVD mortality risks compared with their active and normal-weight counterparts. While two studies[28,29] showed higher CVD mortality risks for inactive-obese than for inactive-normal-weight groups, one study found equal results for these groups.[30]

60.4.3 Coronary Heart Disease

Studies with CHD as the outcome are summarized in Table 60.4. Three studies[31–33] used physical activity, but no studies used fitness as the exposure. BMI was the adiposity exposure variable in two studies,[31,32] and only waist circumference was used in one study.[33] Two studies[31,32] included only women, and one study[33] included men and women. Altogether, these three studies included approximately 149,000 subjects with a mean follow-up ranging from 11 to 20 years.

In two studies,[31,33] CHD risks were significantly higher for inactive participants who were normal-weight or obese and had a low or high waist circumference, compared with their respective active and normal reference groups. In another study,[32] inactive-normal-weight participants did not differ from the reference group.

Consistent findings were observed for the BMI studies[31,32] in which higher CHD risks were observed for low-activity-obese than for low-activity-normal-weight groups. Similar results were observed in one study[33] of waist circumference for women but not for men; CHD risks were more similar for inactive men with low waist and with high waist circumference.

60.4.4 Type 2 Diabetes

Studies with type 2 diabetes as the outcome are summarized in Table 60.5. Two studies[17,21] used fitness and two studies[34,35] used physical activity as the exposure. BMI was the adiposity

TABLE 60.4
Coronary Heart Disease Risk for Combined Activity-Fatness Groups

Reference	Participants	Adiposity Classification	Activity Classification	Mean Follow-up (years)	Activity-Fatness Groups	Adjusted RR (95% CI)
Li et al.[31]	88,393 women, aged 34–59 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0)	Self-reported moderate to vigorous PA: High PA (≥3.5 hours/week) Moderate (Mod) PA (1–3.5 hours/week) Low PA (<1 hours/week)	20	High PA-normal High PA-overweight High PA-obese Mod PA-normal Mod PA-overweight Mod PA-obese Low PA-normal Low PA-overweight Low PA-obese	1.0 1.4 (1.1–1.8) 2.5 (1.8–3.3) 1.3 (1.1–1.6) 1.9 (1.6–2.3) 3.3 (2.7–4.0) 1.5 (1.2–1.8) 2.0 (1.7–2.5) 3.4 (2.8–4.2)
Weinstein et al.[32]	38,987 women, aged 45 years and older, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0)	Self-reported recreational PA: Inactive (<1000 kcal/week) Active (≥1000 kcal/week)	10.9	Active-normal Active-overweight Active-obese Inactive-normal Inactive-overweight Inactive-obese	1.0 1.5 (1.1–2.0) 1.9 (1.3–2.7) 1.1 (0.8–1.4) 1.9 (1.5–2.5) 2.5 (2.0–3.3)
Arsenault et al.[33]	12,165 women and 9564 men aged 45–79 years, United States	WC: Low third (<91.0 cm) Middle third (91.0–97.9 cm) Upper third (>98.0)	Self-reported occupational and leisure time PA: Inactive (sedentary job and no recreational PA) Active (sedentary job with >1-hour recreational PA per day or standing job with >0.5-hour recreational PA per day or physical job with some recreational PA or heavy manual job)	11.4	Women: Active-low WC Active-middle WC Active-upper WC Inactive-low WC Inactive-middle WC Inactive-upper WC Men: Active-low WC Active-middle WC Active-upper WC Inactive-low WC Inactive-middle WC Inactive-upper WC	 1.0 3.5 (1.7–7.2) 3.6 (1.7–7.7) 2.4 (1.1–4.9) 3.7 (1.9–7.3) 4.0 (2.0–7.9) 1.0 1.2 (0.9–1.7) 1.4 (1.0–1.9) 1.4 (1.1–1.9) 1.3 (1.0–1.8) 1.7 (1.3–2.3)

Notes: PA, physical activity; WC, waist circumference.

TABLE 60.5
Type 2 Diabetes Risk for Combined Fitness- or Activity-Fatness Groups

Reference	Participants	Adiposity Classification	Fitness or Activity Classification	Mean Follow-up (years)	Fitness- or Activity-Fatness Groups	Adjusted RR (95% CI)
			Fitness			
Lee et al.[17]	14,006 men, aged 20–79 years, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0) WC: Normal (≤102 cm) Obese (>102 cm) BF: Normal (<25%) Obese (≥25%)	Sex and age group quintiles Fit: quintiles 2–5 Unfit: quintile 1	7.2	Fit-normal Fit-overweight Fit-obese Unfit-normal Unfit-overweight Unfit-obese Fit-normal WC Fit-obese WC Unfit-normal WC Unfit-obese WC Fit-normal BF Fit-obese BF Unfit-normal BF Unfit-obese BF	1.0 1.6 (1.3–2.0) 3.0 (2.1–4.2) 1.6 (0.9–2.8) 2.1 (1.4–3.1) 5.7 (4.0–8.0) 1.0 2.4 (1.8–3.2) 1.8 (1.1–2.9) 4.0 (2.8–5.8) 1.0 1.5 (1.2–1.9) 1.8 (1.2–2.6) 2.8 (2.1–3.7)
Sui et al.[21]	6249 women, mean age 43.8 years, United States	BMI: Normal (<25.0) Overweight (≥25.0)	Sex and age group tertiles Fit: tertiles 2 and 3 Unfit: tertile 1	17	Fit-normal Fit-overweight Unfit-normal Unfit-overweight	1.0 1.8 (1.0–3.4) 1.1 (0.7–1.7) 2.6 (1.5–4.4)
			Physical Activity			
Hu et al.[34]	2352 women and 2017 men, aged 45–64 years, Finland	BMI: Nonobese (<30) Obese (≥30.0)	Self-reported occupational, commuting, and leisure PA: High PA (two or three types of moderate to high PA) Moderate (Mod) PA (1 type of moderate to high PA) Low PA (<30 minutes of light PA)	9.4	High PA-nonobese High PA-obese Mod PA- nonobese Mod PA-obese Low PA- nonobese Low PA-obese	1.0 3.8* 2.2 7.3 1.1 13.2
Weinstein et al.[35]	37,878 women, aged 45 years and older, United States	BMI: Normal (18.5–24.9) Overweight (25.0–29.9) Obese (≥30.0)	Self-reported recreational PA: Inactive (<1000 kcal/week) Active (≥1000 kcal/week)	17.7	Active-normal Active-overweight Active-obese Inactive-normal Inactive-overweight Inactive-obese	1.0 3.7 (2.6–5.2) 11.5 (8.3–15.9) 1.2 (0.8–1.6) 4.2 (3.1–5.7) 11.8 (8.8–16.0)

Notes: BF, body fat; PA, physical activity; WC, waist circumference.
* 95% CI and *p*-value not reported.

exposure variable in four studies[17,21,34,35] (one of which[17] also included waist circumference and percentage body fat). Two studies[21,35] included only women, one study[17] included only men, and one study[34] included men and women. Altogether, these four studies included approximately 62,500 subjects with a mean follow-up ranging from 7 to 18 years.

In both fitness studies,[17,21] unfit-overweight and unfit-obese groups had higher type 2 diabetes risks, but unfit-normal-weight groups did not differ from their respective reference groups. Type 2 diabetes risks were significantly higher for unfit participants who were obese, had a low or high waist circumference, and a low or high percentage body fat compared with their respective fit and normal reference groups.

In both physical activity studies,[34,35] more extreme differences in relative risks were observed for low-activity groups when comparing normal-weight with obese categories (1.1 for BMI < 30 vs. 13.2 for BMI ≥ 30[34] and 1.2 for BMI < 25 vs. 11.8 for BMI ≥ 30[35]).

60.5 DISCUSSION

A growing body of evidence on combined associations of fitness and fatness with health outcomes has focused entirely on the issue of whether higher levels of physical activity or fitness attenuate the increased health risks normally associated with excess adiposity.[6–11] More recently, data on longitudinal changes in fitness and fatness provided compelling evidence that, in terms of mortality risk, preventing a decline in fitness is more important than preventing weight gain.[36] Yet, improving fitness and preventing weight gain may be equally important when it comes to reducing CVD risk factors over time.[37]

In this chapter, we approached the issue from an inactivity/low-fitness perspective and asked a new question: "Does obesity compound the health risks of inactivity or poor fitness?" We attempted to answer this question by reviewing extremely well-collected data from 16 studies on approximately 450,000 adults and by comparing adjusted relative risks for unfit or inactive normal-weight participants to their obese counterparts. We found compelling evidence that the risks for all-cause and CVD mortality, CHD, and diabetes were higher for obese individuals with low fitness or who were inactive compared with their inactive and normal-weight counterparts. As to our second question on the relative importance of poor fitness, inactivity, and obesity as predictors of morbidity and mortality, the findings were less uniform. In the studies that used fitness as the exposure, obesity appeared to have less predictive power among fit individuals. On the contrary, the combination of being unfit and obese was associated with higher health risks, especially for type 2 diabetes, compared with being unfit and of normal weight. Whether poor fitness or inactivity is more important as a risk factor is difficult to ascertain.[38] Since physical activity in all of the studies included in this review was assessed by self-report, we were unable to make adequate comparisons with fitness. Future studies on fitness, fatness, and health outcomes with simultaneous, objective measures of physical activity and fitness are needed to directly address this important question.

In 14 of the 16 studies reviewed, BMI was used to assess obesity status. Since BMI is a crude anthropometric measure that does not indicate the relative amounts of fat mass versus fat-free mass or body fat distribution patterns, some have called into question its utility as a measure of adiposity.[39,40] While higher BMI does not necessarily reflect higher adiposity, Pearson correlations in the range of 0.7–0.8 between BMI and percentage body fat have been reported for both men[41] and women.[18] More specifically, when BMI is $\geq$30 kg/m^2, it appears to be an excellent predictor of excess adiposity in both sexes.[42] Therefore, BMI is a fairly accurate indicator of obesity status in the studies included in this chapter. Moreover, in the studies with simultaneous measures of BMI, waist circumference, and percentage body fat, the results were comparable.

60.5.1 Pathogenic Mechanisms

Several mechanisms have been proposed in an attempt to explain how an increase in fitness or physical activity might ameliorate the health hazards of obesity.[9,43,44] These include anti-inflammatory effects, better glucose control, decreases in atherogenic lipoprotein subfractions, and reductions in visceral fat depots. In contrast, less is known about how obesity, poor fitness, and an inactive lifestyle coalesce into a risk cluster that is greater than the sum of their parts.

In particular, our findings on CHD and type 2 diabetes indicate that the benefits of physical activity or fitness may not be sufficient to counteract the negative influence of obesity. For example, leptin has been shown to increase fatty acid oxidation in skeletal muscle from lean but not obese human subjects,[45] and in an intervention study[46] of 316 older overweight or obese men and women, concentrations of inflammatory markers were reduced with diet-induced weight loss but not exercise. While this may partially explain the independent cardiometabolic risk of obesity, the relationship between inflammatory cytokine secretion from adipose tissue and insulin resistance is not well understood.[47]

Whereas favorable changes in cardiometabolic risk factors are observed after weight loss, there is increasing evidence that the benefits of regular exercise may operate independently of body weight.[8] For example, one important link in the chain of events leading to type 2 diabetes is the role that liver fat plays in insulin resistance.[48] In one study[49] of 19 obese men and women, aerobic exercise training reduced liver fat concentration by 21% after 4 weeks in the absence of a decrease in body weight and abdominal adipose tissue. Another study[50] of 218 apparently healthy men aged 33–73 years found that cardiorespiratory fitness was inversely associated with the prevalence of nonalcoholic fatty liver disease independent of BMI. Compared with men in the upper third of fitness, nonalcoholic fatty liver disease was 10 times more prevalent among men in the lower third of fitness. More recently, in a study[51] of 606 patients with type 2 diabetes, improvements in fitness predicted improvements in CVD risk factors independently of weight loss. The results of these studies suggest that favorable changes in liver fat content and CVD risk factors can occur with regular exercise independent of changes in subcutaneous adiposity. Therefore, interactions among fitness, physical activity, adiposity, and risk factors are complicated by the responsiveness of ectopic and visceral fat stores to changes in fitness and physical activity.

Similarly, intervention trials aimed at evaluating the effect of exercise in improving insulin sensitivity are particularly insightful. In a study[52] of 110 obese women with impaired glucose tolerance from the Indian Diabetes Prevention Program, diabetes incidence was reduced by 29% in the exercise group without significant weight loss. In another study of eight obese and inactive but otherwise healthy men, insulin sensitivity improved after 4 weeks of endurance training without a significant change in body weight or percentage body fat (measured by skinfolds).[53]

60.5.2 Implications For Public Health Policy

Obesity may complicate physical inactivity–induced health risks by making physical activity more arduous and thereby reinforcing an inactive lifestyle. In this regard, avoiding

obesity is a worthwhile public health objective. However, weight loss as the primary strategy to address the health risks of obesity has thus far been ineffective because long-term maintenance of weight loss remains elusive.[54] In addition, evidence indicates that even intentional weight loss can increase mortality risk.[55] Therefore, if higher levels of physical activity or cardiorespiratory fitness can reduce mortality and morbidity in obese persons comparable to the transient risk reduction produced after short-term weight loss, this could lead to preventive strategies that have better prospects for long-term maintenance and that are potentially more cost-effective. Most adults can stay out of the low-fitness category by engaging in 30 minutes of regular physical activity such as brisk walking 5 or more days per week.[5] This in turn can prevent weight gain and reduce residual obesity-related health risks, thereby avoiding the most unhealthy combination of obesity, an inactive lifestyle, and low fitness.

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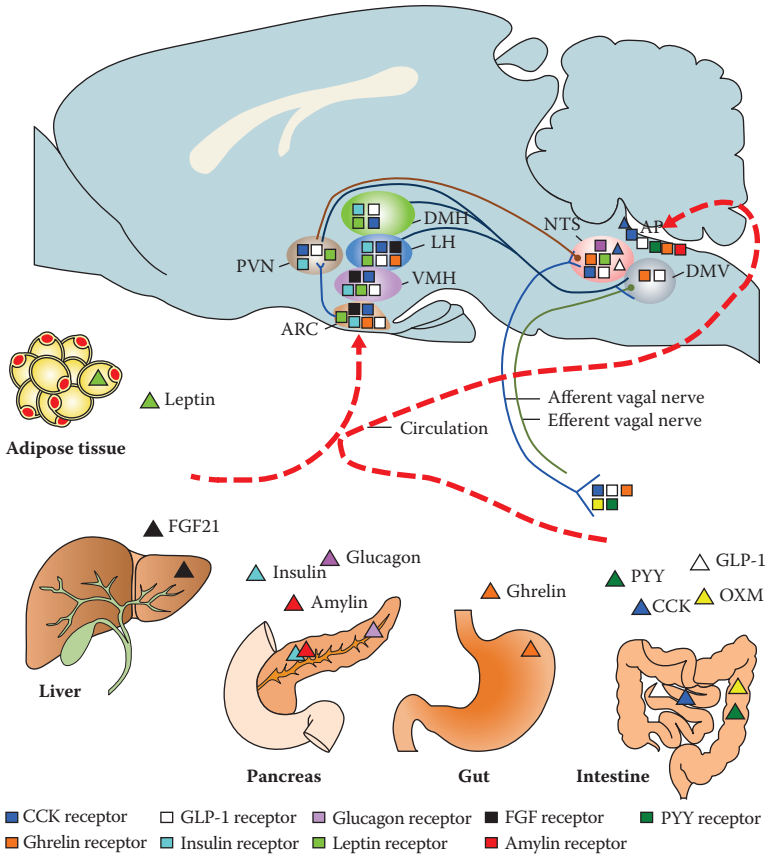

FIGURE 15.1 Schematic of the neuroendocrine regulation of energy metabolism. The gastrointestinal (GI) tract as the largest endocrine organ of the body produces a variety of peptides that are either secreted preprandially in anticipation of or postprandially in response to food intake. In concert, these peptides inform the brain about the GI fuel status. The brain responds to these signals with an activation of signaling cascades that modulate food intake through a regulation of hunger and satiety. ARC, arcuate nucleus; AP, area postrema; CCK, cholecystokinin; DMH, dorsomedial hypothalamus; FGF21, fibroblast growth factor 21; GLP-1, glucagon-like peptide 1; LH, lateral hypothalamus; NTS, nucleus tractus solitarus; OXM, oxyntomodulin; PVN, paraventricular nucleus; PYY, peptide tyrosine tyrosine; VMH, ventromedial hypothalamus.

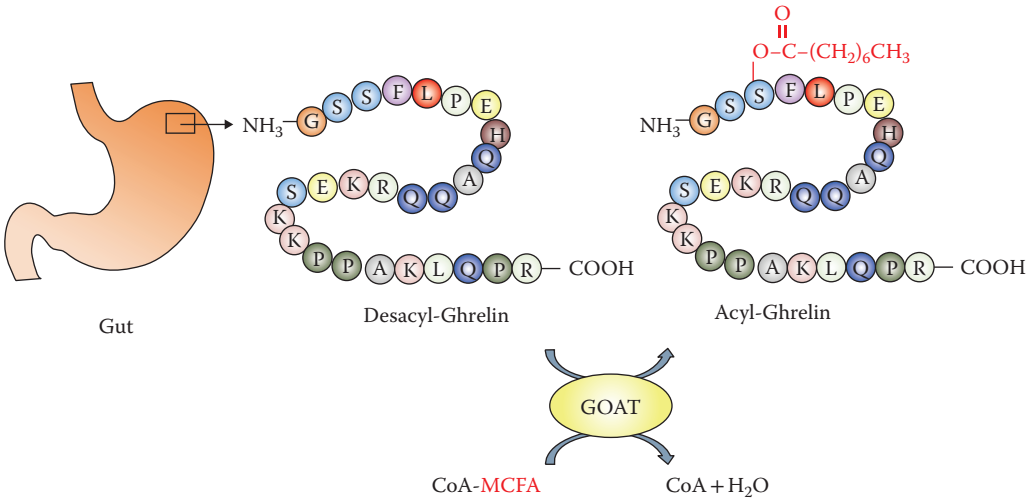

FIGURE 15.2 Posttranslational activation (acylation) of ghrelin. To promote its biological action, ghrelin is acylated at its serine 3 residue by the ghrelin-O-acyltransferase (GOAT).

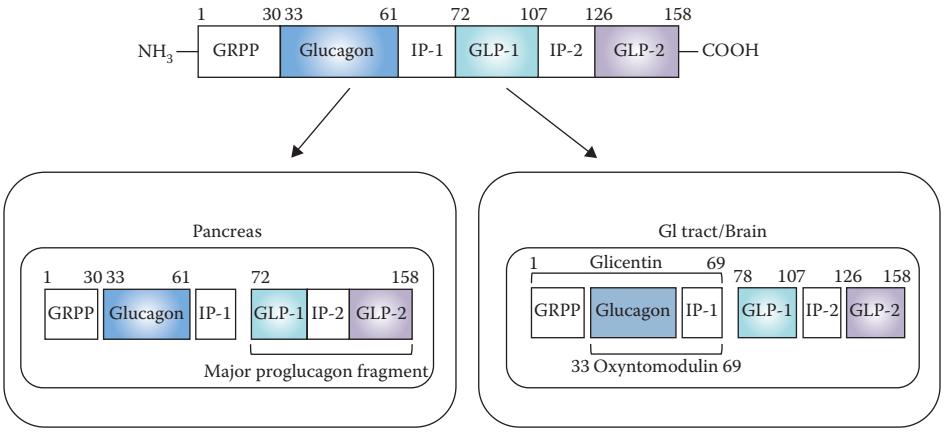

FIGURE 15.3 Cleavage products of proglucagon. Posttranslational cleavage of proglucagon is mediated by the prohormone convertase 1 or 2. In the pancreas, proglucagon is cleaved into either glicentin-related pankreatic peptide (GRPP, amino acids 1–30), glucagon (amino acids 33–61), or the major proglucagon fragment (amino acids 72–158). In the L-cells of the small intestine and the brain, proglucagon is cleaved into glicentin (amino acids 1–69), glucagon-like peptide 1 (GLP-1, amino acids 72–108), intervening peptide 2 (IP-2, amino acids 111–123), and GLP-2 (amino acids 126–158). Glicentin is then further cleaved into GRPP and oxyntomodulin (amino acids 33–69).

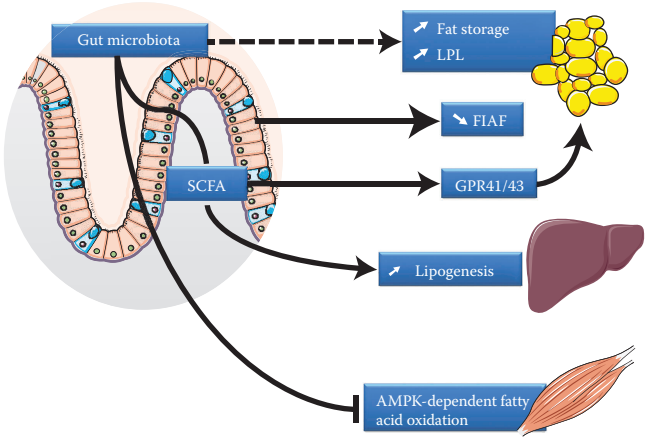

FIGURE 16.2 Mechanisms linking gut microbiota with increased energy storage. Gut microbiota modulates energy storage through various mechanisms, as mostly demonstrated in germ-free mice. Fermentation by the gut microbiota promotes short chain fatty acid (SCFA) production and absorption, thereby increasing the amount of lipogenic substrates available to the host. These SCFAs are involved in hepatic lipogenesis and fat storage through numerous mechanisms, including the suppression of fasting-induced adipose factor (FIAF) in the gut, and eventually indirectly control the activity of the enzyme lipoprotein lipase (LPL). By acting through GPR41 and GPR43, the different SCFAs contribute to fat storage. Finally, AMP-activated protein kinase (AMPK)-dependent fatty acid oxidation is inhibited by the gut microbiota in response to a high-fat diet; however, it should be noted that other unknown direct or indirect mechanisms may exist (dotted line).

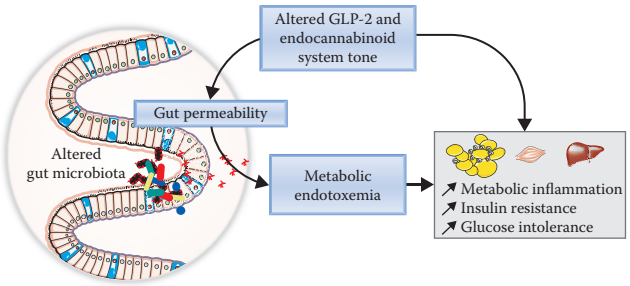

FIGURE 16.4 Metabolic endotoxemia links gut microbiota with metabolic disorders associated with obesity. Both genetic and nutritional obesity are associated with dysbiosis, increased gut permeability, and metabolic endotoxemia. This increased level of lipopolysaccharide production triggers metabolic inflammation, insulin resistance, and type 2 diabetes. Both glucagon-like peptide (GLP)-2 and the endocannabinoid system play a major role in the control of gut barrier function and therefore in the onset of metabolic endotoxemia upon obesity.

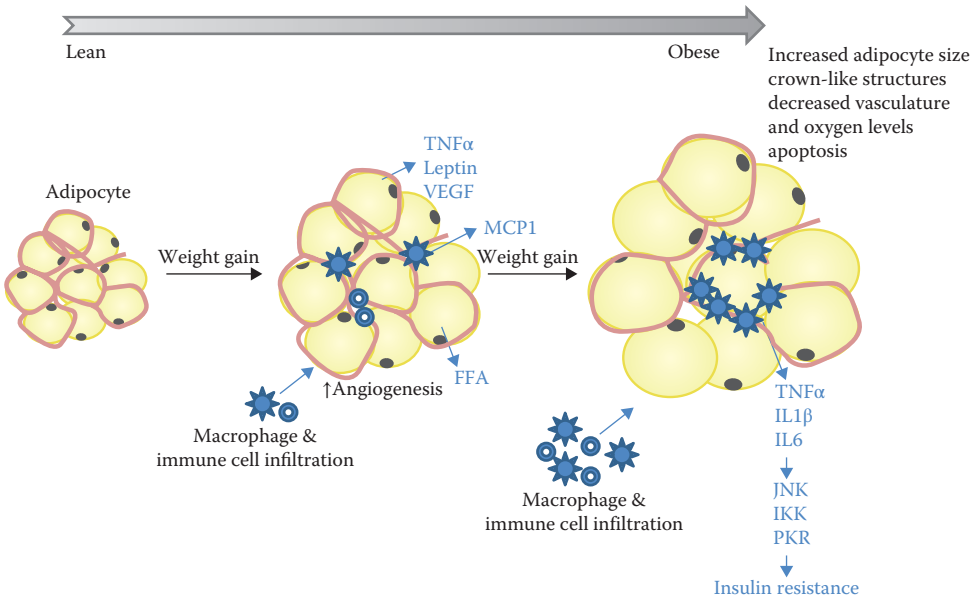

FIGURE 18.2 Inflammatory mechanisms of obesity and insulin resistance. In the lean state, adipose tissue is characterized by relatively small fat cells and a healthy vasculature and extracellular matrix. As weight gain develops, adipocytes expand, secreting leptin and low levels of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). This promotes macrophages and other immune cells (neutrophils, T cells, and mast cells) to infiltrate the adipose tissue, which also secretes proinflammatory cytokines. With obesity, there is a chronic, low-grade state of systemic inflammation and immune cell accumulation. Macrophages surround adipocytes, forming crown-like structures, in an attempt to scavenge the lipid from the dying adipocytes. At the same time, there may be a disconnect between expansion of the fat cell and vasculature, leading to decreased oxygen levels in adipose tissue, which can further promote proinflammatory cytokine secretion. Molecular factors upstream of inflammatory cytokines, including c-jun N-terminal kinase (JNK), inhibitor of kappa B kinase (IKK), and protein kinase R (PKR), are major intracellular contributors to the induction of inflammation in metabolic diseases. MCP1, monocyte chemoattractant protein 1. (Adapted from Wellen KE et al., *J Clin Invest*, 115, 1111–9, 2005.)

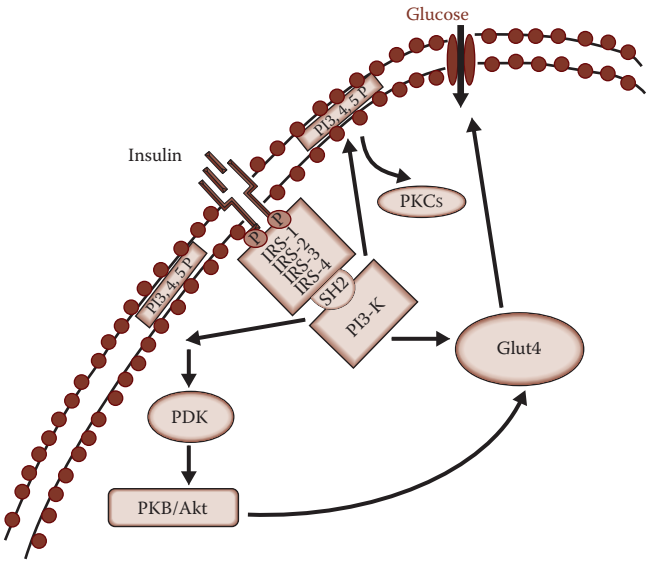

FIGURE 18.3 Molecular mechanism of insulin-mediated glucose transport. The insulin-dependent glucose transporter (GLUT4) is translocated by a phosphatidylinositol 3 kinase (PI3-K)–dependent pathway including protein kinase B (PKB)/v-akt murine thymoma viral oncogene (Akt) and protein kinase C (PKC) stimulation downstream of PI3-K. IRS, insulin receptor substrate; PDK, phosphoinositide-dependent kinase; SH2, Src homology 2. (Adapted from Matthaei S et al., *Endocr. Rev.*, 21, 585–618, 2000.)

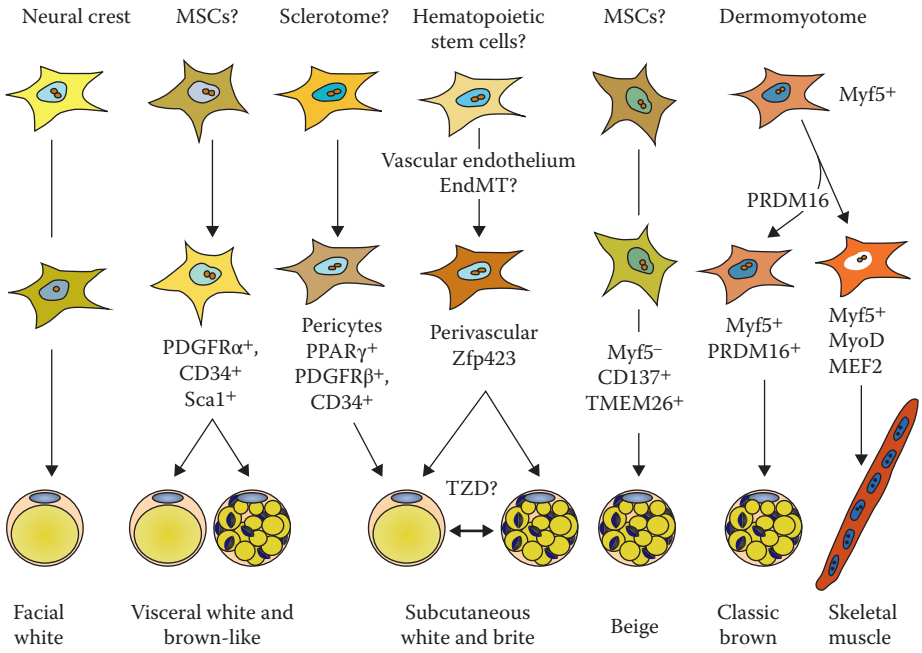

FIGURE 19.2 Putative stem cell lineages that give rise to white and brown adipose depots: CD34, hematopoietic progenitor cell antigen CD34; CD137, tumor necrosis factor receptor superfamily member 9; EndMT, endothelial-to-mesenchymal transition; MEF2, myocyte enhancing factor 2; MyoD, myogenic differentiation 1; Sca1, lymphocyte antigen 6A-2/6E-1.

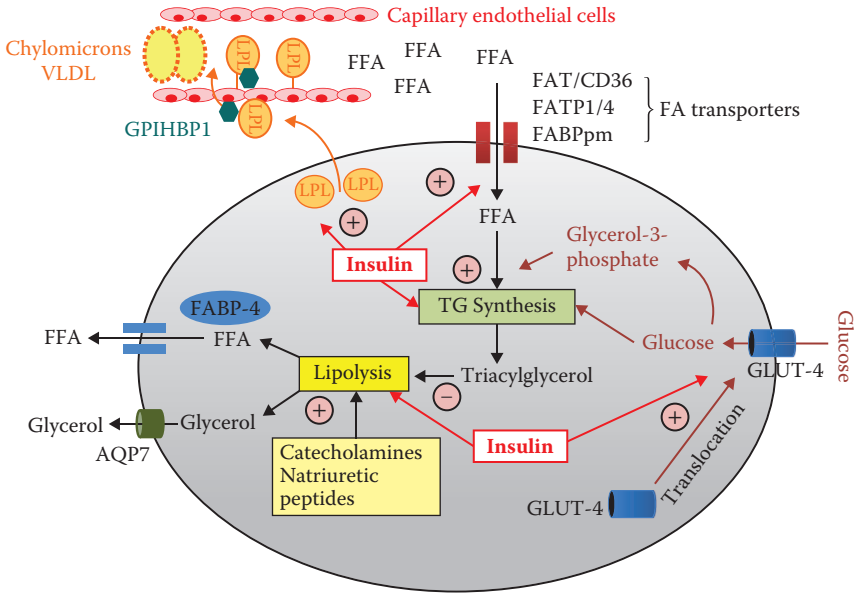

FIGURE 20.1 Overview of fat storage and fat mobilization in the white adipocyte: lipoprotein lipase (LPL) synthesized in the adipocyte is transferred to the capillary lumen. Glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 (GPIHBP1) of capillary endothelial cells shuttles LPL from subendothelial spaces to the capillary lumen. The endothelium-bound LPL acts on chylomicron particles in the vascular space to liberate free fatty acids (FFAs), which then cross the endothelium to be taken up by adipocytes via several fatty acid (FA) transporters. Glucose uptake is under the control of glucose transporter (GLUT-4) translocation. Insulin has major positive impacts on LPL synthesis and activation, FA and glucose uptake, and FA esterification while exerting potent antilipolytic effects. AQP7, aquaporin-7; FABP-4, FA-binding protein 4; FAT/CD36, FA translocase/CD36; FATP1/4, FA transport protein 1/4; FABPpm, plasma membrane FA-binding protein (identical to mitochondrial aspartate aminotransferase); GLUT-4, insulin-responsive glucose transporter type 4; TG, triacylglycerol; VLDL, very-low-density lipoprotein; (+), stimulation; (–), inhibition.

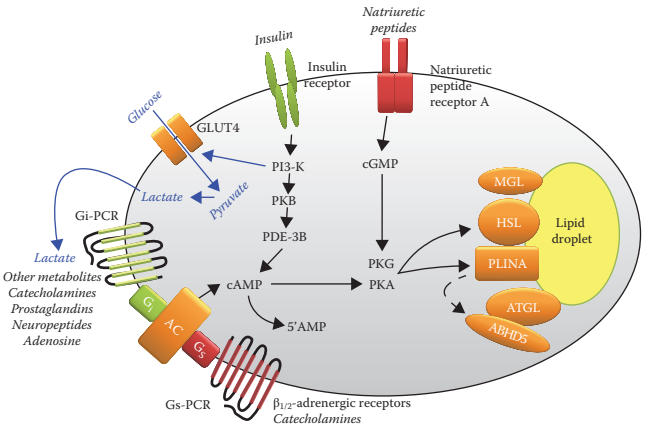

FIGURE 20.3 Regulation of lipolysis in human adipocytes: binding of catecholamines to Gs-protein-coupled $\beta_{1/2}$-adrenergic receptors stimulates cyclic adenosine monophosphate (cAMP) production by adenylyl cyclase and activates protein kinase A (PKA). Conversely, the stimulation of Gi-protein-coupled receptors reduces cAMP and PKA activation. Insulin favors cAMP degradation through the activation of phosphatidylinositol-3 phosphate kinase (PI3-K) and protein kinase B (PKB) and the stimulation of phosphodiesterase 3B (PDE3B) activity. Natriuretic peptides promote cyclic guanosine monophosphate (cGMP) accumulation and protein kinase G (PKG) activation. PKA and PKG phosphorylate hormone-sensitive lipase (HSL) and perilipin A (PLINA). Adipose triglyceride lipase (ATGL) and its cofactor ABHD5 and monoacylglycerol lipase (MGL) also participate in the hydrolysis of triglycerides. A new pathway (shown by blue arrows) involving the glucose transporter GLUT-4, glycolysis-mediated lactate production, and the Gi-protein-coupled lactate receptor GPR81 has been proposed to be involved in the insulin-induced antilipolytic effect. It is unknown whether this pathway participates in the control of human fat cell lipolysis. Gs-PCR and Gi-PCR refer to Gs- and Gi-protein-coupled receptors, respectively.

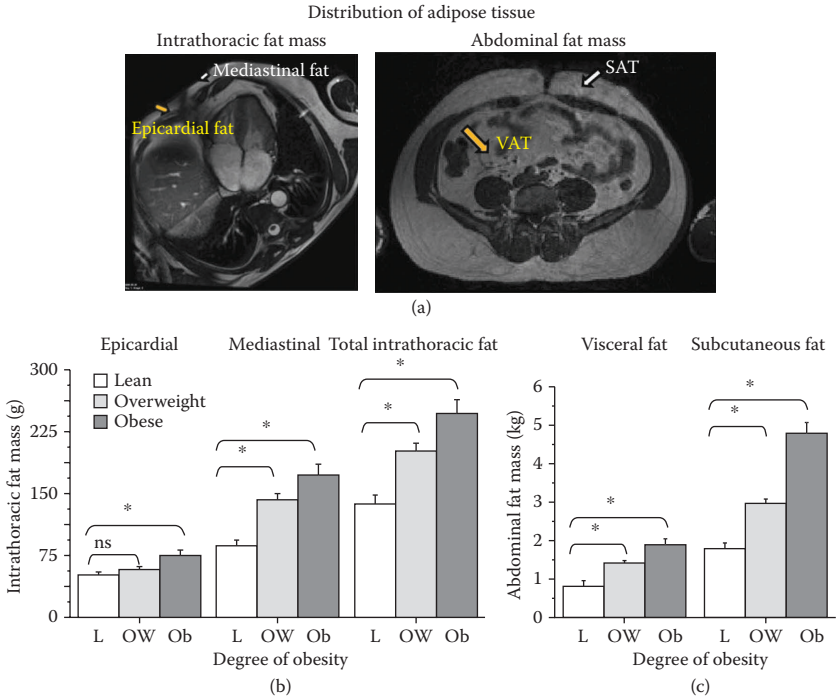

FIGURE 21.1 (a) Intrathoracic and abdominal images obtained using magnetic resonance spectroscopy. (b) Intrathoracic adipose tissue accumulation (epicardial, mediastinal, and total cardiac fat). (c) Abdominal adipose tissue accumulation (visceral and subcutaneous). Data shown for lean (body mass index [BMI] < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obese (BMI > 30 kg/m^2) subjects. * $p < .05$ versus lean in each group. NS = not significant. (Reproduced from Sironi AM et al., *Diabet. Med.*, 29, 622–7, 2012.)

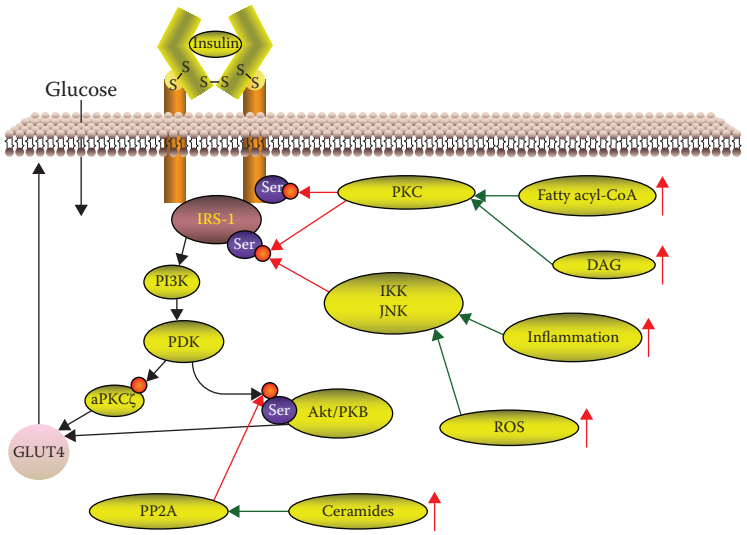

FIGURE 22.1 Mechanism(s) of insulin resistance in muscle of obese individuals. Insulin stimulates glucose transport by first binding to its receptor, with activation of a kinase that tyrosine phosporylates IRS-1. Activated IRS-1 in turn activates PI3K and PDK. PDK activates aPKCζ and Akt through serine/threonine phosphorylation, which leads to the translocation and activation of the insulin-sensitive glucose transporter (GLUT4). The result is insulin resistance in muscle of obese individuals due to the accumulation of lipids (fatty acyl-CoA, DAG, and ceramides), inflammation, and/or the production of reactive oxygen species (ROS). These lead to the activation of kinases (PKC, IKK, and JNK) or phosphatases (PP2A). Insulin signal transduction is reduced when the insulin receptor and IRS-1 become serine phosphorylated (PKC, IKK, and/or JNK) and Akt is dephosphorylated (PP2A). Akt/PKB, protein kinase B; aPKCζ, atypical protein kinase C zeta; DAG, diacylglycerol; IKK, nuclear factor kappa-B kinase; IRS-1, insulin receptor substrate 1; JNK, c-Jun NH2-terminal kinase; PDK, phosphoinositide-dependent protein kinase; PI3K, phosphatidylinositol 3-kinase; PP2A, serine/threonine-protein phosphatase 2A activator.

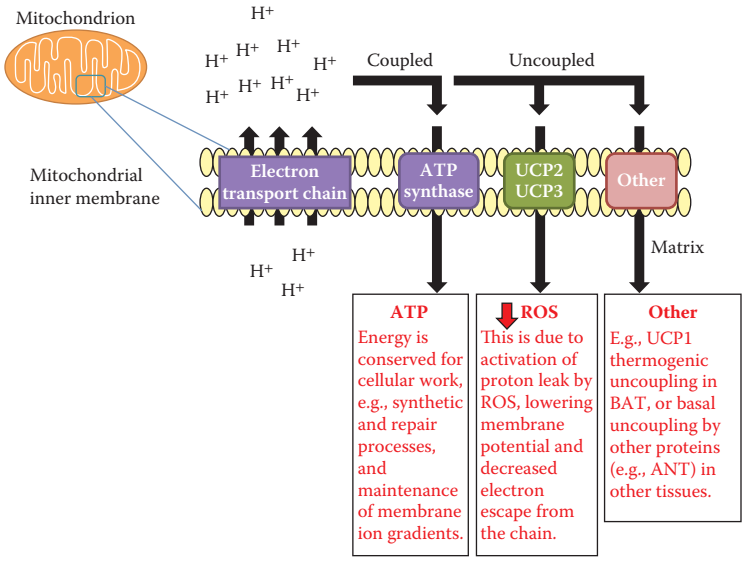

FIGURE 23.1 Coupled and uncoupled oxidative phosphorylation: mitochondria transduce energy, ultimately from dietary sources, to adenosine 5′-triphospate (ATP). Most of a cell's ATP is produced through the process of oxidative phosphorylation, which takes place in the mitochondria of cells. ATP is produced when protons return to the mitochondrial matrix, down their concentration gradient, through ATP synthase. The proton gradient is part of the electrochemical gradient across the mitochondrial inner membrane that is used to drive ATP synthase. ATP is then used to support cellular work. When the need for ATP is low (e.g., when a muscle cell is resting), or when there is a need for thermogenesis in brown adipose tissue (BAT), or when reactive oxygen species trigger uncoupling protein 2 (UCP2) and uncoupling protein 3 (UCP3) proton leaks, protons return to the matrix bypassing ATP synthase. Thus, through uncoupling the energy in the proton gradient is not captured in a form of energy that can be used by cells, and the efficiency of energy transduction from dietary energy to cellular ATP is decreased.

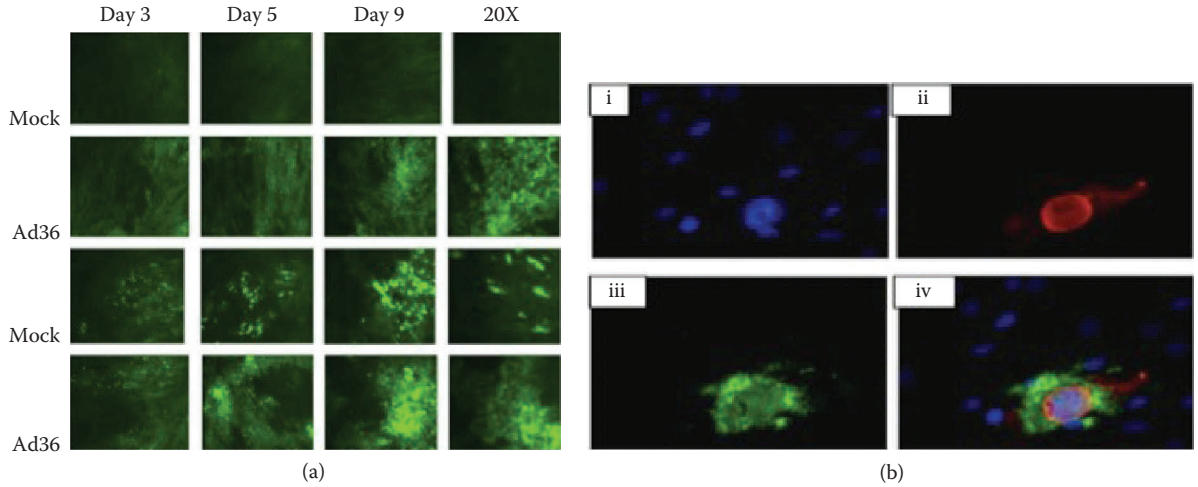

FIGURE 27.3 Lipid accumulation following human adenovirus-36 (Ad36) infection in human adipose–derived stem cells. (a) Lipid accumulation in human adipose tissue–derived stem cells (hASC) after mock or Ad36 infection (3.8 plaque-forming units [PFU]/cell), with (bottom 2 rows) or without (top 2 rows) methyl isobutyl xanthine, dexamethasone, and insulin (MDI). Representative images of lipid-specific boron-dipyrromethene (BODIPY) staining in hASC following Ad36 infection with or without MDI. (b) Several immunochemical stains of the same 40 × field showing that only the Ad36-infected cell accumulates lipid. (i) 4',6-diamidino-2-phenylindole (DAPI) staining of nuclei, (ii) staining of Ad36 hexon protein highlighting one infected cell, (iii) BODIPY staining of lipid in Ad36-infected cell, and (iv) composite image of i, ii, and iii. (Reprinted from Pasarica M et al., *Stem Cells*, 26, 969–78, 2008.).

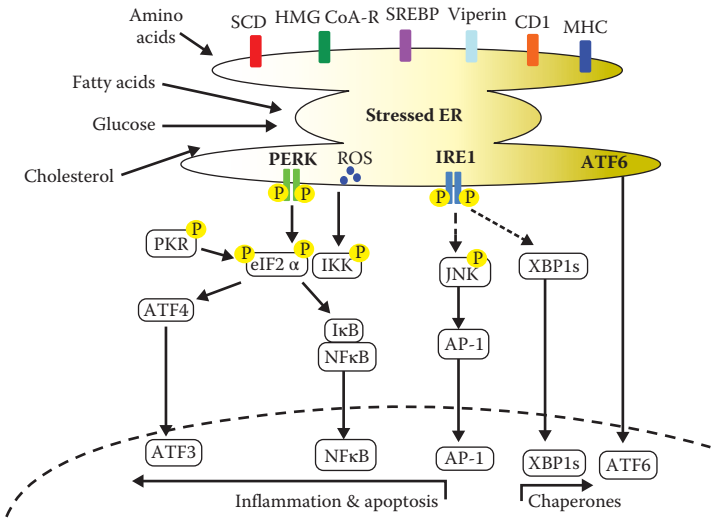

FIGURE 52.3 The endoplasmic reticulum as a potential hub for metabolism, energy, immune, and stress responses. In addition to its well-known roles in protein quality control, folding, secretion, and calcium homeostasis, the endoplasmic reticulum (ER) also plays a critical role in lipid metabolism and lipid droplet formation through harboring central players such as the cholesterol-sensitive transcription factor sterol regulatory element-binding protein-1 (SREBP-1); the key regulating enzyme in cholesterol synthesis 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoAR); and in fatty acid desaturation through stearoyl CoA reductase (SCD1) on its membranes. Studies have now shown that lipid droplets are released from specialized regions of the ER and regulated by proteins like viperin, also associated with ER membranes. Many links also exist between ER responses and glucose metabolism (not depicted here). These myriads of functions are maintained by an adaptive stress response system that emanates from ER membranes, known as the unfolded protein response (UPR). Various stressful situations including accumulation of unfolded proteins, hypoxia, toxins, and acute or chronic excess of nutrients (including fatty acids and free cholesterol) or their deficiency (such as glucose) can activate the UPR. Upon induction, the UPR engages three signaling branches initiated by the pancreatic ER kinase (PERK), inositol-requiring transmembrane kinase/endonuclease 1 (IRE1), and activating transcription factor 6 (ATF6). The major target of the IRE1 endoribonuclease activity is the X-box binding protein 1 (XBP1), which together with the ATF6 branch mounts a complex transcriptional program vital for the execution of UPR. The UPR can also engage inflammatory cascades such as JNK and the IKK–NF-κB pathway, leading to the production of cyclooxygeneases and other pro-inflammatory mediators. Induction of the double-stranded RNA-dependent protein kinase (PKR) can activate the inflammasome, leading to pro-inflammatory responses, and interfere with insulin action.

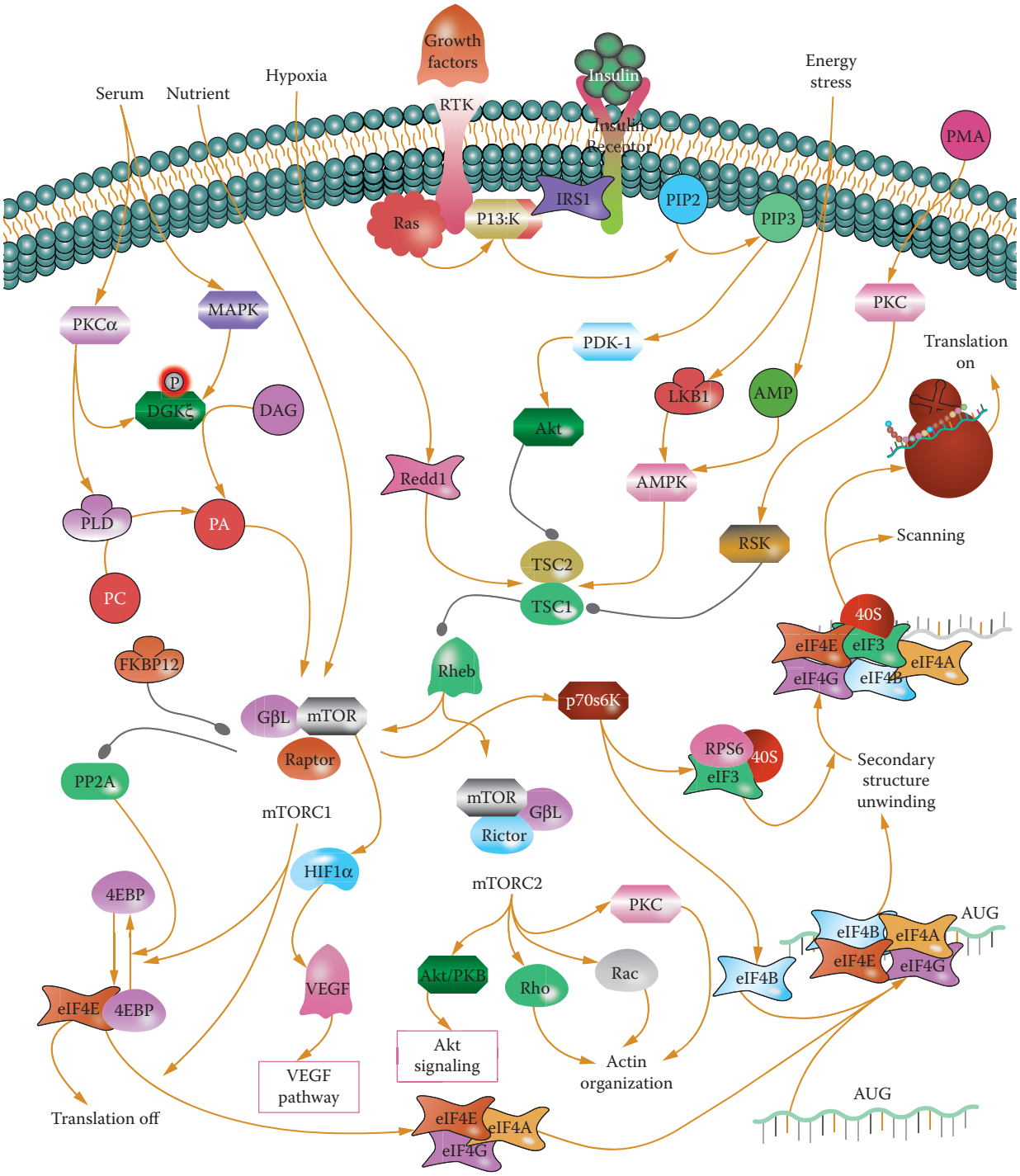

FIGURE 54.1 Mammalian target of rapamycin (mTOR) pathway: VEGF, vascular endothelial growth factor. (Kind permission of Qiagen Company.)

Medicine

Volume 1 - Third Edition

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