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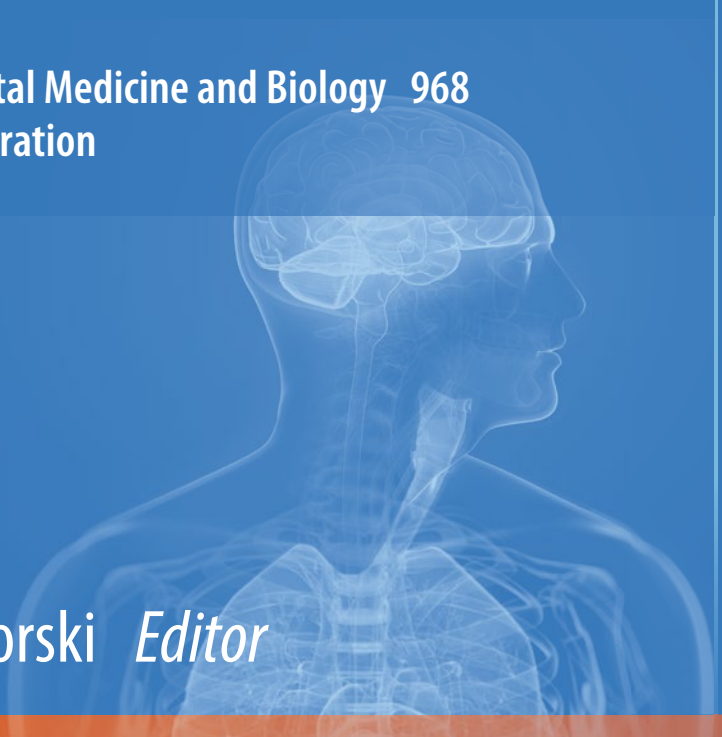

Mieczyslaw Pokorski *Editor*

Influenza and Respiratory Care

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Preface

The book series *Neuroscience and Respiration* presents contributions by expert researchers and clinicians in the multidisciplinary areas of medical research and clinical practice. Particular attention is foused on pulmonary disorders as the respiratory tract is upfront at the first line of defense of the organism against pathogens and environmental or other sources of toxic or disease causing effects. The articles provide timely overviews of contentious issues or recent advances in the diagnosis, classification, and treatment of the entire range of diseases and disorders, both acute and chronic. The texts are thought as a merger of basic and clinical research dealing with biomedicine at both molecular and functional levels, and with the interactive relationship between respiration and other neurobiological systems such as cardiovascular function, immunogenicity, endocrinology and humoral regulation, or the mind-to-body connection. The authors focus on the modern diagnostic techniques and the leading-edge therapeutic concepts, methodologies, and innovative treatments. The action and pharmacology of existing drugs and the development and evaluation of new agents are the heady area of research. Practical, data-driven options to manage patients will be considered. New research is presented regarding older drugs, performed from a modern perspective or from a different pharmacotherapeutic angle. The introduction of new drugs and treatment approaches in both adults and children also is discussed.

Body functions, including lung ventilation and its regulation, are ultimately driven by the brain. However, neuropsychological aspects of disorders are still mostly a matter of conjecture. After decades of misunderstanding and neglect, emotions have been rediscovered as a powerful modifier or even the probable cause of various somatic disorders. Today, the link between stress and health is undeniable. Scientists accept a powerful psychological connection that can directly affect our quality of life and health span. Psychological approaches, by decreasing stress, can play a major role in the development and therapy of diseases.

Neuromolecular and carcinogenetic aspects relating to gene polymorphism and epigenesis, involving both heritable changes in the nucleotide sequence and functionally relevant changes to the genome that do not involve a change in the nucleotide sequence, leading to disorders will also be tackled. Clinical advances stemming from molecular and biochemical research are but possible if the research findings are translated into diagnostic tools,

therapeutic procedures, and education, effectively reaching physicians and patients. All that cannot be achieved without a multidisciplinary, collaborative, bench-to-bedside approach involving both researchers and clinicians. The role of science in shaping medical knowledge and transforming it into practical care is undeniable.

Concerning the respiratory disorders, their societal and economic burden has been on the rise worldwide leading to disabilities and shortening of life span. COPD alone causes more than three million deaths globally each year. Concerted efforts are required to improve this situation, and part of those efforts are gaining insights into the underlying mechanisms of disease and staying abreast with the latest developments in diagnosis and treatment regimens. It is hoped that the articles published in this series will assume a leading position as a source of information on interdisciplinary medical research advancements, addressing the needs of medical professionals and allied health care workers, and become a source of reference and inspiration for future research ideas.

I would like to express my deep gratitude to Mr. Paul Roos, Ms. Tanja Koppejan, and Ms. Cynthia Kroonen of Springer SBM NL for their genuine interest in making this scientific endeavor come through and in the expert management of the production of this novel book series.

Mieczyslaw Pokorski

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Rapid Influenza Diagnostic Tests Improve Suitability of Antiviral Treatment in Hospitalized Children

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Abstract

Influenza may have a complicated course in young children. The aim of the study was to analyze the suitability of influenza treatment among children younger than 5 years hospitalized due to an influenza-like illness. We conducted a comparison of the treatment among children hospitalized in two consecutive years: 2015, when no rapid influenza diagnostic tests (RIDT) were in use, and 2016, when RIDT were implemented into a routine practice in the pediatric ward. In both seasons, nasopharyngeal swabs were collected and examined with real time qRT-PCR. In the 2015 season, influenza was diagnosed in 15/52 (28 %) children and none of them received oseltamivir, while 14/15 (93 %) patients received antibiotics. In the 2016 season, influenza was diagnosed in 11/63 (17 %) children, 7/11 (64 %) of them received oseltamivir and another 7/11 (64 %) received antibiotics. In four cases antibiotics overlapped oseltamivir. These differences in the use of oseltamivir and antibiotics were statistically significant ($p < 0.05$). We conclude that the implementation of RIDT improves the suitability of influenza treatment and decreases the frequency of antibiotic therapy. RIDT should be available in pediatric departments to optimize influenza treatment.

Keywords

Antibiotic Therapy • Antiviral Treatment • Children • Hospitalization • Influenza-Like Illness • Neuraminidase Inhibitors

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1 Introduction

Influenza viruses are responsible for serious acute respiratory tract infections in children, being a leading cause of hospitalization (Jain et al. 2015; Nair et al. 2011). The identification of influenza virus is important for disease management, as the presence of infection may require a specific antiviral treatment (e.g., oseltamivir) and hospital containment measures. The current gold standard for the detection of influenza infection is a real time reverse transcriptase polymerase chain reaction (qRT-PCR) (Kumar and Henrickson 2012). This method is not available in all hospitals, as it requires a molecular diagnostic laboratory with a specialized personnel and equipment. Instead, rapid antigen diagnostic test (RIDT) are used as these assays are easier and few times less expensive to perform and less time-consuming (Chartrand et al. 2012; WHO 2005). However, the result of RIDT may depend on a number of factors including: an interval between onset of disease and sampling, quality and type of specimen, age of a patient, and the epidemiological condition, i.e., prevalence of the disease (Cho et al. 2013; Nitsch-Osuch et al. 2013a). In Poland, there are few data describing the influence of the rapid diagnosis of influenza on the decisions regarding treatment. Previously published results indicate that RIDT may decrease the use of antibiotics in children with influenza, but the observations are related to outpatient settings, not hospitals (Nitsch-Osuch et al. 2013b). It has also been shown that antibiotics are overused in children with influenza (Nitsch-Osuch et al. 2016). The aim of the present study was to describe the influence of the use of RIDT on the suitability of influenza treatment with the specific antiviral oseltamivir.

2 Methods

The study was conducted at the Pediatric Ward of St. Family Hospital in Warsaw, Poland and it was approved by a local Ethics Committee. The ward consists of 20 beds, the majority of patients are infants and children younger than 5 years of age, and the main reason of hospitalizations is a severe acute upper and lower respiratory tract infection (50–53 % of admissions). The underlying reasons for hospitalization are presented in Table 1.

We compared treatment of the laboratory confirmed influenza in children aged 0–60 months. The children were hospitalized due to the presence of influenza-like illness according to the CDC criteria, such as fever > 37.8 °C, cough, or sore throat, during the two consecutive years of 2015 and 2016, from January 1 to March 31 each. In the first year, when RIDT was unavailable, 52 patients fulfilled the inclusion criteria and the retrospective diagnosis of influenza was based on the result of the real time qRT-PCR. In the second year, 63 patients were enrolled into study and all of them were tested with both real time qRT-PCR and RIDT (bioNexia Influenza A+B, bioMerieux; Marcy-l'Étoile, France) according to manufacturer's recommendations. Each year, nasopharyngeal swabs were taken from children by a trained nurse, transported to the laboratory at the National Influenza Center in Warsaw, Poland, collected and tested. The results were obtained in a retrospective manner, after the patient had been discharged from the hospital. The detailed methodology of the real time qRT-PCR was described previously (Nitsch-Osuch et al. 2013b). The demographic characteristics of children included into the study are shown in the

Table 1 Distinguishing features of admissions to Pediatric Ward

Year[a]	2015	2016
Number of hospital admissions	336	331
Number of person-days	498	518
Reasons for admission (%):		
pneumonia	15	14
bronchitis/bronchiolitis	27	24
upper respiratory tract infection	11	12
gastroenterocolitis	22	32
urinary tract infection	9	9
others	16	9

[a]From January 1 to March 31

Table 2 Demographic characteristics of patients

Year[a]	2015	2016
Number of patients (n)	52	63
Gender (n, % of patients)		
boys	29 (56)	43 (69)
girls	23 (44)	20 (31)
Age (n, % of patients)		
≤ 24 months	35 (67 %)	46 (73 %)
25–60 months	17 (33 %)	17 (27 %)

[a]From January 1 to March 31

Table 3 Demographics of patients with influenza

Year[a]	2015	2016
Number of patients (n)	(n = 15)	(n = 11)
Gender (n, % of patients):		
boys	7 (47)	5 (45)
girls	8 (53)	6 (55)
Age (n, % of patients):		
≤ 24 months	10 (67)	3 (27)
25–60 months	5 (33)	8 (73)

[a]From January 1 to March 31

Table 2. There were no significant differences between the patients of the two years. We compared the proportion of patients who received a causative treatment of influenza with oseltamivir and/or antibiotic treatment in the second year when RIDT was available with the antibiotic treatment in the first year under consideration when RIDT was not yet available. The statistical analysis for nominal variables was performed with the chi-squared test; when a sample of patients was too small, Fisher's exact test was used. The level of significance was defined as $\alpha = 0.05$. The calculations were conducted with a medical statistical calculator available at the website www.medcal3000.com.

3 Results

In the 2015 epidemic season when all cases of influenza were recognized retrospectively by real time qRT-PCR, the number of patients with confirmed influenza was 15/52; which amounts to the attack rate of 28 %. There were 2 cases of influenza type B virus, lineage Yamagata, and 13 cases of influenza type A(H3N2) virus. In the following season when influenza was diagnosed with both RIDT and real time qRT-PCR, the number of patients with confirmed influenza was 11/63, which amounts to the attack rate of 17 %. There were two cases of influenza type B, lineage Victoria, and nine cases of influenza type A H1N1 pdm09 virus. The diagnosis of influenza was based on a positive result of RIDT and a positive result of the real time qRT-PCR in 7/11 (64 %) patients, while a false negative results of the RIDT with a positive real time qRT-PCR test were obtained in 4/11 (36 %) patients. The demographic characteristics of children with influenza are presented in Table 3.

In the 2015 season, when RIDT was not available, none of the children with influenza was treated with oseltamivir, while in the 2016 season, when RIDT became available, 7/11 (64 %) patients with influenza received the antiviral treatment (Table 4). This difference in the administration of treatment with oseltamivir in two consecutive years was significant ($p < 0.05$). Antibiotic therapy in children with influenza was statistically more frequently administrated when RIDT was not yet available compared with the time when it was (93 % vs. 64 %, respectively; $p < 0.05$). Although laboratory confirmation of influenza was established, 3/7 (43 %) patients received both oseltamivir and antibiotics. Cefuroxime was co-administered in two cases and amoxicillin with clavulanate in one case due to the presence of clinical symptoms of pneumonia, confirmed by X-ray chest examination. The remaining four patients with confirmed influenza received antibiotics alone (Table 4).

4 Discussion

In the present study, attack rate of influenza among children hospitalized due to influenza-like illness varied from 17 to 28 %. The incidence of the disease was consistent with the literature data (Liu et al. 2015; Marcone et al. 2015). We also found that the implementation of RIDT into a routine practice for a diagnosis of influenza resulted in a more frequent use of the causal treatment with oseltamivir. Our results are

Table 4 Treatment of children with laboratory confirmed influenza in two consecutive years – oseltamivir vs. antibiotic therapy

Year[a]	2015	2016	p-value
RIDT	Unavailable	Available	
Number of children with influenza treated with oseltamivir	0	7/11	$p < 0.05$
Proportion of children with influenza who received oseltamivir	0 %	64 %	
Number of children with influenza treated with antibiotics	14[b]/15	7[c]/11	$p < 0.05$
Proportion of children with influenza treated with antibiotics	93 %	64 %	

[a]From January 1 to March 31
[b]10 courses of amoxicillin with clavulanate, 4 courses with cefuroxime
[c]4 courses of cefuroxime, 3 courses of amoxicillin with clavulanate

in agreement with those described by other researchers. Williams et al. (2016) have reported a rising trend in oseltamivir use among hospitalized children in a post-pandemic era (up to 82 % of pediatric patients with influenza). The prolonged hospital stay, associated with severe and complicated course of influenza, and early diagnosis within 48 hours of symptoms onset have been associated with higher odds of oseltamivir administration.

The use of RIDT contributed to a better diagnosis and more specific treatment of influenza in our patients. Generally, according to the Polish recommendations, treatment with oseltamivir is recommended for patients with a laboratory confirmed disease. However, the decision about starting antiviral treatment should not wait for laboratory results (Hryniewicz et al. 2016). The CDC recommendations for the use of neuraminidase inhibitors seem to be wider as the antiviral treatment is recommended as early as possible for any patient with a confirmed or suspected influenza who: a) is hospitalized; b) has severe, complicated, or progressive illness; or is at higher risk for influenza complications (CDC 2015). From this point of view, all our patients with influenza should have received oseltamivir treatment as all of them were hospitalized and the majority were younger than 24 months. Children aged less than 5 years are also considered at higher risk for complications from influenza, although, the highest risk is for those aged less than 2 years, with the highest hospitalization and death rates among infants aged less than 6 months (Lobo et al. 2014; Yu et al. 2011).

We conclude that our results provide arguments for the need of publication of more detailed recommendations regarding influenza treatment and better availability of antivirals in Poland, where only is oseltamivir, and not zanamivir, registered. Thus, access to the causative treatment of influenza is limited (Brydak and Nitsch-Osuch 2014). Further, oseltamivir is available only a capsule formulation. For infants and young children, a suspension must be prepared ex tempore at the hospital pharmacy. Such obstacle may result in some kind of unwillingness for oseltamivir administration on the part of physicians. A rapid confirmation of influenza could change this inaptitude. Clinical trials and observational data show that early administration of neuraminidase inhibitors can shorten the duration of fever and other symptoms, and may reduce the risk of complications from influenza such as otitis media, pneumonia, respiratory failure, or fever seizures (Esposito and Principi 2016; Yen 2016; Wang et al. 2012). The clinical benefit is greatest when antiviral treatment is administered within 48 hours of influenza onset. However, some studies suggest that antiviral treatment might still be beneficial in hospitalized patients when started up to 4 or 5 days after illness onset (Louie et al. 2013; Yu et al. 2011). An early diagnosis of influenza also provides a prompt implementation of isolation procedures if required (Vanhems et al. 2016).

Although in this study we demonstrate that the use of RIDT resulted in a better treatment outcome of influenza, the test has limitations as it may provide both false positive and false negative results (Moesker et al. 2016). A positive

result of RIDT in the typical epidemic season for the Northern Hemisphere, extending from the beginning of January till the end of March, may be regarded as the true diagnosis of the disease. The real time qRT-PCR method may be used for surveillance purposes as it identifies subtypes of influenza type A viruses and linages of influenza type B viruses (Lacroix et al. 2015). A negative result of RIDT in a child with influenza-like illness during the influenza season may be false negative and may require confirmation with a more sensitive method such as real time qRT-PCR (Chu et al. 2015). In this study, a group of 2/11 (18 %) children with a laboratory confirmed influenza had a negative result of RIDT and a positive result of real time qRT-PCR. Those children were not treated with oseltamivir; they received antibiotic therapy. On the other hand, two of the children who received oseltamivir due to a positive result of RIDT had negative results of real time qRT-PCR. Such a situation may have happened since the antiviral treatment was started promptly, e.g., on the afternoon of the day of obtaining a positive result of RIDT, while samples for real time qRT-PCR testing were transferred to the laboratory the next day. This indicates a need to perform RIDT and qRT-PCR in parallel without undue delay in hospitalized children with influenza-like illness to optimize diagnosis and treatment. In case of a negative result of qRT-PCR, unnecessary antiviral treatment may then be terminated.

Another benefit of the use of RIDT in our patients was less frequent administration of antibiotic courses among children with laboratory confirmed influenza. This finding is consistent with those of other authors (Lacroix et al. 2015). A beneficial effect of the use of RIDT has also been described in Polish children in the outpatient setting (Nitsch-Osuch et al. 2013a, b). Nowadays, it is essential to rationalize antibiotic therapy as the problem of multidrug resistant bacteria is on the rise worldwide (ECDC 2015). However, even after the implementation of RIDT into everyday practice, a high proportion of children with influenza still receive antibiotics. A question that should be asked is of whether the antibiotic courses were really necessary, when oseltamivir had been ordered. The overuse of antibiotics, namely amoxicillin with clavulanate or cefuroxime, in hospitalized children with influenza has been previously described (Nitsch-Osuch et al. 2016). Antibiotics are however indicated when typical for influenza complications develop such as pneumonia or otitis media. Ashdown et al. (2016) have demonstrated a diagnostic uncertainty and a wide variation in the way physicians prescribe antibiotics for children with influenza. A spate of clinical and non-clinical factors are involved in the commencement of antibiotic therapy, which should be considered in the elaboration of future guidelines.

The present observational study was prone to a selection bias due to unknown confounders as well as the information bias due to an unmasked assessment, a small number of patients enrolled into the study, and a retrospective character of influenza diagnosis established by real time qRT-PCR. On the other hand, our observations provide additional arguments that early influenza diagnosis by RIDT improves the suitability of antiviral treatment and favors a judicious use of antibiotics. Rapid diagnostic methods, including both RIDT and real time qRT-PCR, should be introduced into the hospital pediatric settings.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Co-infection with Influenza Viruses and Influenza-Like Virus During the 2015/2016 Epidemic Season

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Abstract

Concerning viral infection of the respiratory system, a single virus can cause a variety of clinical symptoms and the same set of symptoms can be caused by different viruses. Moreover, infection is often caused by a combination of viruses acting at the same time. The present study demonstrates, using multiplex RT-PCR and real-time qRT-PCR, that in the 2015/2016 influenza season, co-infections were confirmed in patients aged 1 month to 90 years. We found 73 co-infections involving influenza viruses, 17 involving influenza viruses and influenza-like viruses, and six involving influenza-like viruses. The first type of co-infections above mentioned was the most common, amounting to 51 cases, with type A and B viruses occurring simultaneously. There also were four cases of co-infections with influenza virus A/H1N1/pdm09 and A/H1N1/ subtypes and two cases with A/H1N1/pdm09 and A/H3N2/ subtypes. The 2015/2016 epidemic season was characterized by a higher number of confirmed co-infections compared with the previous seasons. Infections by more than one respiratory virus were most often found in children and in individuals aged over 65.

Keywords

Co-infections • Epidemic season • Influenza • Multiplex RT-PCR • Respiratory viruses • Viral infections

1 Introduction

Respiratory infections constitute a major public health problem due to a high incidence rate, mortality, and well-documented healthcare and economic burden (Brydak and Nitsch-Osuch 2014; Stefańska et al. 2013). Fifty to eighty

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percent of acute respiratory infections are viral ones (Nitsch-Osuch et al. 2015).

The multiplex RT-PCR method is a highly sensitive alternative to other diagnostic procedures (Templeton et al. 2004). It saves time and reagents necessary to test samples for the presence of genetic material of respiratory viruses, which also expedites the introduction of proper treatment (Stefańska et al. 2012). The methods enables to detect several co-infecting contagions during a single test. The most common respiratory viruses are influenza virus type A and B, respiratory syncytial virus, parainfluenza viruses type 1, 2, 3, and human rhinovirus, human metapneumovirus, adenovirus, and human coronavirus (Do et al. 2011).

Influenza is a disease which, due to its constant evolution, causes persistent epidemics and less frequently pandemics (Brydak 2014). Co-infections with influenza viruses may induce re-assortment between the viruses, leading to a more pathogenic subtype (Liu et al. 2010). In particular, co-infections with different subtypes of influenza A virus constitute a likely source of reassortants that can acquire unpredictable properties (Pajak et al. 2011). A sectional structure of the influenza virus genome brings about the variation of genotype and phenotype of the virus. When the host cell is infected with more than one strain, viruses equipped with a new set of genes may appear. Considering the essential role of co-infections in spread and severity of the disease, the goal of this study was to determine the frequency and a crisscross pattern of co-infections with influenza and influenza-like viruses.

2 Methods

2.1 Material

The study protocol was approved by an institutional Ethics Committee. In total, during the influenza season 2015/2016 in Poland 8542 samples from patients of all ages were tested. Swabs from the nose and throat and the washings from the bronchial tree (BALF) were taken. Specimens were tested in the Department of Influenza Research of the National Influenza Center in the National Institute of Public Health – National Institute of Hygiene and Voivodeship Sanitary Epidemiological Station in Poland. The samples prior to analysis were stored at −80 °C. Clinical specimens were collected from week 40 week of 2015 to week 34 of 2016 (October 1, 2015 – August 28, 2016).

2.2 Isolation of Viral RNA

RNA of respiratory viruses from clinical specimens were isolated using Maxwell 16 Viral Total Nucleic Acid Purification Kit (Promega Corporation, Madison, WI) in 200 µL sample suspended in PBS, according to the manufacturer's instructions. RNA was suspended in 50 µL RNase-free water.

2.3 Real-Time qRT-PCR

The tests were performed using quantitative polymerase chain reaction RT-PCR. The analysis was carried out in the Roche Light Cycler 2.0 system. The qRT-PCR reactions were performed in capillary tubes of 20 µL volume with 0.5 µM primers and 0.2 µM probe for each reaction. The probes and primers were obtained from the Influenza Reagent Resources (IRR) program operated by the Centers for Disease Control and Prevention (CDC 2016). The reaction mixture contained $MgSO_4$, reaction buffer, BSA, RNase free water, Super Script®III/platinum Taq mix, with the addition of 5 µL of RNA for each sample. A positive control consisted of RNA strains being components of the influenza vaccine for the season 2015/2016: A/California/7/2009 (H1N1pdm09), A/Switzerland/9715293/2013 (H3N2), B/Phuket/3073/2013, and a negative control was provided by RNase-free water. Before the start of amplification, viral RNA was rewritten to cDNA, using the reverse transcriptase enzyme at 50 °C for 30 min. Then, samples were analyzed according to the following scheme: initialization at 95 °C for 2 min and

45 cycles of amplification: denaturation at 95 °C for 15 s, annealing at 55 °C for 30 s, and extension at 72 °C for 2 min.

2.4 Conventional Multiplex RT-PCR

Samples were tested using an RV12 ACE Detection Kit (Seegene; Seoul, South Korea) that enables to detect such respiratory viruses as influenza type A and B, adenovirus (AdV), human respiratory syncytial virus A and B (RSV A and B), human coronavirus OC43 (hCoV OC43), human metapneumovirus (hMPV), rhinovirus A/B (RVA/B), human coronavirus 229/NL63 (hCoV 229/NL63), and parainfluenza type 1, 2 and 3 (PIV-1, PIV-2, PIV-3). Random hexamer-primed cDNA synthesis products were generated using the first strand cDNA synthesis kit (Fermentas; York, UK), according to the manufacturer's instructions. Each cDNA preparation was subjected to the RV12 PCR procedure according to the manufacturer's instructions (Seegene; Seoul, South Korea). The reaction products were detected using agarose gel electrophoresis.

3 Results

In the influenza season 2015/2016 73, -co-infections with influenza viruses were reported, as shown in Table 1.

The following types of co-infections were confirmed: subtype A/H1N1/pdm09 with subtype A/H1N1/ (4 cases), subtype A/H1N1/pdm09 and subtype A/H3N2/ (2 cases), subtype A/H1N1/ and influenza virus B type (1 case), subtype A/H1N1/pdm09 and influenza type B (15 cases), and co-infection of unsubtyped type A with type B virus (51 cases).

Co-infections were reported in people of all ages, from month 1 to 90 years of age. Most co-infections caused by influenza viruses were reported among children up to 4 years of age (22 cases), in the other age-groups the number of co-infections was lower: 5–9 years – 18 cases, 10–14 years – 5 cases, 15–25 years – 3 cases,

Table 1 Influenza co-infections during the 2015/2016 epidemic season

	Age (n)
Influenza type A viruses	
A/H1N1/pdm09 + A/H1N1/	1 yr (1)
A/H1N1/pdm09 + A/H1N1/	4 yr (1)
A/H1N1/pdm09 + A/H3N2/	5 yr (1)
A/H1N1/pdm09 + A/H1N1/	46 yr (1)
A/H1N1/pdm09 + A/H3N2/	63 yr (1)
A/H1N1/pdm09 + A/H1N1/	65 yr (1)
Influenza type A + B	
A/H1N1/pdm09 + B	1 mo (1)
A/H1N1/pdm09 + B	1 yr (2)
A/H1N1/pdm09 + B	2 yr (2)
A/H1N1/pdm09 + B	7 yr (1)
A/H1N1/pdm09 + B	9 yr (1)
A/H1N1/pdm09 + B	12 yr (2)
A/H1N1/pdm09 + B	29 yr (1)
A/H1N1/pdm09 + B	34 yr (1)
A/H1N1/pdm09 + B	49 yr (1)
A/H1N1/ + B	65 yr (1)
A/H1N1/pdm09 + B	67 yr (1)
A/H1N1/pdm09 + B	71 yr (1)
A/H1N1/pdm09 + B	75 yr (1)
A/H1N1/pdm09 + B	82 yr (1)
A/H1N1/pdm09 + B	90 yr (1)
Unsubtyped influenza virus type A + B	
A + B	1 yr (6)
A + B	2 yr (8)
A + B	3 yr (1)
A + B	4 yr (1)
A + B	5 yr (4)
A + B	6 yr (1)
A + B	7 yr (7)
A + B	8 yr (2)
A + B	9 yr (2)
A + B	10 yr (1)
A + B	11 yr (1)
A + B	13 yr (1)
A + B	17 yr (1)
A + B	22 yr (1)
A + B	25 yr (1)
A + B	30 yr (1)
A + B	51 yr (1)
A + B	52 yr (1)
A + B	55 yr (1)
A + B	57 yr (1)
A + B	62 yr (1)
A + B	64 yr (1)
A + B	71 yr (2)
A + B	74 yr (3)
A + B	84 yr (1)

mo months of age, *yr* years of age

26–44 years – 3 cases, 45–64 years – 9 cases, and ≥ 65 years of age – 13 cases (Table 1).

In the epidemic season 2015/2016 co-infections between influenza viruses and influenza-like viruses and among influenza-like viruses were noted, as shown in Table 2. Seventeen cases co-infections with influenza and influenza-like viruses were recorded. The following types of co-infections were confirmed: subtype A/H1N1/pdm09 and RSV (5 cases), A/H1N1/pdm09 and RSV and RV A/B (3 cases), A/H1N1/pdm09 with influenza type B virus and RSV (1 case), A/H1N1/pdm09 and hCoV OC43 (2 cases), A/H1N1/pdm09 and influenza type B virus and hCoV OC43 (1 case), A/H1N1/pdm09 and influenza type B virus, hMPV and RSV (1 case), influenza virus type A and RSV (2 cases), influenza virus type A and hCoV OC43 (1 case), and influenza virus type A with RV A/B (1 case). Furthermore, six co-infections of influenza-like viruses were confirmed: RSV and hCoV 229/NL63 (2 cases), RSV and RVA/B (1 case), RSV and PIV-1 (1 case), AdV and hCoV 229/NL63 (1 case), hCoV 229/NL63, and RSV and PIV-2 (1 case) (Table 2).

Concerning the regional distribution of co-infections, most of those caused by another influenza virus were observed in the provinces of Mazovia (39 cases) and Lesser-Poland (25 cases), co-infections with more than one influenza virus were noted in Sub-Carpathian (3 cases), Lower-Silesia (2 cases), and single cases in Kuyavian-Pomeranian, Silesia, and Lublin provinces (Table 3).

Co-infections of subtype A/H1N1/pdm09 with A/H1N1/, subtype A/H1N1/pdm09 with A/H3N2/, and A/H1N1/ with influenza B virus were confirmed only in the province of Mazovia (4, 2, 1 cases, respectively). Co-infections of subtype A/H1N1/pdm09 with influenza B virus were reported in Mazovia (8 cases), Sub-Carpathian, Lesser-Poland (in 2 cases), Lower-Silesia, Kuyavian-Pomeranian, and Lublin provinces (1 case each). The most frequently confirmed co-infection was a combination of infection with influenza virus type A and B, with the most cases reported in Mazovia (25) and Lesser-Poland Province (23). Moreover, in Sub-Carpathian, Silesia and Lower-Silesia Provinces one case was confirmed per each region (Table 3).

4 Discussion

The 2015/2016 epidemic season was dominated by co-infections of unsubtyped influenza A and B virus (51 cases), reported among people from 1 to 84 years of age. There were also 15 cases of subtype A/H1N1/pdm09 and influenza virus type B co-infections. Moreover, there were detected single cases of co-infections of subtype A/H1N1/ with influenza virus type B (65 years of age) and of subtype A/H1N1/pdm09 with A/H3N2/ (63 and 5 years of age). There also were four confirmed cases of co-infections between subtypes A/H1N1/pdm09 and A/H1N1/ among children up to 4 years of age and adults above 46 years of age.

Co-infections of influenza viruses with influenza-like viruses and co-infections among influenza-like viruses were reported only in children up to 11 years of age. Here, the following co-infection were detected: subtype A/H1N1/pdm09 with influenza type B virus, hMPV, and RSV (1.5 years of age). There were also four cases of co-infections with three respiratory viruses: three cases of co-infections with subtype A/H1N1/pdm09 and RSV and RV A/B, and one case of co-infection with subtype A/H1N1/pdm09, influenza type B virus and hCoV OC43 (Table 2).

In the 2015/2016 epidemic season, there was a higher number of confirmed co-infections with influenza and respiratory influenza-like viruses, compared with previous seasons. In the 2012/2013 season, co-infections were as follows: ten of subtype A/H1N1/pdm09 with A/H3N2/ and 8 of A/H3N2/ with type B virus (Czarkowski et al. 2014). In the 2013/2014 season, co-infections were as follows: two of subtype A/H1N1/pdm09 with A/H3N2/, seven of influenza with influenza-like viruses (two of influenza type A virus, RSV A virus, and RV A/B virus in one-day old and one-month-old children each),

Table 2 Influenza and influenza-like viruses co-infections during the 2015/2016 epidemic season

Co-infections	Age (n)
Influenza and influenza like viruses	
A/H1N1/pdm09 + RSV + rhinovirus	1 mo (1)
A/H1N1/pdm09 + B + RSV	1 mo (1)
Unsubtyped A + RSV	3 mo (1)
A/H1N1/pdm09 + RSV	6 mo (1)
A/H1N1/pdm09 + coronavirus OC43	1 yr (1)
A/H1N1/pdm09 + RSV	1 yr (2)
Unsubtyped A + rhinovirus	1 yr (1)
A/H1N1/pdm09 + B + metapneumovirus + RSV	1.5 yr (1)
A/H1N1/pdm09 + RSV	2 yr (2)
A/H1N1/pdm09 + RSV + rhinovirus	2 yr (2)
Unsubtyped A + coronavirus OC43	2 yr (1)
Unsubtyped A + RSV	3.5 yr (1)
A/H1N1/pdm09 + B + coronavirus OC43	9 yr (1)
A/H1N1/pdm09 + coronavirus OC43	11 yr (1)
Influenza-like viruses	
RSV + hCoV 229	1 mo (2)
RSV + RV A/B	3 mo (1)
RSV + PIV-1	16 mo (1)
AdV + hCoV 229	2 yr (1)
RSV + hCoV 229 + PIV-2	2 yr (1)

mo months of age, *yr* years of age, *RSV A* respiratory syncytial virus A, *hCoV 229* human coronavirus 229, *PIV 1* parainfluenzavirus 1, *AdV* adenovirus, *RV A/B* rhinovirus A/B

Table 3 Influenza co-infections in voivodeships of Poland during the 2015/2016 epidemic season

	Voivodeships							
Co-infections	Masovian	Sub-Carpathian	Lesser-Poland	Lower-Silesian	Kuyavian-Pomeranian	Silesian	Lublin	Total
A/H1N1/ pdm09 + A/H1N1/	4	0	0	0	0	0	0	4
A/H1N1/ pdm09 + A/H3N2/	2	0	0	0	0	0	0	2
A/H1N1/ pdm09 + B	8	2	2	1	1	0	1	15
A/H1N1/ + B	1	0	0	0	0	0	0	1
A + B	25	1	23	1	0	1	0	51
Total	40	3	25	2	1	1	1	73

and three of influenza-like viruses (Bednarska et al. 2015). In the 2014/2015 season, in a framework of the I-MOVE (Influenza Monitoring of Vaccine Effectiveness) program, the following co-infections were detected: seven of subtype A/H1N1/pdm09 with type B virus and eight of subtype A/H3N2/ with type B virus. In that last season, in addition, one co-infection of influenza viruses and four of influenza viruses with influenza-like viruses were noted in children under 14 years of age (Hallmann-Szelińska et al. 2016). A significant increase in the number of infections with more than one respiratory virus in the 2015/2016 season could be associated with a higher number of samples tested (8542 samples) compared with the two preceding seasons (2479 and 2416 samples, respectively) (Bednarska et al. 2016; Bednarska et al. 2015). Nonetheless, influenza viruses constantly evolve, undergoing antigenic changes, which provides

them the ability to elude the host immune response system (Webster et al. 2013).

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Influenza and Influenza-like Viruses in Children in the Epidemic Season 2015/2016 in Poland

K. Cieślak, K. Szymański, D. Kowalczyk, and L.B. Brydak

Abstract

Influenza is an infectious disease caused by influenza A and B viruses. Children are the group which is the most exposed to influenza and influenza-like infections. They are considered as carriers of influenza infections in the population. In the epidemic season 2015/2016 more than 8000 samples were tested, of which over 30 % specimens were collected from patients aged 0–14 years. In 42.3 % cases the influenza or influenza-like viruses were confirmed. The most common subtype was A/H1N1/pdm09. Analysis of positive specimens was categorized into three smaller groups 0–4, 5–9, 10–14. Differences in the frequency of virus detections in younger age groups appeared. This study has shown that children are a very important group in the spread of the influenza virus in the population. A higher percentage of vaccinated children would decrease the number of infected patients in the whole population.

Keywords

Children • Influenza • Molecular Biology • Respiratory Virus • Vaccine • Virology

1 Introduction

Influenza is a disease caused by viruses A, B, and C belonging to the family Orthomyxoviridae. Cases of infection with influenza type C are much rarer. Therefore, laboratory diagnostics of influenza viruses are based on the confirmation of the presence of A and B influenza viruses (Brydak 2012). The main symptoms of influenza infection are sudden onset of disease, fever, chills, cough, sore throat, muscle pain, headache, and general malaise. The course of influenza infection in children is further characterized by symptoms from the gastrointestinal tract. It is worth noting that the symptoms above mentioned

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are not specific to influenza infection, but also for infections caused by other respiratory viruses (influenza-like viruses), which makes the diagnosis difficult (WHO 2014).

Children are a group particularly affected by influenza virus infection. Their immune system is not yet fully formed. For this reason, children are considered a higher risk group and vaccination from the 6th month of life up to 18 years of age is recommended (Hallmann-Szelińska et al. 2015). Despite the recommendation presented at the beginning of 2015, vaccination coverage rate in Polish children amounts to merely 0.73 % (Epimeld 2016). This is outrageously low compared to the percentage of vaccinated children in other European countries.

The basic methods of detection of influenza viruses from material taken from a patient belong to the molecular biology. A quick diagnostic confirmation of the virus, especially in children, enables a rapid implementation of antiviral treatment, and thus reduces the chance of serious complications from influenza, including fatal course of disease.

In the influenza season 2015/2016, five deaths of children under the age of 14 years caused by influenza were reported (NIPH-NIH 2016). Children are exposed not only to influenza infection, but also to influenza-like viruses, which circulate at the same time, and resemble the influenza infection. The most frequently diagnosed influenza-like viruses include parainfluenza 1, 2, 3, human respiratory syncytial viruses A and B (RSV A, RSV B), human corona viruses 229E/NL63 and OC42 (hCoV), human rhinovirus (RV), human adenovirus (ADV), and human metapneumovirus (hMPV) (Brydak 2008).

In the first 3 months of the epidemic season 2015/2016 (October–December, 2015) there were 406 more cases of confirmed and suspected cases of influenza in children up to 14 years of age compared with the preceding epidemic season in Poland (NIPH-NIH 2016). The increased number of influenza infection could augur a higher activity of the virus in the months ahead as well. In the present study, therefore, we seek to determine the overall activity of influenza and influenza-like viruses in children under 14 years of age in the epidemic season 2015/2016 in Poland.

2 Methods

2.1 Collection of Specimens

The study protocol was approved by an institutional Ethics Committee and the study was conducted in accordance with the principles for biomedical human research as set by the Declaration of Helsinki.

The material for testing were swabs taken from the nose and throat, collected within the framework the non-sentinel and sentinel influenza surveillance programs (WHO 2009). There were 3376 specimens taken from children up to 14 years of age tested in the epidemic season 2015/2016 in Poland. The specimens were analyzed at the Department of Influenza Research, National Influenza Centre at National Institute of Public Health – National Institute of Hygiene in Warsaw, Poland, as well as in 16 Voivodeship Sanitary Epidemiological Stations throughout the country. The National Influenza Centre served as the reference laboratory. The patients were divided into three age groups: 0–4, 5–9, 10–14 years, according to the division introduced in the reporting system updated in 2014 (Bednarska et al. 2016).

For RNA isolation, Maxwell 16 Total Viral Nucleic Acid Purification Kit (Promega Corporation; Madison, WI) was used. The isolation was performed according to the instructions of the manufacturer from 200 µl of sample suspended in saline and RNA was eluted using 50 µl of RNase-free water.

2.2 Real-Time RT- PCR

Real-time PCR was performed to confirm the genetic material of influenza virus type A and B and the viral subtypes, using Light Cycler 2.0 System (Roche Diagnostics; Rotkreuz, Switzerland). The reaction was performed in capillaries with a volume of 20 µl. Primers and

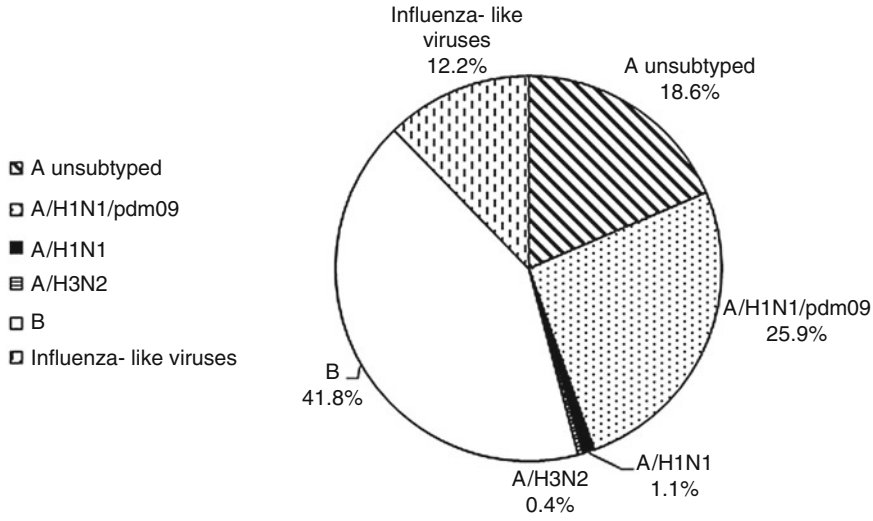

Fig. 1 Percentage of influenza virus and influenza-like virus infections in children aged 0–14 years age in the epidemic season 2015/2016

probes derived from the Influenza Reagent Resources (IRR) program operated by the Centers for Disease Control and Prevention (CDC) were used in the analysis. The reaction mixture included: buffer, BSA, $MgSO_4$, RNase-free water, and the SuperScript III/Platinum Taq Mix (Invitrogen Life Technologies – Thermo Fisher Scientific; Carlsband, CA). Five microliters of RNA were added to each capillary tube. The positive control for the reactions were viruses included in the vaccine for the epidemic season 2015/2016: A/California/7/2009 (H1N1) pdm09, A/Switzerland/9715293/2013, and B/Phuket/3073/2013. The negative control was the RNase-free water provided in the kit. Before the amplification process, cDNA was subjected to a reverse transcription (30 min 50 °C). The DNA was subjected to a process of initiation (1 cycle 95 °C for 2 min), followed by 45 cycles of amplification: denaturation at 95 °C for 15 s, annealing at 55 °C for 30 s, and elongation at 72 °C for 20 s.

2.3 Conventional Multiplex RT-PCR

To confirm the genetic material of influenza-like viruses, RT-PCR reaction using RV12 ACE detection kit (Seegene; Seul, South Korea) was performed. Influenza A virus, influenza B virus, ADV, RSV A, RSV B, hMPV, hCoV, PIV-1, PIV-2, PIV-3, and RV could be detected. Random hexamer-primed cDNA synthesis products were generated using the RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific; Carlsband, CA), according to the of manufacturer's instructions. Amplicons were detected by gel electrophoresis.

3 Results

There were 8542 specimens tested during the epidemic season 2015/2016, in Poland, of which 3376 were collected from children 0–14 years of age. In 1428 (42.3 %) out of the 3376 specimens the genetic material of influenza and influenza-like virus was detected. Influenza A virus was confirmed in 46.0 % of cases, influenza B in 41.8 % of cases, and influenza-like viruses in 12.2 % of cases (Fig. 1).

The dominant subtype of influenza A virus was A/H1N1/pdm09 (57 %), while 40 % of cases were represented by unsubtyped influenza A virus. The smallest group consisted of the A/H1N1/ and A/H3N2/ subtypes, which accounted for 2 % and 1 % respectively (Fig. 2).

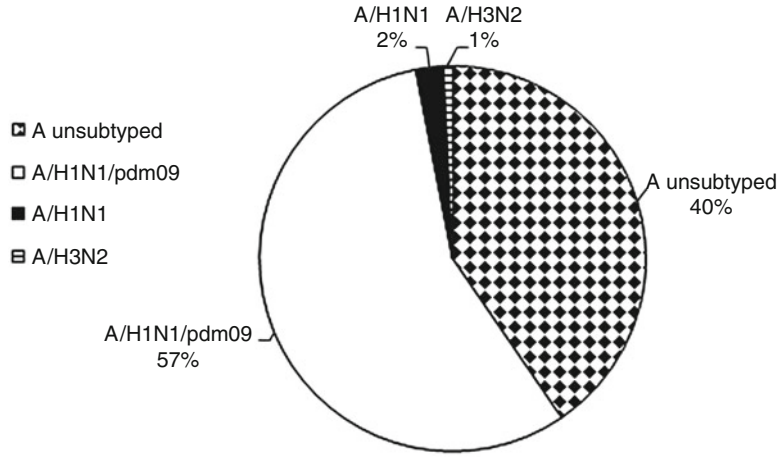

Fig. 2 Percentage of influenza A virus subtypes in children's infection in the age-group of 0–14 years in the epidemic season 2015/2016

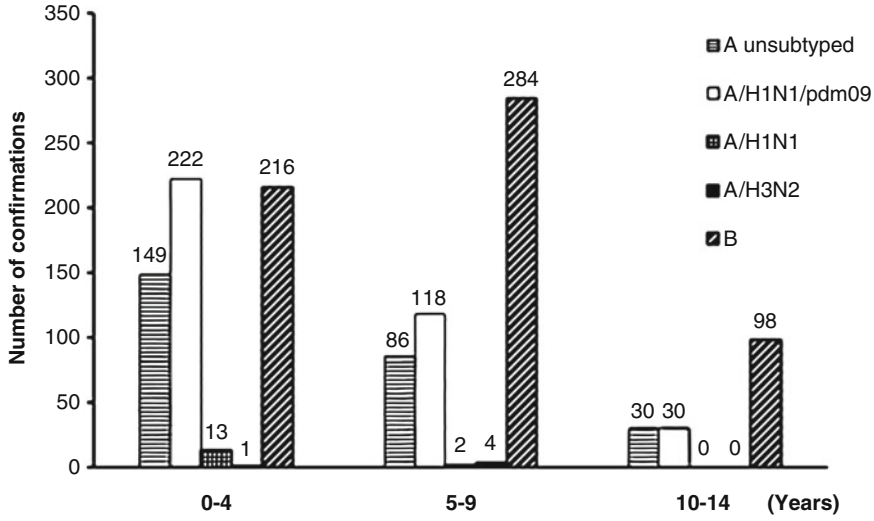

Fig. 3 Confirmed cases of the influenza virus infection in children aged 0–4, 5–9, and 10–14 years in the epidemic season 2015/2016

Confirmations of the influenza virus in the three junior age groups: 0–4, 5–9, 10–14 years of age demonstrate that in children of 0–4 years of age infections caused by both influenza B and A were common. The youngest patient in this age group was a 14-day old baby. The age group of 5–9 years of age was dominated by influenza B infections. The number of confirmations of infections with all subtypes of influenza A virus was distinctly lower in this group. In the age group of 10–14 years of age, the rate of influenza virus infections (158 cases) was markedly lower than the 601 cases in children aged 0–4 and the 494 cases in children aged 5–9. In this oldest age group infections with influenza B virus also dominated (Fig. 3).

Out of the genetically confirmed influenza-like viruses, RSV virus was detected exclusively in the group of 0–4 years of age. Other viruses were only sporadically present (Fig. 4).

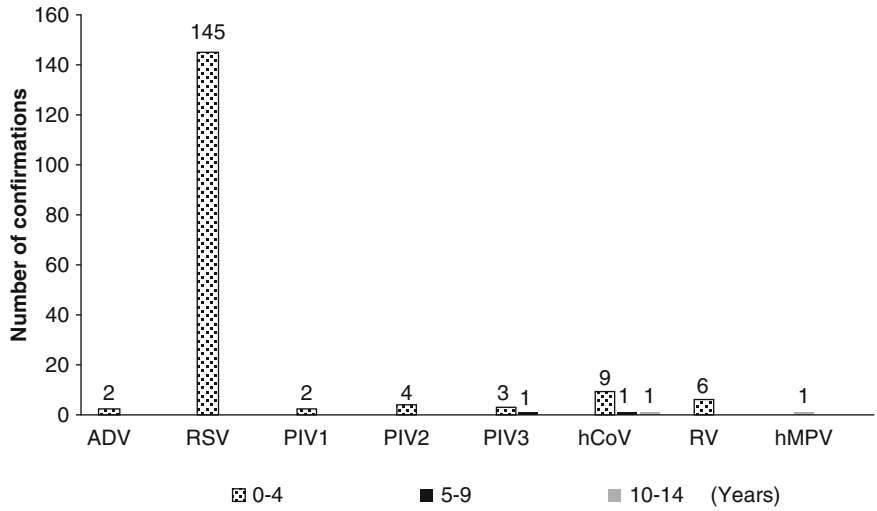

Fig. 4 Respiratory viruses detected in children aged 0–14 years in the epidemic season 2015/2016

4 Discussion

Influenza virus A predominated in the epidemic season 2015/2016 in Poland, with the dominant subtype A/H1N1/pdm09. Predomination of this virus in Poland is in line with similar observations noted in other European countries (ECDC 2016). The results also confirm the frequent presence of influenza and influenza-like viruses in children aged 0–14 years. In addition, in the youngest age-group of 0–4 years, the presence of also virus type B was confirmed, which shows that young children have a poorly developed immune system, making them more vulnerable to disease. Large gatherings of people contribute to influenza infections. Children due to daily stays in kindergartens and schools are particularly susceptible to infection and also are carriers of infection (Hallmann-Szelińska et al. 2015, 2016). The RSV virus is a leading cause of respiratory tract infections in infants. This infection usually runs a mild course in older children and adults, but is severe in infants who often require hospitalization (Brydak 2008).

Due to an extremely low percentage of vaccinated children, the number of cases of influenza steadily increases from season to season. This widely spreading tendency could be overcome through the implementation of vaccination against influenza from the sixth month of age, which is recommended by the Advisory Committee on Immunization Practices (ACIP) (CDC 2016) and by other associations, including the American Academy of Pediatrics (AAP 2016). Unfortunately, few parents undertake a decision to vaccinate their children, which in case of infection may end up with life-threatening complications. The same holds true for vaccination of pregnant women, which actually provides immunization for both mother and child. A confirmed case of influenza in a 14-day old child we observed in the present study pointedly shows that the mother was not vaccinated during pregnancy, although such vaccinations are recommended in Poland in the Preventive Vaccination Plan.

A study on the association between the number of vaccinated school children and influenza morbidity in the elderly, conducted in Japan in 2001, demonstrates that influenza vaccination of children has resulted in a reduction of morbidity and mortality in the elderly (Reichert et al. 2001). Children are a special segment of population that has a substantial impact on the spread of influenza virus. Therefore, a need for influenza vaccination in children should not be underestimated.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Influenza Vaccination Coverage Among Polish Patients with Chronic Diseases

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Abstract

Patients at a high-risk of severe influenza, because of their underlying health disorders, are recommended to receive a seasonal influenza vaccination. In Poland, influenza coverage rate in the general population is very low (3.4 %). However, there is little known about the coverage rate among high-risk patients. The aim of this study was to describe a general knowledge, perception, and influenza vaccination coverage rate among Polish patients with enhanced risk for influenza. We conducted a self-reported survey among 500 patients with chronic disorders: 120 pulmonary, 80 hemodialyzed, 100 thyroid cancer, and 200 cardiovascular patients. We found the following influenza vaccination coverage in the respective groups of patients: 58 % in pulmonary, 34 % in hemodialyzed, 32 % in cardiovascular, and 9 % in thyroid cancer patients. The difference between the coverage rate in pulmonary patients compared with the other risk groups was significant ($p < 0.05$). In pulmonary patients, the most important barrier for influenza vaccination was a lack of recommendations from healthcare workers, while a high awareness of influenza was the most powerful driver for vaccination ($p < 0.05$). We conclude that although the influenza vaccination coverage in Polish patients with chronic diseases is higher than that reported in the general population, this rate remains much below the recommended level and should be improved.

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Chronic disease • Influenza • Prevention • Prophylaxis • Risk group • Vaccination

1 Introduction

Globally, acute lower respiratory infections are the second most common cause of illness in all age groups and the third common cause of death (WHO 2015). Influenza is an underappreciated contributor to global mortality, current estimates indicate that seasonal influenza affects 5–10 % of the world's population resulting in between 250,000 and 500,000 deaths each year (WHO 2015). In addition to extreme ages, chronic medical conditions are considered important predisposing conditions for complicated infection, hospitalizations, and deaths from influenza (Grohskopf et al. 2016).

In the European Union countries about 25 % of the population belongs to one or both of the two major risk groups for influenza complications, i.e., the elderly and the presence of chronic medical conditions. A total of the population in question is estimated at around 124 million people, with 81 million falling into the 65 years or older bracket and 43 million constituting the chronic illness risk group (ECDC 2008).

Despite distinct recommendations, there are very few pieces of information regarding the influenza vaccination coverage among patients with chronic medical conditions in the European countries. In the 2011/2012 season, only did seven countries report this rate (the United Kingdom, Norway, Ireland, Germany, the Netherlands, France, and Portugal) indicating that the median coverage rate was 45.6 %, ranging from 28.0 to 80.2% (ECDC 2015). Poland does not report such data to the European Center for Diseases Control and Prevention (ECDC). In the present study, therefore, we found it of medical interest and utility to seek to determine the influenza vaccination coverage rate among Polish patients with chronic medical conditions.

2 Methods

The approval of a local institutional Bioethics Board was obtained prior to the execution of this study. We performed a cross-sectional descriptive study involving 500 patients older than 19 years of age with chronic diseases referred to a hospital with the following medical conditions: malignancy (100 patients with a thyroid cancer after surgical treatment and before a radio-iodine therapy), chronic cardiovascular diseases, except isolated hypertension (200 patients), chronic pulmonary disease (120 patients), and chronic renal insufficiency requiring hemodialysis treatment (80 patients). All patients were admitted to the corresponding tertiary level hospital wards of oncology, cardiology, and pulmonary diseases in Warsaw, Poland from October 1 to December 31, 2015. Influenza vaccination coverage rates, demographic data (age and gender), medical conditions, and immunization status against influenza were obtained from short interviews with each patient conducted by a nurse. The survey contained also questions regarding a general knowledge, perception of influenza vaccine, barriers and drive for influenza vaccination. The characteristics of patients included into the study are presented in Table 1. The vaccination coverage rate was defined as a proportion of vaccinated subjects in relation to the number of eligible patients. Data analysis was performed using a medical statistical calculator available on http://www.medcalc3000.com. The

Table 1 Characteristics of study patients

Patients with chronic disorders	Gender		Age	
	Male n (%)	Female n (%)	< 65 years n (%)	≥ 65 years n (%)
Cardiovascular (n = 200)[a]	94 (47)	106 (53)	134 (67)	66 (33)
Pulmonary (n = 120)[b]	67 (56)	53 (44)	110 (92)	10 (8)
Hemodialyzed (n = 80)	46 (58)	34 (42)	33 (42)	47 (58)
Thyroid cancer (n = 100)	44 (44)	56 (56)	75 (75)	25 (25)

[a]53 (26 %) patients with cardiac arrhythmias, 44 (22 %) patients with hypertension associated with other diseases, 41 (21 %) patients with cardiac insufficiency, 56 (28 %) patients with ischemic disease (including 32 patients after myocardial infarct), and 6 (3 %) patients with other cardiac diseases

[b]51 (42 %) patients with bronchial asthma, 56 (46 %) patients with chronic obstructive pulmonary disease (COPD), and 13 (12 %) with other chronic respiratory diseases

chi-squared test or exact Fisher test was used for nominal variables. Odds ratio (OR) and 95 % confidence intervals were calculated with the Wald or Fisher method. A p-value <0.05 was considered as an indicator of statistically significant results.

3 Results

The highest influenza vaccination rate in the 2015 autumn season was reported by patients with chronic pulmonary diseases (58 %), while the lowest one was among cancer patients (9 %) (Table 2). The difference between the influenza vaccination coverage in pulmonary patients and other chronically ill patients was significant ($p < 0.05$), while there was no such difference between the cardiovascular and hemodialyzed patients. The patients with thyroid cancer were less frequently vaccinated against influenza in the season compared with other chronically ill patients ($p < 0.05$) (Table 2a).

The patients with pulmonary diseases have the best awareness of being a risk group for a severe and complicated course of influenza (65 %), while hemodialysis and cancer patients have the worse perception of influenza infection (22 %) (Table 3). These differences were significant ($p < 0.05$) (Table 3a).

The influenza vaccine was found safe by more than half of hemodialyzed (64 %) and pulmonary patients (57 %) and by mere 29 % of cancer patients (Table 4). Cancer patients significantly more often declared a concern concerning the vaccine safety compared with the patients of the other risk groups ($p < 0.05$) (Table 4a).

The majority of patients with cardiovascular (52 %) and pulmonary disorders (54 %), and hemodialyzed patients (64 %) believe the influenza vaccine is effective, but only 39 % of cancer patients share this positive opinion (Table 5). Cancer patients compared with pulmonary and hemodialyzed patients were significantly more often unable to precisely answer the question regarding influenza vaccine effectiveness ($p < 0.05$) (Table 5a).

The most common barriers for influenza vaccination reported by high-risk patients were the following: low awareness of disease incidence and severity (54 % hemodialyzed patients), lack of recommendation from healthcare workers (21 % cardiovascular and 20 % cancer patients), concerns about vaccine effectiveness (22 % pulmonary patients), while concerns about vaccine safety and a lack of reimbursement were raised rarely (1–9 % responders) (Table 6). A lack of recommendation from healthcare workers was statistically less often reported by pulmonary patients compared with the other groups of high-risk patients ($p < 0.05$). A lack of reimbursement was not found as an important factor discouraging from vaccination in any of the patient group (Table 6a).

A high awareness of disease incidence and severity was the reason to take an influenza flu shot for 9–50 % patients, healthcare workers' recommendation was a strong driver for 25 %

Table 2 Influenza vaccination coverage among patients of high-risk for the illness

Patients with chronic disorders	Vaccinated in current season		
	Total – irrespective of previous vaccination; n (%)	Previous vaccination status	
		Occasionally vaccinated before; n (%)[a]	Never before vaccinated; n (%)
Cardiovascular (n = 200)	64 (32)	58 (29)	78 (39)
Pulmonary (n = 120)	69 (58)	5 (4)	46 (38)
Hemodialyzed (n = 80)	27 (34)	10 (12)	43 (54)
Thyroid cancer (n = 100)	9 (9)	37 (37)	54 (54)

[a]*Occasionally vaccinated,* vaccinated in previous seasons but not in the current season or vaccinated at least once in the past

Table 2a Disparities in the influenza vaccination coverage among patients of high-risk for the illness

	p-value	OR (95 %CI)
Irrespective of previous vaccination		
Pulmonary *vs*. cardiovascular patients	<0.05	2.93 (1.58 – 5.46)
Pulmonary *vs*. hemodialysis patients	<0.05	2.68 (1.45 – 4.96)
Pulmonary *vs*. thyroid cancer patients	<0.05	13.96 (5.98 – 33.51)
Cardiovascular *vs*. hemodialysis patients	ns	0.91 (0.48 – 1.71)
Cardiovascular *vs*. thyroid cancer patients	<0.05	4.75 (2.01 – 11.54)
Hemodialysis *vs*. thyroid cancer patients	<0.05	5.20 (2.21 – 12.59)
Occasionally vaccinated before		
Pulmonary *vs*. cardiovascular patients	<0.05	9.80 (3.09 – 34.54)
Pulmonary *vs*. hemodialysis patients	ns	0.30 (0.08 – 1.07)
Pulmonary *vs*. thyroid cancer patients	<0.05	0.07 (0.02 – 0.22)
Cardiovascular *vs*. hemodialysis patients	<0.05	2.90 (1.35 – 6.73)
Cardiovascular *vs*. thyroid cancer patients	ns	0.69 (0.36 – 1.31)
Hemodialysis *vs*. thyroid cancer patients	<0.05	0.23 (0.10 – 0.50)
Never before vaccinated		
Pulmonary *vs*. cardiovascular patients	ns	0.95 (0.52 – 1.76)
Pulmonary *vs*. hemodialysis patients	<0.05	0.52 (0.28 – 0.95)
Pulmonary *vs*. thyroid cancer patients	<0.05	0.52 (0.28 – 0.95)
Cardiovascular *vs*. hemodialysis patients	<0.05	0.54 (0.29 – 0.99)
Cardiovascular *vs*. thyroid cancer patients	<0.05	0.54 (0.29 – 0.99)
Hemodialysis *vs*. thyroid cancer patients	ns	1.00 (0.55 – 1.81)

ns non-significant, *OR* odds ratio, *CI* confidence intervals

of patients with pulmonary disorders (Table 7). A recommendation from medical staff was significantly more often reported as a driving force for vaccination by cardiovascular compared with hemodialysis or cancer patients ($p < 0.05$) (Table 7a). One third of patients of high-risk groups described their knowledge regarding influenza vaccination as sufficient (28–36 %) (Table 8). However, pulmonary patients quite often found themselves not enough educated or were unable to define their level of knowledge regarding influenza vaccination (Table 8a).

The main sources of knowledge on the influenza subject for patients of high-risk groups were the healthcare workers (24–60 %) and the internet (9–78 %). More in detail, the source of

Table 3 Patients' perception of being in a high-risk group for severe and complicated influenza

Patients with chronic disorders	Yes, my disease places me at risk for severe and complicated influenza; n (%)	No, my disease does not place me at risk for severe and complicated influenza; n (%)	I do not know if my disease places me at risk for severe and complicated influenza; n (%)
Cardiovascular (n = 200)	118 (59)	18 (9)	64 (32)
Pulmonary (n = 120)	78 (65)	18 (15)	24 (20)
Hemodialyzed (n = 80)	18 (22)	20 (25)	42 (53)
Thyroid cancer (n = 100)	47 (47)	11 (11)	42 (42)

Table 3a Disparities in the patients' perception of being in a high-risk group for severe and complicated influenza

	p-value	OR (95%CI)
Yes, my disease places me in a risk group for severe and complicated influenza		
Pulmonary *vs*. cardiovascular patients	ns	1.29 (0.70 – 2.38)
Pulmonary *vs*. hemodialysis patients	<0.05	7.42 (3.81 – 14.57)
Pulmonary *vs*. cancer patients	<0.05	2.09 (1.14 – 3.85)
Cardiovascular *vs*. hemodialysis patients	ns	1.69 (0.89 – 2.95)
Cardiovascular *vs*. cancer patients	ns	1.62 (0.89 – 2.95)
Hemodialysis *vs*. cancer patients	<0.05	0.31 (0.16 – 0.61)
No, my disease does not place me in a risk group for severe and complicated influenza		
Pulmonary *vs*. cardiovascular patients	ns	1.78 (0.68 – 4.69)
Pulmonary *vs*. hemodialysis patients	ns	0.52 (0.24 – 1.13)
Pulmonary *vs*. cancer patients	ns	1.42 (0.57 – 3.55)
Cardiovascular *vs*. hemodialysis patients	<0.05	0.29 (0.12 – 0.71)
Cardiovascular *vs*. cancer patients	ns	0.80 (0.28 – 2.20)
Hemodialysis *vs*. cancer patients	<0.05	2.69 (1.17 – 6.28)
I do not know if my disease places me in a risk group for severe and complicated influenza		
Pulmonary *vs*. cardiovascular patients	ns	0.53 (0.26 – 1.06)
Pulmonary *vs*. hemodialysis patients	<0.05	0.22 (0.11 – 0.43)
Pulmonary *vs*. cancer patients	<0.05	0.34 (0.17 – 0.67)
Cardiovascular *vs*. hemodialysis patients	ns	1.57 (0.86 – 2.89)
Cardiovascular *vs*. cancer patients	<0.05	2.45 (1.33 – 4.52)
Hemodialysis *vs*. cancer patients	ns	1.55 (0.85 – 2.83)

ns non-significant, *OR* odds ratio, *CI* confidence intervals

knowledge for patients with pulmonary disorders was friends and family (72 %) (Table 9). Pulmonary patients significantly more often indicated healthcare workers as the main source of knowledge and information regarding influenza vaccination compared with hemodialysis and cancer patients ($p < 0.05$). Such a difference was not reported between pulmonary and cardiovascular patients. The internet was also found more often as a possible source of information for pulmonary patients ($p < 0.05$) (Table 9a).

4 Discussion

In the present study, the influenza vaccination coverage in high-risk patients varied from 9 % in patients with thyroid cancer to 58 % in pulmonary patients. This rate was higher than that reported for the general population as during the season 2015/2016 season only was 3.4 % of the Polish population vaccinated against seasonal influenza (Vaccinations in Poland 2015). Our

Table 4 Perception of influenza vaccine safety among high-risk patients

Patients with chronic disorders	Yes, I believe the influenza vaccine is safe; n (%)	No, I do not believe the influenza vaccine is safe; n (%)	I do not know if the influenza vaccine is safe; n (%)
Cardiovascular (n = 200)	98 (49)	18 (9)	84 (42)
Pulmonary (n = 120)	68 (57)	9 (8)	43 (35)
Hemodialyzed (n = 80)	51 (64)	3 (4)	26 (32)
Thyroid cancer (n = 100)	29 (29)	11 (11)	60 (60)

Table 4a Disparities in the perception of influenza vaccine safety among high-risk patients

	p-value	OR (95%CI)
Yes, I believe the influenza vaccine is safe		
Pulmonary *vs.* cardiovascular patients	ns	1.38 (0.76 – 2.50)
Pulmonary *vs.* hemodialysis patients	ns	0.74 (0.40 – 1.37)
Pulmonary *vs.* cancer patients	<0.05	3.24 (1.73 – 6.09)
Cardiovascular *vs.* hemodialysis patients	<0.05	0.54 (0.29 – 0.99)
Cardiovascular *vs.* cancer patients	<0.05	2.39 (1.26 –4.40)
Hemodialysis *vs.* cancer patients	<0.05	4.35 (2.30 – 8.26)
No, I do not believe the influenza vaccine is safe		
Pulmonary *vs.* cardiovascular patients	ns	0.87 (0.29 – 2.62)
Pulmonary *vs.* hemodialysis patients	ns	2.08 (0.54 – 8.57)
Pulmonary *vs.* cancer patients	ns	0.70 (0.24 – 1.99)
Cardiovascular *vs.* hemodialysis patients	ns	3.19 (0.76 – 15.42)
Cardiovascular *vs.* cancer patients	ns	0.90 (0.28 – 2.20)
Hemodialysis *vs.* cancer patients	ns	1.20 (0.09 – 1.20)
I do not know if the influenza vaccine is safe		
Pulmonary *vs.* cardiovascular patients	ns	0.74 (0.40 – 1.37)
Pulmonary *vs.* hemodialysis patients	ns	1.14 (0.61 – 2.14)
Pulmonary *vs.* cancer patients	<0.05	0.35 (0.19 – 0.66)
Cardiovascular *vs.* hemodialysis patients	ns	1.53 (0.82 – 2.86)
Cardiovascular *vs.* cancer patients	<0.05	0.48 (0.26 – 0.88)
Hemodialysis *vs.* cancer patients	<0.05	0.31 (0.16 – 0.58)

ns non-significant, *OR* odds ratio, *CI* confidence intervals

results are in agreement with those obtained by other researchers. Dower et al. (2011) have found that influenza vaccination coverage in adults with chronic diseases is 47 %. Astray-Mochales et al. (2016) have reported that influenza vaccine uptake among subjects with a chronic disease is three times higher than that in subjects who do not have such conditions. A possible explanation for this rather unexpectedly high influenza vaccination coverage among the Polish high-risk patients may be that the majority of them are of advanced age (> 65 years) and are entitled to a free of charge vaccine provided by local governments, while for younger patients there is no reimbursement for influenza vaccine. The influenza vaccination coverage is price sensitive and free or reimbursed vaccination has been reported as an incentive to become vaccinated in the adult population (Yeung et al. 2015).

We found that the highest influenza vaccination coverage was among patients with chronic pulmonary diseases, including bronchial asthma and chronic obstructive pulmonary disease. Lu et al. (2016) have found that the uptake of

Table 5 Perception of influenza vaccine effectiveness among high-risk patients

Patients with chronic disorders	Yes, I believe the influenza vaccine is effective; n (%)	No, I do not believe the influenza vaccine is effective; n (%)	I do not know if the influenza vaccine is effective; n (%)
Cardiovascular (n = 200)	104 (52)	24 (12)	72 (36)
Pulmonary (n = 120)	65 (54)	36 (30)	19 (16)
Hemodialyzed (n = 80)	51 (64)	6 (7)	23 (29)
Thyroid cancer (n = 100)	39 (39)	16 (16)	45 (45)

Table 5a Disparities in the perception of influenza vaccine effectiveness among high-risk patients

	p-value	OR (95%CI)
Yes, I believe the influenza vaccine is effective		
Pulmonary *vs.* cardiovascular patients	ns	1.98 (0.59 – 1.96)
Pulmonary *vs.* hemodialysis patients	ns	0.66 (0.36 – 1.21)
Pulmonary *vs.* cancer patients	<0.05	1.83 (1.07 – 3.35)
Cardiovascular *vs.* hemodialysis patients	ns	0.60 (0.33 – 1.11)
Cardiovascular *vs.* cancer patients	ns	1.69 (0.93 – 3.09)
Hemodialysis *vs.* cancer patients	<0.05	2.78 (1.50 – 5.14)
No, I do not believe the influenza vaccine is effective		
Pulmonary *vs.* cardiovascular patients	<0.05	3.14 (1.40 – 7.05)
Pulmonary *vs.* hemodialysis patients	<0.05	5.69 (2.20 – 15.18)
Pulmonary *vs.* cancer patients	<0.05	2.25 (1.07 – 4.72)
Cardiovascular *vs.* hemodialysis patients	ns	1.81 (0.62 – 5.36)
Cardiovascular *vs.* cancer patients	ns	0.71 (0.29 – 1.71)
Hemodialysis *vs.* cancer patients	ns	0.38 (0.13 – 1.09)
I do not know if the influenza vaccine is effective		
Pulmonary *vs.* cardiovascular patients	<0.05	0.33 (0.16 – 0.69)
Pulmonary *vs.* hemodialysis patients	<0.05	0.46 (0.22 – 0.97)
Pulmonary *vs.* cancer patients	<0.05	0.23 (0.11 – 0.47)
Cardiovascular *vs.* hemodialysis patients	ns	1.37 (0.72 – 2.60)
Cardiovascular *vs.* cancer patients	ns	0.68 (0.37 – 1.26)
Hemodialysis *vs.* cancer patients	<0.05	0.49 (0.26 – 0.93)

ns non-significant, *OR* odds ratio, *CI* confidence intervals

influenza vaccine among patients with chronic lung disease is 46.2 %, while Yang et al. (2015) have reported an even higher rate in this group of patients of 67.6 %. Cha et al. (2016) have observed that subjects with normal pulmonary function are less likely to get vaccinated and those who have obstructive dysfunction. It is possible that people with pulmonary dysfunction more often pay visits to a doctor's office and use healthcare services on a regular basis, thereby have a better possibility to obtain vaccination (Blank et al. 2008, 2009; Kroneman et al. 2006). Regular health checkups can be used as a chance to recommend or implement influenza vaccination for high-risk populations, which is an effective health promoting strategy.

Another reasonable interpretation of the high uptake of influenza shots among subjects with chronic pulmonary disorders can be a better awareness of benefits of vaccination since the association between the exacerbations of bronchial asthma or chronic obstructive pulmonary

Table 6 Barriers for influenza vaccination among high-risk patients[a]

Patients with chronic disorders	Lack of recommendations from healthcare workers; n (%)	Lack of reimbursement; n (%)	Vaccine safety concerns; n (%)	Vaccine effectiveness concerns; n (%)	Low awareness of illness severity; n (%)	Other reasons; n (%)	No barriers indicated; n (%)
Cardiovascular (n = 200)	42 (21)	14 (7)	18 (9)	18 (9)	22 (11)	22 (11)	64 (32)
Pulmonary (n = 120)	2 (1.5)	0 (0)	4 (3)	26 (21.5)	17 (14)	2 (2)	69 (58)
Hemodialyzed (n = 80)	12 (15)	1 (1)	2 (3)	5 (6)	43 (54)	0 (0)	17 (22)
Thyroid cancer (n = 100)	20 (20)	7 (7)	1 (1)	24 (24)	14 (14)	15 (15)	19 (19)

[a]patients were asked to indicate the single most important barrier

Table 6a Disparities concerning the barriers for influenza vaccination among high-risk patients

	p-value	OR (95%CI)
Lack of recommendations from healthcare workers		
Pulmonary *vs*. cardiovascular patients	<0.05	0.07 (0.01 – 0.35)
Pulmonary *vs*. hemodialysis patients	<0.05	0.11 (0.01 – 0.50)
Pulmonary *vs*. cancer patients	<0.05	0.08 (0.01 – 0.37)
Cardiovascular *vs*. hemodialysis patients	ns	1.50 (0.68 – 3.32)
Cardiovascular *vs*. cancer patients	ns	1.06 (0.50 – 2.23)
Hemodialysis *vs*. cancer patients	ns	0.70 (0.30 – 1.50)
Lack of reimbursement		
Pulmonary *vs*. cardiovascular patients	ns	0.13 (0.06 – 1.11)
Pulmonary *vs*. hemodialysis patients	ns	0.90 (0.03 – 37.1)
Pulmonary *vs*. cancer patients	ns	0.13 (0.06 – 1.11)
Cardiovascular *vs*. hemodialysis patients	ns	0.13 (0.06 – 1.11)
Cardiovascular *vs*. cancer patients	ns	0.13 (0.06 – 1.11)
Hemodialysis *vs*. cancer patients	ns	0.13 (0.06 – 1.11)
Vaccine safety concerns		
Pulmonary *vs*. cardiovascular patients	ns	0.36 (0.06 – 1.37)
Pulmonary *vs*. hemodialysis patients	ns	1.50 (0.20 – 13.28)
Pulmonary *vs*. cancer patients	ns	3.06 (0.27 – 77.70)
Cardiovascular *vs*. hemodialysis patients	ns	3.18 (0.76 – 15.42)
Cardiovascular *vs*. cancer patients	<0.05	9.70 (1.23 – 21.04)
Hemodialysis *vs*. cancer patients	ns	3.06 (0.27 – 77.10)
Vaccine effectiveness concerns		
Pulmonary *vs*. cardiovascular patients	ns	1.70 (0.78 – 3.80)
Pulmonary *vs*. hemodialysis patients	<0.05	4.40 (1.59 – 12.80)
Pulmonary *vs*. cancer patients	ns	0.89 (0.43 – 1.81)
Cardiovascular *vs*. hemodialysis patients	ns	2.55 (0.86 – 7.83)
Cardiovascular *vs*. cancer patients	ns	0.51 (0.23 – 1.12)
Hemodialysis *vs*. cancer patients	<0.05	0.20 (0.07 – 0.55)
Low awareness of illness severity		
Pulmonary *vs*. cardiovascular patients	ns	1.31 (0.52 – 3.31)
Pulmonary *vs*. hemodialysis patients	<0.05	0.13 (0.06 – 0.26)
Pulmonary *vs*. cancer patients	ns	1.00 (0.41 – 2.38)
Cardiovascular *vs*. hemodialysis patients	<0.05	0.10 (0.04 – 0.23)
Cardiovascular *vs*. cancer patients	ns	0.79 (0.30 – 1.89)
Hemodialysis *vs*. cancer patients	<0.05	7.20 (3.45 – 15.37)

ns non-significant, *OR* odds ratio, *CI* confidence intervals

disease and influenza infection is well known (Paulin-Prado et al. 2016; Sandrock and Norris 2015). A high influenza vaccination coverage in pulmonary patients in the present study was associated with a perception that the vaccine is safe (57 % of respondents) and effective (54 % of respondents). That perception is in line with the research that has shown the safety and effectiveness of influenza vaccine is related to a better coverage rate (Dower et al. 2011; Santos-Sancho et al. 2012; Lu et al. 2016).

Surprisingly, only did 28 % of our patients with chronic pulmonary diseases consider their knowledge on vaccines and vaccination against influenza as sufficient. On the other hand, the majority of them find the internet, friends, and family as sources of a relevant knowledge. It should be kept in mind, however, that social media may not provide accurate, complete, and objective information in the field of vaccinology. The optimistic observation is that the majority of patients with pulmonary diseases indicated

Table 7 Driving force for influenza vaccination among high-risk patients[a]

Patients with chronic disorders	Recommendations from healthcare workers; n (%)	Vaccine effectiveness belief; n (%)	Vaccine safety belief; n (%)	Low awareness of illness severity; n (%)	Vaccine reimbursement; n (%)	Other reasons n (%)	No driving force indicated; n (%)
Cardiovascular diseases (n = 200)	12 (6)	14 (7)	8 (4)	48 (24)	10 (5)	30 (15)	78 (39)
Pulmonary diseases (n = 120)	14 (12)	3 (2.5)	3 (2.5)	60 (50)	1 (1)	0 (0)	39 (32)
Hemodialyzed (n = 80)	8 (10)	6 (8)	6 (8)	7 (9)	1 (1)	9 (11)	43 (53)
Thyroid cancer (n = 100)	48 (48)	3 (3)	4 (4)	9 (9)	1 (1)	1 (1)	34 (34)

[a]patients were asked to indicate the single most important driving force

Table 7a Disparities in the driving force for influenza vaccination among high-risk patients

	p-value	OR (95%CI)
Recommendations from healthcare workers		
Pulmonary *vs*. cardiovascular patients	ns	0.82 (0.21 – 3.18)
Pulmonary *vs*. hemodialysis patients	<0.05	0.15 (0.05 – 0.46)
Pulmonary *vs*. cancer patients	ns	5.21 (0.57 – 120.11)
Cardiovascular *vs*. hemodialysis patients	<0.05	0.19 (0.06 – 0.52)
Cardiovascular *vs*. cancer patients	<0.05	0.19 (0.06 – 0.52)
Hemodialysis *vs*. cancer patients	<0.05	33.00 (4.59 –66.9)
Vaccine effectiveness belief		
Pulmonary *vs*. cardiovascular patients	ns	0.41 (0.08 – 1.83)
Pulmonary *vs*. hemodialysis patients	ns	0.41 (0.08 – 1.83)
Pulmonary *vs*. cancer patients	ns	1.00 (0.15 – 6.39)
Cardiovascular *vs*. hemodialysis patients	ns	0.86 (0.26 – 2.76)
Cardiovascular *vs*. cancer patients	ns	2.43 (0.54 – 12.28)
Hemodialysis *vs*. cancer patients	ns	2.81 (0.65 – 13.80)
Vaccine safety belief		
Pulmonary *vs*. cardiovascular patients	ns	0.74 (0.12 – 4.57)
Pulmonary *vs*. hemodialysis patients	ns	0.35 (0.07 – 1.53)
Pulmonary *vs*. cancer patients	ns	0.74 (0.12 – 4.05)
Cardiovascular *vs*. hemodialysis patients	ns	0.47 (0.11 – 1.83)
Cardiovascular *vs*. cancer patients	ns	1.00 (0.20 – 4.92)
Hemodialysis *vs*. cancer patients	ns	2.08 (0.54 – 8.57)
Low awareness of illness severity		
Pulmonary *vs*. cardiovascular patients	<0.05	3.16 (1.66 – 6.06)
Pulmonary *vs*. hemodialysis patients	<0.05	10.11 (4.34 – 24.17)
Pulmonary *vs*. cancer patients	<0.05	10.11 (4.34 – 24.17)
Cardiovascular *vs*. hemodialysis patients	<0.05	3.19 (1.31 – 7.92)
Cardiovascular *vs*. cancer patients	<0.05	3.19 (1.31 – 7.92)
Hemodialysis *vs*. cancer patients	ns	1.00 (0.34 – 2.90)
Vaccine reimbursement		
Pulmonary *vs*. cardiovascular patients	<0.05	0.09 (0.00 – 0.71)
Pulmonary *vs*. hemodialysis patients	ns	1.00 (0.03 – 37.15)
Pulmonary *vs*. cancer patients	ns	1.00 (0.30 – 37.15)
Cardiovascular *vs*. hemodialysis patients	ns	5.21 (0.57 – 120.11)
Cardiovascular *vs*. cancer patients	ns	5.21 (0.57 – 120.11)
Hemodialysis *vs*. cancer patients	ns	1.00 (0.03 – 37.15)

ns non-significant, *OR* odds ratio, *CI* confidence intervals

healthcare workers as the main source of information regarding vaccination. According to the literature data, recommendations by healthcare workers are the single most powerful driving force for influenza vaccination (Yamin et al. 2014). Studies have shown that healthcare providers' recommendations can override patients' negative opinions about influenza vaccination (Lindley et al. 2006). Healthcare providers should be encouraged to take every opportunity to recommend and administer the influenza vaccine to patients, in particular to high-risk patients.

The influenza vaccine uptake among patients with cardiovascular and hemodialyzed patients stood at a moderate 32 and 34 %, respectively. For comparison, vaccine uptake is 52 % in Spain (Astray-Mochales et al. 2016), 66.7 % in Korea, and 50.5 % in the US for patients with heart conditions, and 62.5 and 68.7 % for patients with chronic renal conditions in the US and Korea, respectively (Lu et al. 2016; Yang et al.

Table 8 Perception of knowledge on influenza vaccination among high-risk patients

Patients with chronic disorders	Yes, I have enough knowledge on influenza vaccination; n (%)	No, I do not have enough knowledge on influenza vaccination; n (%)	I do not know if I have enough knowledge on influenza vaccination; n (%)
Cardiovascular (n = 200)	68 (34)	62 (31)	70 (35)
Pulmonary (n = 120)	34 (28)	17 (14)	69 (58)
Hemodialyzed (n = 80)	29 (36)	14 (18)	37 (46)
Thyroid cancer (n = 100)	34 (34)	58 (58)	8 (8)

Table 8a Disparities in the perception of knowledge on influenza vaccination among high-risk patients

	p-value	OR (95 %CI)
Yes, I have enough knowledge on influenza vaccination		
Pulmonary *vs*. cardiovascular patients	ns	1.15 (0.60 – 2.21)
Pulmonary *vs*. hemodialysis patients	ns	0.81 (0.42 – 1.53)
Pulmonary *vs*. cancer patients	ns	0.90 (0.47 – 1.70)
Cardiovascular *vs*. hemodialysis patients	ns	0.91 (0.49 – 1.70)
Cardiovascular *vs*. cancer patients	ns	1.00 (0.53 – 1.87)
Hemodialysis *vs*. cancer patients	ns	1.09 (0.58 – 2.03)
No, I do not have enough knowledge on influenza vaccination		
Pulmonary *vs*. cardiovascular patients	<0.05	0.36 (0.16 – 0.70)
Pulmonary *vs*. hemodialysis patients	ns	1.01 (0.59 – 1.72)
Pulmonary *vs*. cancer patients	ns	0.74 (0.32 – 1.69)
Cardiovascular *vs*. hemodialysis patients	ns	2.04 (1.00 – 4.19)
Cardiovascular *vs*. cancer patients	<0.05	0.32 (0.17 – 0.60)
Hemodialysis *vs*. cancer patients	<0.05	0.15 (0.07 – 0.31)
I do not know if I have enough knowledge on influenza vaccination		
Pulmonary *vs*. cardiovascular patients	<0.05	2.56 (1.39 – 4.73)
Pulmonary *vs*. hemodialysis patients	ns	1.62 (0.89 – 2.94)
Pulmonary *vs*. cancer patients	<0.05	15.88 (6.57 – 39.69)
Cardiovascular *vs*. hemodialysis patients	ns	0.63 (0.34 – 1.16)
Cardiovascular *vs*. cancer patients	<0.05	6.19 (2.54 – 15.56)
Hemodialysis *vs*. cancer patients	<0.05	9.79 (4.06 – 24.4)

ns non-significant, *OR* odds ratio, *CI* confidence intervals

2015). International guidelines strongly recommend the annual influenza vaccination in persons with coronary and other atherosclerotic vascular disease. Nonetheless, influenza vaccination remains at a low rate due to several quite well identified factors such as a lack of awareness of vaccination benefits by both patients and physicians, a common belief that vaccination is unnecessary or it invoke a full-fledged disease, and the concern about possible adverse effects especially in patients taking antiplatelet treatment or anticoagulants (Penfold et al. 2011; Madjid et al. 2009; Jones et al. 2004). In the present study, recommendations from healthcare workers were a strong driving force for influenza vaccination for cardiovascular patients, which points to a key role of medical staff in increasing the vaccination coverage rate. Phrommintikul et al. (2014) have shown that the main tool to expand vaccine coverage consists of the physician and healthcare team-led education of patients about the benefits and risks of

Table 9 Source of knowledge about influenza vaccination among high-risk patients[a]

Patients with chronic disorders	Healthcare workers; n (%)	Internet; n (%)	Traditional media; n (%)	Friends and family; n (%)
Cardiovascular (n = 200)	110 (50)	56 (28)	24 (12)	22 (11)
Pulmonary (n = 120)	72 (60)	94 (78)	38 (32)	86 (72)
Hemodialyzed (n = 80)	19 (24)	7 (9)	47 (59)	2 (3)
Thyroid cancer (n = 100)	29 (29)	18 (18)	23 (23)	24 (24)

[a]Patients could choose more than one answer or declared they had not looked for any sources of knowledge regarding influenza vaccination as was the case in 5 (6 %) of hemodialyzed and 6 (6 %) of thyroid cancer patients. Therefore, the number of patients summated in the categories of source of knowledge does not add up to the number of patients with a given disorder

Table 9a Disparities in the source of knowledge about influenza vaccination among high-risk patients

	p-value	OR (95 %CI)
Healthcare workers		
Pulmonary *vs*. cardiovascular patients	ns	1.50 (0.82 – 2.73)
Pulmonary *vs*. hemodialysis patients	<0.05	4.75 (2.47 – 9.16)
Pulmonary *vs*. cancer patients	<0.05	3.67 (1.55 – 6.92)
Cardiovascular *vs*. hemodialysis patients	<0.05	3.16 (1.66 – 6.06)
Cardiovascular *vs*. cancer patients	<0.05	2.44 (1.31 – 4.58)
Hemodialysis *vs*. cancer patients	ns	0.77 (0.39 – 1.52)
Internet		
Pulmonary *vs*. cardiovascular patients	<0.05	9.11 (4.57 – 18.35)
Pulmonary *vs*. hemodialysis patients	<0.05	35.84 (14.61 – 90.73)
Pulmonary *vs*. cancer patients	<0.05	16.15 (7.64 – 34.62)
Cardiovascular *vs*. hemodialysis patients	<0.05	3.93 (1.64 – 9.63)
Cardiovascular *vs*. cancer patients	ns	1.77 (0.86 – 3.66)
Hemodialysis *vs*. cancer patients	ns	0.45 (0.17 – 1.13)
Traditional media[a]		
Pulmonary *vs*. cardiovascular patients	<0.05	3.45 (1.56 – 7.70)
Pulmonary *vs*. hemodialysis patients	<0.05	0.32 (0.17 – 0.60)
Pulmonary *vs*. cancer patients	ns	1.57 (0.80 – 3.09)
Cardiovascular *vs*. hemodialysis patients	<0.05	0.09 (0.04 – 0.20)
Cardiovascular *vs*. cancer patients	ns	0.45 (0.19 – 1.03)
Hemodialysis *vs*. cancer patients	<0.05	4.81 (2.50 – 9.34)
Friends and family		
Pulmonary *vs*. cardiovascular patients	<0.05	20.80 (9.15 – 48.33)
Pulmonary *vs*. hemodialysis patients	<0.05	83.10 (22.79 – 359.10)
Pulmonary *vs*. cancer patients	<0.05	8.14 (4.10 – 16.10)
Cardiovascular *vs*. hemodialysis patients	ns	3.99 (0.98 – 18.70)
Cardiovascular *vs*. cancer patients	<0.05	0.39 (0.16 – 0.90)
Hemodialysis *vs*. cancer patients	<0.05	0.09 (0.02 – 0.36)

ns non-significant, *OR* odds ratio, *CI* confidence intervals
[a]press, radio, TV

vaccination, and encouraging patients to receive the vaccine.

The influenza vaccination is recommended for cancer patients and cancer survivors, including those who are not currently undergoing treatment. Cancer patients have a higher risk of morbidity and mortality due to influenza compared with the general population. Death from influenza-related infections occurs in 9 % of cancer patients (Cooksley et al. 2005). Somewhat in

opposition to the notion above outlined, in the present study the lowest 9 % influenza vaccine uptake was present in cancer patients. These results are, however, in agreement with other published data. Poeppl et al. (2015) have reported that 18 % of patients with malignancies are vaccinated against influenza and the rate is higher in hematological diseases (22 %) compared with solid tumors (13 %). Rodríguez-Rieiro et al. (2011) have also reported a meager 10 % of malignant patients vaccinated against influenza. On the other hand, in some other studies 57 % of cancer patients declared receiving the influenza shot in the US (Underwood et al. 2012) and 75 % in the UK (Khan et al. 2010). A possible explanation of a low influenza vaccination coverage among cancer patients of the present study could be the type of cancer and the phase of treatment. We conducted a survey among thyroid cancer patients after surgical treatment and before radioiodine therapy. Although the interval between surgery and radiotherapy is a good time for vaccination, safety and effectiveness concerns, on the part of both physicians and patients, might play a role in delaying a decision on vaccination (Oh et al. 2015). It should be underscored that the ideal time to administer the influenza vaccine is unclear. However, a majority of cancer patients who do not receive immunosuppressive therapy for more than 30 days mount immunologically favorable reactions to influenza vaccination (Pollyea et al. 2010). Another factor that could influence our results was the age of thyroid cancer patients; 75 % of them were younger than 65 years of age. Oh et al. (2015) have shown in the Korean population that influenza vaccination coverage increases significantly with age; form 26.1 % of those aged 19–49 to 77.7 % of those aged over 65. In that study, similar to the Polish social and economic conditions, the subjects over 65 years of age were vaccinated free of charge, but younger ones were not reimbursed. Hence, older subjects are likely to receive vaccination due to their age rather than cancer *per se*. A lower vaccination coverage in younger cancer patients might be due to less social support, differences in health status, and provider bias (Oh et al. 2015). Previous studies have indicated that some oncologists may not be aware that cancer patients should receive the influenza vaccine (Choi et al. 2014). A role of healthcare workers' recommendations as an encouraging trigger to vaccinate is rightly emphasized. By contrast, information on influenza and its prophylaxis acquired from the media or internet is not associated with the highest influenza vaccine uptake (Poeppl et al. 2015).

The present study has some limitations. Firstly, this is an observational study; thus having less power than randomized, prospective, and blinded research. Secondly, the size of the population studied was relatively small. Thirdly, vaccination against influenza was self-reported by responders and there is risk that not all declared cases of vaccination took actually place. We believe, however, that the study reflects the current state of influenza vaccination coverage in Polish high-risk patients. In addition, the present findings highlight the importance of influenza vaccine promotion in high-risk patients. Multiple strategies focusing on providers and patients are needed to improve influenza vaccination coverage.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Circulation of Antibodies Against Influenza Virus Hemagglutinins in the 2014/2015 Epidemic Season in Poland

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Abstract

The aim of this study was to determine the level of anti-hemagglutinin antibodies in the serum of people in different age-groups during the 2014/2015 epidemic influenza season in Poland. A total of 1050 sera were tested. The level of anti-hemagglutinin antibodies was determined using the hemagglutinin inhibition test. The results provided information on the incidence of circulating A/California/7/2009(H1N1)pdm09, A/Texas/50/2012(H3N2), and B/Massachusetts/2/2012 viruses. The level of antibodies against influenza differed between age-groups. The protection rate was the highest for the antigen B/Massachusetts/2/2012, with the decreasing order of values in the following age-groups: ≥65 years (76.7 %), 15–25 years (72.7 %), and 0–4 years (62.0 %). The average values of the protection rate in other age-groups were as follows: 43.3 % in 22–64 years, 40% in 5–9 years, and 39.3 % in 45–64 years of age, while the lowest value of 22.7 % was in 10–14 years old subjects. In the 2014/2015 epidemic season in Poland only were 3.6 % of the population vaccinated. That is why the presented results could be interpreted as a response of the immune system of patients after infection caused by influenza virus.

Keywords

Age • Antibodies • Influenza • Hemagglutinin inhibition test • Protection rate • Vaccination

1 Introduction

Influenza is an infectious disease caused by influenza virus, which is divided into four types: influenza A, B, C, and D, of which influenza type C is asymptomatic, while influenza type D

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does not cause infections in humans (Ferguson et al. 2015). Infections with influenza viruses lead to an epidemic in every season and occasionally cause pandemics in the human population.

In the case of influenza infections, laboratory diagnostics is essential to confirm the presence of the virus with molecular biology methods, which enables to commence antiviral treatment with neuraminidase inhibitors. For the diagnostic purpose, it is also important to determine whether anti-hemagglutinin antibodies increase in the patient serum (Brydak 2008). At the time of influenza infection, antibodies against the glycoproteins hemagglutinin (HA) and neuraminidase (NA) present on the surface of influenza virus are produced. Due to the continuing evolution of the virus, 18 types of HA and 11 of NA can be distinguished. Combinations of HA and NA form the various subtypes of influenza A virus. Also, surface glycoproteins of influenza A virus are different from those of influenza B (Wu et al. 2014; Brydak 2008). The presence of antibodies against HA in the human sera indicates infection or is a result of vaccination against influenza. The anti-HA antibodies provide resistance against a particular viral strain. They also can alleviate the symptoms of infection with another variant of influenza virus, reducing risk of complications. It has been shown that anti-HA antibodies have the ability to cross-react and to disrupt proliferation and release of viral particles of other influenza viruses (Mandelboim et al. 2014; Ekiert et al. 2011; Throsby et al. 2008). That makes every seasonal vaccination of key importance to increase resistance against infection, and thus to reduce risk of complications caused by influenza (Nichol 2008).

Every epidemic season, the WHO, based on data collected under the influenza surveillance program in the world, issues recommendations concerning the vaccine composition for the next season. For the 2014/2015 epidemic season, the strain of influenza virus subtype A/H3N2/ was changed, while the subtypes A/H1N1/pdm09 and influenza B type remained unchanged, compared with the previous season.

During the 2014/2015 influenza season, 3,776,518 cases and suspected cases of influenza and influenza-like illness were registered in Poland, with morbidity amounting to 9814.6 cases per 100,000 people, and a total of 12,273 hospitalizations and 11 deaths as a result of influenza complications in the season (NIPH-NIH 2016). It should be noted that the percentage of vaccinated population in Poland was barely 3.6 % (Brydak 2015). In comparison with the 2013/2014 influenza season, the number of influenza cases and hospitalizations increased, whereas the percentage of vaccinated population decreased, despite the local governments offers of free of charge vaccination for people over 50 years of age in some voivodeships.

The aim of the present study was to determine the level of antibodies against hemagglutinin of influenza viruses in the serum of people in different age-groups during the influenza 2014/2015 epidemic season in Poland.

2 Methods

The study protocol was approved by an institutional Ethics Committee. The sera of people stratified into the following age-groups 0–4, 5–9, 10–14, 15–25, 26–44, 45–64, and $\geq$65 years of age were collected by departments of epidemiology of Voivodeship Sanitary Epidemiological Stations in Poland and stored at −80 °C until further use in the Department of Influezna Research, National Influenza Center (NIC in Poland) in National Institute of Public Health-National Institute of Hygiene (NIPH-PIH). A total of 1050 serum samples were tested; 150 samples in each age-group. The level of antibodies was determined by hemagglutinin inhibition test (HAI), using the antigens recommended by the WHO for influenza epidemic season of 2014/2015, as listed in Table 1. All antigens were propagated in chicken embryos and prepared in NIC in Poland, according to the WHO protocol (WHO 2011). The HAI test was performed using eight hemagglutinin units of the virus, and the serum was inactivated prior to the test.

Table 1 Strains of influenza virus used for hemagglutinin inhibition test

	Influenza virus strain		
Epidemic season 2014–2015	A/H1N1/	A/H3N2/	B
	A/California/7/2009(H1N1) pdm09-like virus	A/Texas/50/2012(H3N2) – like virus	B/Massachusetts/2/2012 – like virus

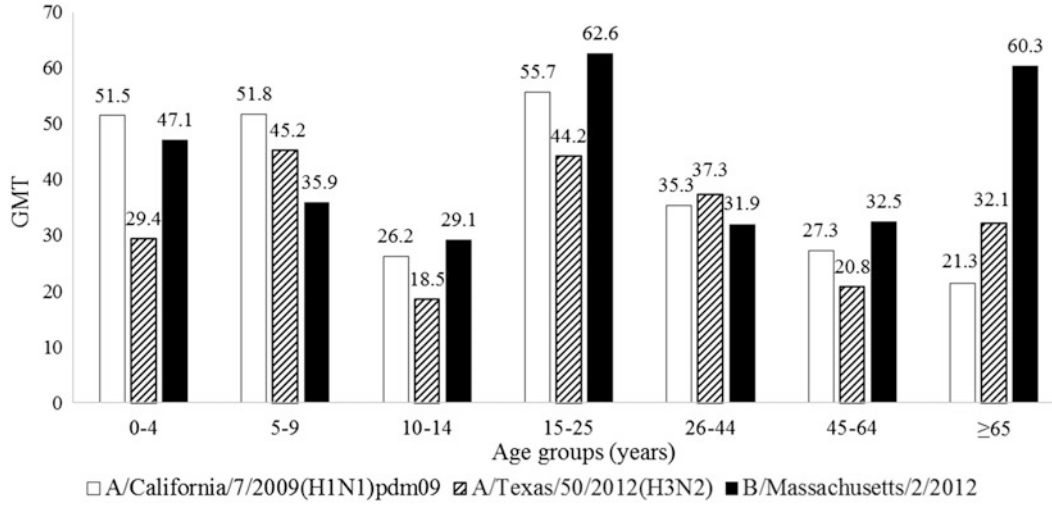

Fig. 1 Geometric mean titers (GMT) of anti-hemagglutinin antibodies in the serum of people in successive age-groups in the 2014/2015 epidemic season

3 Results and Discussion

The following indices were used to describe the level of antibodies against HA of influenza virus in the human serum: geometric mean of HA antibody titer (GMT) and the protection rate, i.e., percentage of people with the level of HA antibodies ≥1:40 appearing after vaccination or previous infection by influenza virus (Brydak 2008). These results are shown in Figs. 1 and 2.

The highest level of anti-HA antibodies for hemagglutinin H1 was present in the age-groups of 15–25 (GMT = 55.7), 5–9 (GMT = 51.8), and 0–4 years (GMT = 51.5). The lowest level of these antibodies was in the age-groups of 26–44 (GMT = 35.3), 45–64 (GMT = 27.3), 10–14 (GMT = 26.2), and ≥65 years (GMT = 21.3). Concerning the anti-H3 antibodies, the highest GMT were present in the subjects aged 5–9 (GMT = 45.2) and 15–25 years (GMT = 44.2), followed closely by those aged 26–44, ≥65, and 0–4 years of age (GMT of 37.3, 32.1, and 29.4, respectively). The lowest values of anti-H3 antibodies were present in the subjects aged 45–64 (GMT = 20.8) and 10–14 years (GMT = 18.5). Concerning type B hemagglutinin, the highest values of anti-HA antibodies were present in the subjects aged 15–25 (GMT = 62.6) and ≥65 years (GMT = 60.3). In the remaining age-groups, appreciably lower values of anti-HA type B antibodies were present; the respective GMT values amounted to 47.1 in 0–4, 35.9 in 5–9, 29.2 in 10–14, 31.9 in 26–44, and 32.5 in 45–64 years of age. In the subjects of 15–25 years of age, GMT for antibodies for all types of hemagglutinins (H1, H3, and B) was greater than 40, amounting to 55.7, 44.2, and 62.6, respectively (Fig. 1).

Concerning the effectiveness of vaccination against influenza, the protection rate appeared age-dependent. For anti-HA type B antibodies, this rate achieved 76.7 % for people aged ≥65, 72.7 % for people aged 15–25, and 62.0 % for children aged 0–4 years. The lowest values of the

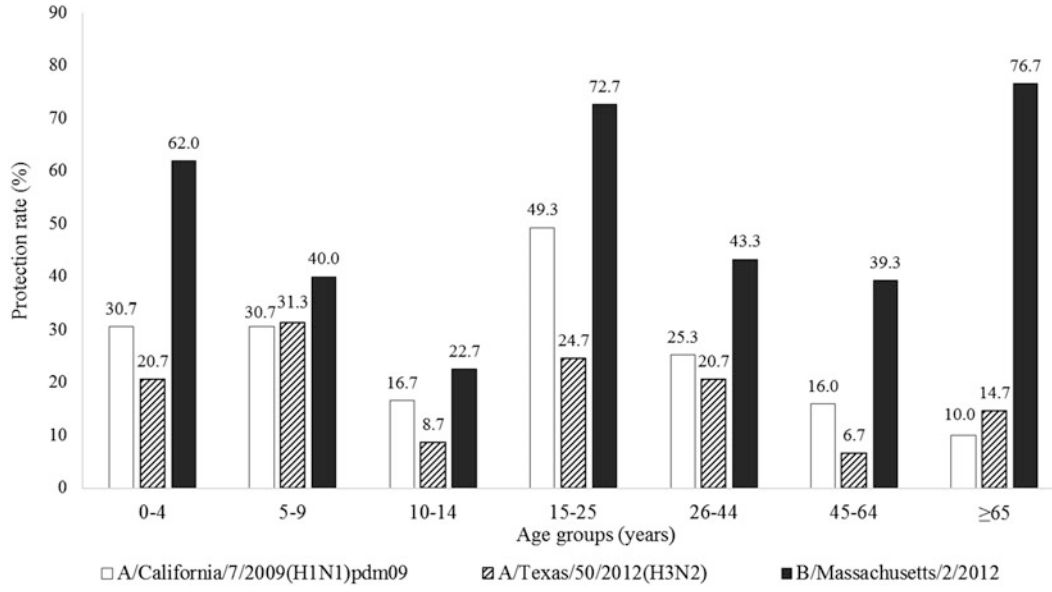

Fig. 2 The percentage of cases with a protective level of anti-hemagglutinin antibodies in successive age-groups in the 2014–2015 epidemic season

Table 2 Protection rate (%) during the consecutive epidemic seasons in the successive age-groups

	Age-group (years)				
Antigen	15–25	26–44	45–64	≥65	Epidemic season
A/H1	26.5	23.0	12.3	8.6	2012/2013
	26.7	28.0	22.7	18.0	2013/2014
	49.3	25.3	16.0	10.0	2014/2015
A/H3	9.9	29.7	5.3	6.4	2012/2013
	16.7	20.7	16.0	26.0	2013/2014
	24.7	20.7	6.7	14.7	2014/2015
B	14.6	21.6	8.2	17.1	2012/2013
	43.3	36.4	31.3	32.0	2013/2014
	72.7	43.3	39.3	76.7	2014/2015

protection rate were noted for anti-H3 HA antibodies, where it amounted to 8.7 and 6.7 % in the age-groups of 10–14 and 45–64 years. Considering the protection rate across all types of anti-HA antibodies in the context of age, it was at a close level of 31–40 % only in the group of 5–9-year olds. It should also be noted that the protection rate was the lowest in children aged 10–14 years for all types of hemagglutinin (H1, H3, and B), compared with the values obtained in the other age-groups (Fig. 2). According to the data distributed by the NIPH-NIH (2016), the percentage of the vaccinated children in the age-group of 5–14 years was 0.96 and 0.86 % in 2014 and 2015, respectively.

Comparing the protection rate during the consecutive epidemic seasons of 2012/2013, 2013/2014, and 2014/2015, attention should be raised to the level of anti-H1 HA antibodies. Influenza virus subtype A/California/7/2009(H1N1)pdm09, a component of a trivalent influenza vaccine recommended by the WHO for the northern hemisphere, including Poland, has been circulating in the population since 2009. The protection rate

Table 3 Antigenic composition of influenza vaccines during three consecutive epidemic seasons

Antigen	Epidemic season
A/California/7/2009(H1N1)pdm09	2012/2013
A/Victoria/361/2011(H3N2)	
B/Wisconsin/1/2010	
A/California/7/2009(H1N1)pdm09	2013/2014
A/Victoria/361/2011(H3N2)	
B/Massachusetts/2/2012	
A/California/7/2009(H1N1)pdm09	2014/2015
A/Texas/50/2012(H3N2)	
B/Massachusetts/2/2012	

values obtained for this antigen during the three epidemic seasons were lower than 60 % in the successive age-groups (Table 2). The lowest value was observed for the range ≥65 years of age. That corresponds with the low 7–8 % of the people vaccinated against influenza in this age-group, belonging to a higher risk population. In the case of anti-H3 HA antibodies, the lowest titer was noted in the 45–64 age-group in the 2012/2013 epidemic season. Concerning the 26–44 age-group, comparable low values of the protection rate were obtained in the three successive seasons (Table 2), although the influenza virus strain was different in the 2014/2015 season than in the two preceding seasons (Table 3). Compared with the anti-H1 HA antibodies, protection rate for hemagglutinin type B was higher during the three epidemic seasons in all age-groups, reaching as much as 72.7 and 76.7 % for the 15–25 and ≥65 years old, respectively, in the 2014/2015 season (Table 2). Given a low percentage of the vaccinated population in Poland during the epidemic seasons compared in this study, amounting to about 1.5 % and 7–8 % for the 15–25 and ≥65 years old, respectively NIPH-NIH (2016), the results could be interpreted as a response of the immune system of the patients who had underwent infection with influenza virus.

Due to recent changes introduced in influenza surveillance in Poland, we could not directly compare the protection rate in children younger than 14 years of age during the epidemic seasons under consideration in the present study. However, it can be seen that the greatest protection was achieved for hemagglutinin B type, exceeding 60 % in several age-groups during the 2014/2015 season (Fig. 2), which is in line with previous reports (Bednarska et al. 2015, 2016).

4 Conclusions

Serological screening of the serum taken from people of different age-groups during the 2014/2015 epidemic season in Poland, confirmed that (1) there were three influenza virus strains circulating: A/California/7/2009(H1N1)pdm09, A/Texas/50/2012(H3N2), and B/Massachusetts/2/2012; (2) only was the protection rate for antigen B greater than 60%; and (3) a low percentage of people vaccinated across different age-groups suggests that the level of protection observed is a result of past infection caused by influenza virus.

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Influence of Socioeconomic and Anthropometric Factors on Respiratory Function in Female University Students

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Abstract

The purpose of this study was to evaluate lung function in healthy young female university students and to seek the relation of lung function to socioeconomic and anthropometric indices. The methodology consisted of spirometry tests, anthropometric measures and a questionnaire conducted in November of 2015 among 152 female university students. At first, lung function was analyzed for any relationship with socioeconomic factors and smoking. The results of a multi-factor analysis of variance demonstrate significant differences in the FEV1/FVC ratio depending on the general socioeconomic status. Then, anthropometric and spirometric parameters were tested for correlations. A comparison of underweight, normal weigh, overweight, and obese subjects revealed statistically significant differences for FVC% and FEV1/FVC, with the highest values noted in the subjects of normal weight. Individuals with abdominal obesity had lower FVC% and FEV1% and a higher FEV1/FVC ratio. The findings of our study confirm that both general obesity and abdominal obesity are related to a reduced lung function.

Keywords

Body Shape • Obesity • Respiratory Function • Spirometry

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1 Introduction

Many European countries have been reporting a constant increase in the prevalence of chronic respiratory diseases. This is mainly caused by

civilization progress, which results in air pollution and changes in lifestyle (Hamra et al. 2014; Andersen et al. 2011; Clancy et al. 2002). Poland is among the countries in which air quality is the worst (Gehring et al. 2013). Certain habits which favor the development of respiratory diseases, i.e., smoking, physical inactivity, unhealthy diet, and the resulting high prevalence of obesity are common in the Polish society.

Spirometry is one of the basic methods of testing the pulmonary function. Despite being non-invasive and relatively inexpensive, spirometry is performed quite rarely, mostly among the employees exposed to increased occupational risk of respiratory diseases. However, air quality in Poland, particularly in large cities, is so poor that the risk of respiratory disorders is heightened not only among specific occupations, but in the whole population. The above is also confirmed by morbidly and mortality rates. For this reason screening tests are recommended, as they enable early diagnosis of respiratory diseases as well as their effective treatment. For example, more than one half of all subjects who participated in screening tests performed as part of the Polish Spirometry Day 2013 (Dabrowiecki et al. 2013) and World Spirometry Day 2014 had never had any lung function test performed. In the course of the tests, cases of obstruction were detected in 17% subjects (EEA Report No 5/ 2015).

Inter-individual variation in lung function is related not only to exposure to air pollution, but also to smoking (Dąbrowiecki et al. 2015; Patil et al. 2012), body size and shape – mainly stature (Nawafleh et al. 2012; Prasad et al. 2003), obesity and abdominal obesity (Bhatti et al. 2014; Khan and Chen 2014), and body circumferences (Cotes et al. 2001; Chen et al. 2001). Certain studies indicate the presence of a relationship between respiratory function and socio-economic status (SES) (Menezes et al. 2011; Hegewald and Crapo 2007; Raju et al. 2005), which is an indirect indicator of living conditions and lifestyle (Maiolo et al. 2003; Mohamed et al. 2002).

The purpose of this study was to evaluate lung function among healthy young female university students and to determine potentially correlated factors such as socio-economic status and anthropometric parameters.

2 Methods

Tests were performed in November 2015 among 152 female students of the Jagiellonian University and the Wrocław University of Environmental and Life Sciences. The mean age was 20.0 ± 1.6 years and ranged between 19 and 24 years. The study protocol was approved by a local Ethics Committee. Data were collected following the ethical principles as stated in the Declaration of Helsinki. Participants of the tests did not include persons with diagnosed chronic diseases with the exception of food and/or respiratory allergy.

Lung function tests were undertaken using a portable Spirolab III (Medical International Research; Waukesha, WI). All measures were made by a single operator. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were measured, using the best of three forced maneuvers. FEV1% and FVC% of the predicted values and FEV1/FVC ratio were recorded.

Body height, body mass, chest, waist and hip circumferences were measured according to current anthropometric methodology. The following indices were also calculated: body mass index (BMI), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). On the basis of BMI three categories were differentiated applying WHO recommendations: underweight (BMI $<$ 18.5 kg/m^2), norm (BMI = 18.5–25.0 kg/m^2), overweight and obesity (BMI $>$ 25.0 kg/m^2). The waist circumference measurement was used to define abdominal type of obesity. According to the guidelines, the correct value was accepted at the level of 80 cm and below. The presence of excessive adiposity in the central region was also assessed based on the WHR and WHtR. The following categories were differentiated: no obesity – WHR $<$ 0.8, obesity occurrence – WHR $\geq$ 0.8. The WHtR was applied to distinguish three categories as follows. The amount of fat in the abdominal region was found too low at the index

values not exceeding 0.4, correct for the values range of 0.41–0.50, and the values greater than 0.50 and were classified as abdominal obesity. Depending on the body height the following categories were created: short (< mean−1 SD), medium (mean ± 1 SD), tall (> mean +1 SD).

A survey on the prevalence of chronic diseases, especially respiratory conditions, allergies, smoking, and SES status was administered. Each socio-economic factor was analyzed separately and a complex SES index was also developed by the use of factor analysis with the principal components method (concerning size of dwelling place, number of siblings, father and mother's education). Scores of the first component, which explained 52% of variance and its eigenvalue accounted to 2.92, were included into further analyses as a proxy for SES. Three groups of SES (low, medium, and high) were based on the tertile.

2.1 Statistical Methods

The Shapiro-Wilk test was used to examine the normality of the preliminary quantity variables. The association between pulmonary function variables and anthropometric measures was tested by using multivariate multiple regression analysis (height, BMI, WHR, WHtR, waist, and hip and chest circumference as continuous variables) or multivariate analysis of variance (MANOVA) (height, BMI, and WHtR as categorical variables). Student's *t*-test was used to analyze the difference in spirometric parameters in relation to the prevalence of abdominal obesity. MANOVA was used to evaluated differences in lung function depending on SES and to verify the interactions between these variables in the effect on the anthropometric measures. A *p*-value <0.05 was taken to indicate statistically significant differences.

3 Results

Spirometric parameters, anthropometric, and socio-economic characteristics of the subjects are presented in Table 1. The results of spirometric tests were contained in the normal range for all subjects, which is not surprising in view of the young age of the individuals and their generally good health. First, lung function was analyzed for any relationship with socio-economic factors and smoking. The results of a multi-factor analysis of variance indicate significant differences in the FEV1/FVC ratio depending on the general SES (Table 2). Intriguingly, lower values of the pseudo-Tiffeneau index were also reported in the students whose fathers had secondary education. The index rose with the increase of SES.

Table 1 Spirometric and anthropometric parameters in subjects

	Mean ±SD	Median
FVC (L)	3.57 ±0.53	3.54
FVC (%pred.)	96.4 ±13.2	96.0
FEV1 (L/s)	3.14 ±0.46	3.13
FEV1 (%pred.)	96.3 ±13.1	98.0
FEV1/FVC	0.88 ±0.09	0.90
Height (cm)	164.0 ±6.0	164.3
BMI (kg/m^2)	21.8 ±3.1	21.4
CC (cm)	74.6 ±6.7	73.7
WC (cm)	70.1 ±7.2	69.6
WHtR	0.43 ±0.04	0.42
WHR	0.75 ±0.07	0.74

FVC forced vital capacity, *FEV1* forced expired volume in 1 s. *BMI* body mass index, *CC* chest circumference, *WC* waist circumference, *WHtR* waist-to-height ratio, *WHR* waist-to-hip ratio

The absence of differences in spirometric parameters between smokers and non-smokers is rather surprising (Table 2). This is probably due to the fact that the subjects were young persons whose average daily cigarette consumption was relatively low. For two thirds of smokers, the period of addiction did not exceed 3 years, and one half of the subjects declared that they smoked only one or two cigarettes per day. No statistically significant differences between allergic and non-allergic individuals were noticed; this holds true for both all allergies and respiratory allergies considered separately.

In the next phase of analysis, anthropometric and spirometric parameters were tested for correlations. Results of multiple regression

Table 2 Results of multifactor analyses of variance on FEV1%, FVC%, and FEV1/FVC ratio

	FVC%		FEV1%		FEV1/FVC	
	F	p	F	p	F	p
Dwelling place	0.65	0.524	0.26	0.771	1.49	0.228
Mother's education level	1.91	0.152	2.55	0.082	0.22	0.803
Father's education level	0.27	0.765	2.62	0.076	**3.51**	**0.032**
Number of sibilings	1.07	0.363	0.34	0.797	1.02	0.384
SES	0.81	0.447	0.59	0.555	**3.15**	**0.046**
Smoking	0.83	0.365	0.83	0.365	0.05	0.825
Allergy	0.01	0.921	0.29	0.589	0.47	0.496

SES socioeconomic status, ***Bold type*** indicates statistically significant difference ($p < 0.05$)

Table 3 Multiple linear regression models of anthropometric indices on FEV1%, FVC%, and FEV1/FVC ratio

	FVC%		FEV1%		FEV1/FVC	
	B-coefficient	p-value	B-coefficient	p-value	B-coefficient	p-value
Height (cm)	0.017	0.840	0.054	0.531	0.037	0.666
BMI (kg/m^2)	−0.042	0.630	−0.139	0.120	−0.099	0.272
CC (cm)	**0.292**	**0.039**	0.104	0.469	−0.241	0.096
WC (cm)	−0.009	0.946	0.068	0.627	0.093	0.508
WHtR	−0.082	0.335	−0.044	0.608	0.072	0.409
WHR	0.131	0.120	0.162	0.060	0.040	0.643
	$R^2 = 0.06$; $F(6.13) = 2.54$; $p = 0.023$		$R^2 = 0.02$; $F(6.13) = 1.58$; $p = 0.158$		$R^2 = 0.01$; $F(6.13) = 1.32$; $p = 0.250$	

BMI body mass index, *CC* chest circumference, *WC* waist circumference, *WHtR* waist-to-height ratio, *WHR* waist-to-hip ratio, ***Bold type*** statistically significant difference ($p < 0.05$)

analysis are shown in Table 3. A statistically significant correlation was observed only for chest circumference and FVC%. Subsequently, differences in spirometric parameters depending on the body height category (short, medium, and tall) and the presence of obesity and abdominal obesity were analyzed. Because of considerable relationship between anthropometric and socio-economic parameters, these factors were tested for interactions.

Tall subjects had a much higher mean FVC% than medium-height or short persons. Increased FEV1% and lower FEV1/FVC ratio were observed in tall individuals in comparison to medium-height and short subjects. However, the differences were not statistically significant. A comparison of underweight, normal body mass, and overweight or obese subjects revealed statistically significant differences for FVC% and FEV1/FVC. The highest values of the indices were reported for subjects with normal body weight (BMI 18.5–25.0 kg/m^2). A similar tendency was found also for FEV1%, although without a statistically significant difference. No statistically significant differences for spirometric parameters depending on the presence of abdominal obesity were found. Nevertheless, a clear tendency was identified for individuals with abdominal obesity determined both by the waist size criterion and the WHtR and WHR criterions: such individuals were characterized by lower FVC% and FEV1% and a higher FEV1/FVC ratio (Table 4).

Analyses of interactions between socio-economic factors and anthropometric parameters did not show any statistically significant relationships. Socio-economic status did not influence the relationship between any spirometric and anthropometric parameters.

Table 4 FEV1%, FVC%, and FEV1/FVC ratio in relation to anthropometric variables

		n	FVC (%pred.)	FEV1 (%pred.)	FEV1/FVC
Height (cm)	Short	27	95.1 ± 14.2	93.7 ±16.2	0.89 ±0.09
	Medium	107	96.3 ± 13.2	96.1 ±11.9	0.89 ±0.09
	Tall	18	104.3 ± 11.4	101.1 ±10.0	0.86 ±0.07
			F =2.98	F = 1.69	F = 1.02
			p = 0.110	p = 0.189	p = 0.363
BMI (kg/m^2)	<18.5	16	89.1 ± 16.1	93.4 ±18.1	0.88 ±0.08
	18.5–25.0	116	102.3 ± 13.0	97.9 ±12.3	0.91 ±0.12
	>25	20	95.5 ± 12.2	95.1 ±12.4	0.85 ±0.07
			F= 4.09	F = 0.48	**F = 2.63**
			p = 0.010	p = 0.619	**p = 0.046**
WC (cm)	≤80	133	98.4 ± 12.9	95.7 ±12.9	0.84 ±0.08
	>80	16	95.8 ± 12.1	92.2 ±6.4	0.88 ±0.09
			t = −0.08	t = −2.71	t = 0.75
			p = 0.943	p = 0.206	p = 0.080
WHtR	≤0.5	138	96.9 ± 13.3	96.2 ±13.2	0.87 ±0.09
	>0.5	11	93.1 ± 13.9	93.0 ±11.4	0.89 ±0.08
			t = −0.807	t = −0.650	t = −0.270
			p = 0.409	p = 0.519	p = 0.813
WHR	<0.8	119	99.4 ± 6.3	99.4 ±8.2	0.86 ±0.06
	≥0.8	30	96.2 ±7.4	95.7 ±6.9	0.89 ±0.07
			t = −1.13	t = −1.25	t = −0.36
			p = 0.261	p = 0.214	p = 0.720

BMI body mass index, *WC* waist circumference, *WHtR* waist-to-height ratio, *WHR* waist-to-hip ratio, ***Bold type*** statistically significant difference ($p < 0.05$)

4 Discussion

Intra-individual differences identified in the values of spirometric parameters may be caused by environmental factors, e.g., air pollution exposure to certain chemicals, large amount of particulate matter (Hamra et al. 2014; Gehring et al. 2013; Andersen et al. 2011; Clancy et al. 2002), or by lifestyle. Unhealthy habits which leads to reduced lung function include mainly smoking and insufficient physical activity (Nawafleh et al. 2012; Patil et al. 2012; Prasad et al. 2003).

Socio-economic status is an indirect indicator of living conditions and lifestyle. There are marked differences between groups of different status in terms of housing, working conditions, eating habits, pastime, physical activity, and smoking. Overall, persons of lower status are exposed to a greater extent to factors which may negatively affect their biological condition, and their lifestyle includes unhealthy habits to a greater degree than in case of individuals of high status (Cornman et al. 2015; Pampel et al. 2010; Steckel 2009; Komlos 2000). As a consequence, there are disparities in respiratory health. Data obtained from literature show reduced lung function among persons of low SES when compared to persons of high status (Hegewald and Crapo 2007; Raju et al. 2005; Menezes et al. 2011). This dependence is noticeable both in adults and children. Our findings demonstrate a limited influence of socio-economic factors on the spirometric parameters of surveyed females. This could be explained by the fact that the subjects of the tests were students. What attracts many young Poles to colleges or universities is the absence of tuition fees and the presence of a well-developed system of welfare benefits from the state; difficulties in finding a job upon completing a secondary education are also a factor. However, higher education is still inaccessible for the poorest. Thus, we may conclude that

persons of the lowest status in the group of university students enjoyed optimum living conditions.

Differences in lung function due to SES may result from direct exposure to negative environmental factors and, indirectly, from the somatotype. Living conditions at an early stage of the ontogenetic development influence the process of growth and are reflected in body size and shape (Martínez-Briseño et al. 2015; Menezes et al. 2011).

Some researchers also stress the ethnic differences in spirometric parameters (Whitrow and Seeromanie 2008; Whittaker et al. 2005). Most studies show that such differences can be explained by somatotype, mainly by stature and chest size. It has been demonstrated that FVC increases together with body height (Bhatti et al. 2014; Adesola et al. 2013). This is explained by the allometric relationship between height and chest size, and consequently the lung capacities. About 50% of variability in lung function may be attributed to differences in age and body height (Kiefer et al. 2011). Chest width displays a much lower correlation with spirometric parameters (Whittaker et al. 2005).

Other anthropometric parameters frequently associated with lung function are body circumferences and body mass. The initial focus of scientific research was on circumferences of the trunk, in particular of the chest, but the global increase of the prevalence of obesity steered researchers in the direction of searching for the relationship between obesity and spirometric parameters. Adiposity affects chest wall movement, airway size, respiratory muscle function, and ventilation perfusion ratio, and in consequence may cause respiratory dysfunction (Littleton 2012). Furthermore, central adiposity is correlated with raised level of inflammatory markers and hormonal factors, which also is known to be associated with impaired airway function (Fantuzzi 2005; Armellini et al. 2000).

Many studies undertake to analyze the relationship between BMI and lung function (Vatrella et al. 2016; Bednarek-Tupikowska et al. 2012; Steele et al. 2009a; Janssen et al. 2005). Our present study indicated inferior spirometric parameters in both underweight, overweight, and obese individuals compared to the norm. Some researchers point out that BMI is not a perfect measure of adiposity. Medical sources mention patients with excessive body mass who do not demonstrate any symptoms of metabolic syndrome as well as persons with normal weight who are metabolically obese (Bednarek-Tupikowska et al. 2012). For this reason other adiposity indices are recommended. There are relatively few publications on the relationship between pulmonary function, the metabolic syndrome, and the body fat percentage measured by more direct methods (Cotes et al. 2001; Steele et al. 2009b). For example, Cotes et al. (2001) have investigated the relationship between body fat percentage, estimated from skinfolds thickness, and spirometric parameters. The body fat percentage was clearly correlated with the function of the respiratory system.

When analyzing the relationship between spirometric parameters and adiposity, most researchers uses linear correlation or compare two groups – normal weight and overweight. Such division may complicate finding the connection between the two parameters. Research methodology should also include the incidence of underweight, as not only excessive but also insufficient amount of adiposity has negative health consequences (Aune et al. 2016; Tsugane et al. 2002).

In any assessment of the negative effect of obesity one must consider not only the overall amount of body fat but also its distribution. Studies reveal that particularly excess visceral adiposity, i.e., abdominal obesity, is a risk factor contributing to respiratory function disorders, demonstrated by lower FEV1 and FVC, and an increased FEV1/FVC (Vatrella et al. 2016; Lessard et al. 2011; Chen et al. 2007). Our present findings indicate a similar tendency. Irrespective of the criterion applied for the assessment of abdominal obesity (waist size, WHR, or WHtR), in non-obese persons FEV1 and FVC are higher and FEV1/FVC is lower in comparison with individuals with abdominal obesity. The lack of statistically significant differences may result from a relatively low

number of subjects in the group. Of note is that the subjects were young persons and their history of obesity was relatively short. Moreover, most obesity indices exceeded the norm only to a small extent. We may expect that such differences will grow with subjects' age and waist size, a natural phenomenon among women.

The findings of our study confirm that both obesity and abdominal obesity are related to reduced lung function. Differences may arise already at an early age and even with low degree of obesity. In addition, study findings emphasize the importance of monitoring the lung function among young people to help prevent or identify lung function decline.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Relationships Between Quality of Life in the Psychological Domain, Acceptance of Illness, and Healthcare Services in Patients with Asthma

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Abstract

Asthma patients should be considered not only in terms of the medical aspects, but also the nonmedical issues associated with the psychological domain, since these are factors that can significantly improve patients' health state, quality of life, and illness acceptance, and can contribute to the reduction of healthcare utilization. The purpose of this study was to assess the acceptance of illness among asthma patients and their quality of life in the psychological domain, as well as to identify factors that influence illness acceptance and quality of life in the psychological domain. We examined 172 patients with asthma (median age: 58; range: 18–89 years) recruited from two pulmonology wards. We demonstrate that the patients with low levels of illness acceptance and a high healthcare service index had low quality of life in the mental domain. Older age; being separated, divorced, or widowed; and having BMI $>$ 25, all significantly affect the levels of quality of life and illness acceptance. In conclusion, measurements of health-related quality of life and illness acceptance are useful for estimating the impact and progression of asthma. These results confirm that psychological functioning should be taken into account alongside the somatic state.

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Keywords
Asthma • Elderly • Illness acceptance • Psychological functioning • Somatic index • Morbidity • Quality of life

1 Introduction

Asthma is a common chronic respiratory disease which, according to estimates, affects 1–18 % of the populations in various countries. It is a heterogeneous disease characterized by chronic respiratory tract inflammation. The severity of symptoms and the level of restraint on exhaled air flow alter over time (GINA 2015), causing fatigue and limitation of physical and everyday activities, as well as psychological discomfort, a worsening of health, and sleep problems (Nakken et al. 2015; Hazell et al. 2003). These symptoms have negative effects on patients' professional activity, hobbies, and sexual life (Schroedl et al. 2014; Wong et al. 2014), leading to loneliness, social isolation, anxiety, and depression (Panagioti et al. 2014). Hence, it is necessary to find out what psychological reserves and interventions may neutralize the adverse effects of the disease (Baiardini et al. 2015).

Asthma for a long time has been regarded as a condition in which psychological factors play a role. It is counted among the psychosomatic diseases that affect social and physical functioning of patients (Coban and Aydemir 2014; Moes-Wójtowicz et al. 2012; Alexander 1952). Psychological variables, such as bodily image and appearance; negative feelings (anxiety, depression); positive feelings; self-esteem; spirituality, religion, and personal beliefs; thinking, learning, memory, and concentration are all essential elements in asthma therapy, since they influence the adherence to treatment recommendations, check-up visits, lifestyle, and the symptoms that are reported to the doctor. Increasing evidence suggests that the relationship between asthma and psychological factors not only influences the interpretation of asthma symptoms by the patient, but also affects the objective measurable physiological changes and immunological markers of asthma (van Lieshout and MacQueen 2008). Yorke et al. (2007) have suggested that stress can speed up or intensify the symptoms of acute and chronic asthma. On the other hand, the presence of a chronic disease that potentially threatens life can evoke anxiety or depressive disorders. According to van Lieshout and MacQueen (2008), psychological barriers, such as the false attribution of pathological symptoms, accepting or rejecting the role of an ill person, and low self-esteem, can have an impact on the process of treatment and on the exacerbation of asthma. The life of patients with chronic asthma requires that the disease symptoms be overcome, and their reduction may result in a better quality of life (QoL) in the psychological, physical, and social domains (Oğuztürk et al. 2005), as well as in a higher acceptance of illness (AI). AI gives patients the feeling of safety and decreases the intensity of negative health-related reactions. The higher the AI, the lower the feeling of mental discomfort. At present, both healthcare systems and the patients themselves are expected to aim toward a good QoL, as it is a final outcome and a measure of success attained in asthma therapy (Oğuztürk et al. 2005; Jones 1994; Hyland et al. 1991). Hence, one of the main purposes of healthcare for asthma patients is to maintain satisfactory QoL as an important health effect. The literature contains few reports on the influence of QoL in the psychological domain on the form of healthcare for asthma patients. Therefore, the question of whether poor functioning in the psychological domain is a risk factor for lower QoL remains clinically important.

The purpose of this study was to assess the risk of low QoL in the psychological domain in cases of low illness acceptance, depending on the severity of asthma, taking account of forced expiratory volume in one second (FEV_1) being less than 60 % of the predicted value, age, sex,

marital status, place of residence, and body mass index (BMI). It was assumed that the higher the healthcare service index, the more severe the asthma and the lower the QoL in the psychological domain (Kurpas et al. 2015).

2 Methods

The research followed the Declaration of Helsinki and was approved by the Bioethical Commission of the Pomeranian Medical University (approval no. KB-422/2014). The main inclusion criteria were age (at least 18 years old) and a diagnosis of asthma. The manager of the hospital in Szczecin-Zdunowo gave consent for carrying out the study among hospitalized patients and participants of the asthma school.

The study group included 172 adult asthma patients; nearly all were hospitalized in two wards of pulmonary medicine due to exacerbation of the disease. In this group, 24 (14.0 %) asthma patients had also COPD, and almost every tenth patient (16, 9.3 %) was a participant of the asthma school. Men constituted the majority (104, 60.5 %) of patients, and there were 68 women (39.5 %). The median age was 58 (range 18–89 years). The sociodemographic data of the patients are presented in Table 1.

All patients underwent spirometry; 37 (21.5 %) of them had FEV_1 less than 60 % of predicted value. The highest number of concomitant chronic diseases was eight (median 2.0) and the median healthcare service index was 5.2 (Q_1: 2.4, Q_3: 26.7; range: 1–113.8). QoL was assessed using a Polish version of WHO Quality of Life Instrument Short Form (WHOQoL-BREF), which measures QoL in four domains: physical, psychological, social relationships, and environmental. Answers to all questions, including two questions on satisfaction with QoL and health status, were given on a five-point Likert-type scale.

Based on the patients' answers, the feeling of anxiety was assessed as occurring never (37, 21.5 %), seldom (72, 41.9 %), quite often (27, 15.7 %), very often (23, 13.4 %), and always (13, 7.6 %). The reliability of the WHOQoL-BREF questionnaire was verified using Cronbach's alpha coefficient: values for particular domains ranged from 0.81 to 0.69, and the coefficient for the questionnaire as a whole was 0.90. The patients' adaptation to life with disease was assessed using the Acceptance of Illness Scale, which contains eight statements on negative consequences of health state, each statement being rated on a five-point Likert-type scale with 1 denoting poor adaptation to disease and 5 its full acceptance. The score for acceptance of illness (AI) is a total of all points and ranges from 8 to 40. Low scores (8–29) indicate a lack of acceptance and adaptation to illness and an intense feeling of mental discomfort. High scores (35–40) indicate the acceptance of illness, manifesting as a lack of negative emotions associated with it. Cronbach's α was 0.85 for the Polish version and 0.82 for the original version. A somatic index was calculated for each patient. The somatic symptoms reported by the patients were assigned values from 1 (symptoms occurring once a year) to 7 (symptoms present all the time). The index was calculated by adding up the values and dividing the result by 49 (the highest possible result for the frequency of somatic symptoms). The healthcare service index was calculated by adding up the services received and dividing by the number of types of the service provided during visits to a doctor, during nurse interventions, and during hospitalizations over the last 12 months. Higher values of this index correspond with a higher utilization of healthcare services. The number of hospitalizations over 3 years denotes the number of hospital stays in the years 2013–2015.

2.1 Statistical Elaboration

For quantitative variables, the basic descriptive statistics were calculated: mean, standard deviation, median, quartiles, and minimum and maximum values. All quantitative variables, except for body weight, had a normal distribution ($p = 0.001$), which was tested using the Shapiro–Wilk test of normality. In the next stage of the analysis, Spearman's rank correlation coefficient

Table 1 Sociodemographic data of the patients (n = 172)[a]

	Category	n (%)
Gender	Female	68 (39.5)
	Male	104 (60.5)
Age (years)	18–24	11 (11.0)
	25–44	16 (6.4)
	45–64	87 (16.0)
	65–84	54 (9.4)
	85 and above	3 (1.7)
Population of place of residence	200,000 and above	3 (87.0)
	100,000–199,999	9 (5.2)
	50,000–99,999	36 (20.9)
	20,000–49,999	31 (18.0)
	10,000–19,999	22 (12.8)
	5,000–9,999	18 (10.5)
	2,000–4,999	9 (5.2)
	Rural area	44 (21.6)
Education	Primary	24 (14.0)
	Vocational	60 (34.9)
	Secondary	46 (26.7)
	Post-secondary	22 (12.8)
	Higher	19 (11.0)
Marital status	Single	15 (8.7)
	Married	106 (61.6)
	Widowed	25 (14.5)
	Separated	13 (7.6)
	Divorced	13 (7.6)

[a]The figures in column *n* do not sum up to 172 due to gaps in the questionnaires completed by the patients

was calculated. In the case of qualitative variables, categories were encoded with natural numbers. Correlation analysis was supplemented with the calculation of odds ratios for four field tables formed by pairs of two-categorical variables. These variables emerged from primary variables or were created by encoding values above and below the median in the case of quantitative variables, or by joining categories in cases of qualitative variables. A 95 % confidence interval was calculated for each odds ratio. Additionally, Fisher's exact test of independence was performed for each four field table. The critical level of significance was set as 0.05 for all tests. Calculations were performed using an Apple MacBook Pro computer with OS X El Capitan ver. 10.11.5. The R statistical software ver. 3.1.3 was employed.

3 Results

3.1 Significant Correlations

QoL levels in the mental domain positively correlated with satisfaction with QoL (in all cases $p < 0.001$) and satisfaction with health state (in both cases $r = 0.65$), with physical domain ($r = 0.85$), social relationship domain ($r = 0.68$), and the environmental domain ($r = 0.82$). QoL in the psychological domain was rated higher by patients without coexisting

COPD ($r = 0.16$, $p = 0.034$) and with high AI levels ($r = 0.63$).

Lower QoL in the psychological domain was observed among patients over 45 years of age ($r = -0.43$, $p < 0.001$), those with BMI > 25 ($r = -0.18$, $p = 0.021$), widowed, separated, and divorced ($r = -0.24$, $p = 0.001$); those with a high healthcare service index ($r = -0.31$, $p < 0.001$) and a high somatic index ($r = -0.37$, $p < 0.001$); and those with a high number of concomitant chronic diseases ($r = -0.32$, $p < 0.001$). Lower QoL in the psychological domain was also seen in the patients who were hospitalized more frequently in 2013–2015 ($r = -0.30$, $p < 0.001$), those receiving higher numbers of home visits ($r = -0.22$, $p = 0.004$), phone consultations ($r = -0.15$, $p = 0.046$) and district nurse interventions ($r = -0.25$, $p = 0.001$). The patients' QoL in the psychological domain did not correlate with gender, place of residence, or $FEV_1 < 60$ %.

Illness acceptance correlated positively (in all cases $p < 0.001$) with satisfaction with general QoL ($r = 0.52$), satisfaction with health state ($r = 0.57$), physical domain ($r = 0.67$), social relationship domain ($r = 0.68$), and the environmental domain ($r = 0.68$). Negative correlations of AI were observed with marital status, age ($r = -0.45$, $p < 0.001$), place of residence ($r = -0.17$, $p = 0.024$), and BMI ($r = -0.20$, $p = 0.01$). Lower AI levels were observed in widowed, separated, or divorced persons ($r = -0.24$, $p = 0.002$), older persons ($r = -0.45$, $p < 0.001$), those with BMI > 25 ($r = -0.20$, $p = 0.01$), high healthcare service ($r = -0.34$, $p < 0.001$) and somatic indices ($r = -0.37$, $p < 0.001$), and those having a higher number of concomitant chronic diseases ($r = -0.44$, $p = 0.001$).

Low AI levels were observed in the patients with a high number of hospital stays in 2013–2015 ($r = -0.44$, $p = 0.001$), those receiving higher numbers of home visits ($r = -0.30$, $p = 0.001$), phone consultations ($r = -0.21$, $p = 0.005$), and district nurse interventions ($r = -0.28$, $p = 0.001$), and those without somatic improvement ($r = -0.26$, $p = 0.002$). There was no significant correlation between the psychological domain and the severity of asthma ($r = -0.12$, $p = 0.379$).

3.2 Odds Ratios (OR) - Psychological Domain

The odds ratios for selected variables are presented in Table 2. The odds in favor of a **low score** in the psychological domain (below 14 points) were as follows:

- **23.91** times higher for patients with low scores in the physical domain (≤ 13.1) than for those with scores > 13.1 in this domain; the proportions of patients with low scores in the psychological domain in these groups were 81.6 and 15.3 %, respectively ($p < 0.001$);
- **16.67** times higher for patients with at least one nurse's intervention at home than for those without such an intervention; the proportions of patients with low scores in the psychological domain in these groups were 93.3 and 44.6 %, respectively ($p < 0.001$);
- **12.75** times higher for patients with low scores in the social relationship domain (≤ 14.7) than in those with scores > 14.7; the proportions of patients with low scores in the psychological domain in these groups were 75.0 and 18.0 %, respectively ($p < 0.001$);
- **12.23** times higher for patients with low scores in the environmental domain (≤ 13.8) than for those with scores > 13.8; the proportions of patients with low scores in the psychological domain in these groups were 76.7 and 20.9 %, respectively ($p < 0.001$);
- **12.20** times higher for patients with low satisfaction with QoL (< 4) than for those with scores ≥ 4; the proportions of patients with low scores in the psychological domain in these groups were 77.4 and 21.6 %, respectively ($p < 0.001$);
- **6.54** times higher for patients with poor health state (< 3) than for those with scores ≥ 3); the proportions of patients with low scores in the psychological domain in these groups were 75.8 and 32.1 %, respectively ($p < 0.001$);

Table 2 Odds ratio (OR) for 2 × 2 contingency tables of WHOQoL-BREF psychological domain by other variables

		Score of WHOQoL-BREF psychological domain				Score of acceptance of illness			
Variable		<14	≥14	OR	p	<27	≥27	OR	p
		n (%)	n (%)	$CI_1 - CI_2$		n (%)	n (%)	$CI_1 - CI_2$	
Gender	Male	57 (46.2)	56 (53.8)	0.76	0.436	48 (46.2)	56 (53.8)	0.72	0.345
	Female	48 (52.9)	32 (47.1)	0.39 − 1.47		36 (54.5)	30 (45.5)	0.37 − 1.39	
Age (year)	≤58	30 (34.1)	58 (65.9)	0.30	0.001	28 (32.6)	58 (67.4)	0.25	0.001
	>58	53 (63.9)	30 (36.1)	0.15 − 0.57		55 (66.3)	28 (33.7)	0.12 − 0.49	
Height (cm)	≤168	46 (53.5)	40 (46.5)	1.53	0.171	46 (54.1)	39 (45.9)	1.46	0.222
	>168	36 (42.9)	48 (57.1)	0.80 − 2.94		37 (44.6)	46 (55.4)	0.76 − 2.82	
Weight (kg)	≤72	41 (46.6)	47 (53.4)	0.87	0.759	36 (41.9)	50 (58.1)	0.54	0.063
	>72	41 (50.0)	41 (50.0)	0.46 − 1.66		47 (57.3)	35 (42.7)	0.28 − 1.03	
Marital status	Single/ married	52 (43.0)	69 (57.0)	0.45	0.020	51 (42.9)	68 (57.1)	0.41	0.011
	Others	32 (62.7)	19 (37.3)	0.21 − 0.92		33 (64.7)	18 (35.3)	0.19 − 0.85	
Place of residence	City	72 (48.6)	72 (51.4)	0.95	1	67 (45.9)	79 (54.1)	0.35	0.028
	Rural area	12 (50.0)	12 (50.0)	0.36 − 2.47		17 (70.8)	7 (29.2)	0.12 − 0.96	
Hospitalizations over three years (n)	<2	32 (40.0)	48 (60.0)	0.51	0.033	28 (35.9)	50 (64.1)	0.36	0.002
	≥2	52 (56.5)	40 (43.5)	0.27 − 0.98		56 (60.9)	36 (39.1)	0.18 − 0.70	
Number of home visits	0	66 (44.3)	83 (55.7)	0.22	0.003	66 (44.9)	81 (55.1)	0.23	0.003
	>0	18 (78.3)	5 (21.7)	0.06 − 0.67		18 (78.3)	5 (21.7)	0.06 − 0.68	
Consultations over phone (n)	0	59 (46.8)	67 (53.2)	0.74	0.395	57 (46.0)	67 (54.0)	0.60	0.168
	>0	25 (54.3)	21 (45.7)	0.35 − 1.54		27 (58.7)	19 (41.3)	0.28 − 1.25	
District nurse interventions (n)	0	70 (44.6)	87 (55.4)	0.06	0.001	71 (45.8)	84 (54.2)	0.13	0.003
	>0	14 (93.3)	1 (6.7)	0.00 − 0.40		13 (86.7)	2 (13.3)	0.01 − 0.61	
Somatic improvement in past 12 months	Yes	51 (42.5)	69 (57.5)	0.62	0.35	46 (38.7)	73 (61.3)	0.25	0.008
	No	12 (54.5)	10 (45.5)	0.22 − 1.70		15 (71.4)	6 (28.6)	0.08 − 0.76	
Mental improvement in past 12 months	Yes	53 (44.5)	66 (55.5)	1.04	1	51 (43.6)	66 (56.4)	0.71	0.496
	No	10 (43.5)	13 (56.5)	0.39 − 2.89		12 (52.2)	11 (47.8)	0.26 − 1.92	

(continued)

Table 2 (continued)

		Score of WHOQoL-BREF psychological domain				Score of acceptance of illness			
Variable		<14	≥14	OR	p	<27	≥27	OR	p
		n (%)	n (%)	$CI_1 - CI_2$		n (%)	n (%)	$CI_1 - CI_2$	
Chronic obstructive pulmonary disease	Yes	20 (64.5)	11 (35.5)	2.18	0.073	20 (69.0)	9 (31.0)	2.66	0.025
	No	64 (45.4)	77 (54.6)	0.92 – 5.43		64 (45.4)	77 (54.6)	1.07 – 7.13	
Asthma severity	Mild	21 (58.3)	15 (41.7)	1.00	1	25 (69.4)	11 (30.6)	0.81	0.775
	Moderate/ severe	14 (58.3)	10 (41.7)	0.31 – 3.22		17 (73.9)	6 (26.1)	0.20 – 2.95	
Illness acceptance (score)	<27	59 (70.2)	25 (29.8)	6.38	0.00001	–	–	–	–
	≥27	23 (26.7)	63 (73.3)	3.15 – 13.34		–	–	–	–
Satisfaction with QoL (score)	<4	65 (77.4)	19 (22.6)	12.20	0.00001	56 (67.5)	27 (32.5)	4.33	0.00001
	≥4	19 (21.6)	69 (78.4)	5.72 – 27.29		28 (32.2)	59 (67.8)	2.19 – 8.75	
Satisfaction with QoH (score)	<3	50 (75.8)	16 (24.2)	6.54	0.00001	52 (78.8)	14 (21.2)	8.24	0.00001
	≥3	34 (32.1)	72 (67.9)	3.14 – 14.19		32 (30.8)	72 (69.2)	3.86 – 18.56	
Domains of QoL:									
Physical	≤13.1	71 (81.6)	16 (18.4)	23.91	0	61 (71.8)	24 (28.2)	6.76	0.00001
	>13.1	13 (15.3)	72 (84.7)	10.33 – 59.59		23 (27.1)	62 (72.9)	3.33 – 14.21	
Psychological	<14	–	–	–	–	59 (72.0)	23 (28.0)	6.38	0.00001
	≥14	–	–	–	–	25 (28.4)	63 (71.6)	3.15 – 13.34	
Social relationship	≤14.7	69 (75.0)	23 (25.0)	12.75	0.00001	60 (65.9)	31 (34.1)	4.39	0.00001
	>14.7	15 (18.8)	65 (81.2)	5.91 – 29.08		24 (30.4)	55 (69.6)	2.22 – 8.93	
Environmental	≤13.8	66 (76.7)	20 (23.3)	12.23	0.00001	64 (76.2)	20 (23.8)	10.38	0.00001
	>13.8	18 (20.9)	68 (79.1)	5.73 – 27.41		20 (23.3)	66 (76.7)	4.92 – 22.87	
BMI (kg/m^2)	≤25.3	38 (44.7)	47 (55.3)	0.75	0.443	36 (43.4)	47 (56.6)	0.62	0.126
	>25.3	44 (51.8)	41 (48.2)	0.39 – 1.44		47 (55.3)	38 (44.7)	0.32 – 1.19	
Healthcare services index	≤5.2	34 (39.5)	52 (60.5)	0.47	0.022	33 (38.8)	52 (61.2)	0.43	0.009
	>5.2	50 (58.1)	36 (41.9)	0.24 – 0.90		51 (60.0)	34 (40.0)	0.22 – 0.82	
Somatic index	≤0.4	30 (33.7)	59 (66.3)	0.28	0.001	33 (37.5)	55 (62.5)	0.37	0.002
	>0.4	54 (65.1)	29 (34.9)	0.14 – 0.54		51 (62.2)	31 (37.8)	0.19 – 0.71	

(continued)

Table 2 (continued)

		Score of WHOQoL-BREF psychological domain				Score of acceptance of illness			
Variable		<14	≥14	OR	p	<27	≥27	OR	p
		n (%)	n (%)	$CI_1 - CI_2$		n (%)	n (%)	$CI_1 - CI_2$	
Chronic diseases (n)	<2	28 (33.3)	56 (66.7)	0.29	0.001	27 (32.1)	57 (67.9)	0.24	0.00001
	≥2	56 (63.6)	32 (36.4)	0.15 – 0.56		57 (66.3)	29 (33.7)	0.12 – 0.48	

AI acceptance of illness, *QoL* quality of life, *QoH* quality of health, *BMI* body mass index, *OR* odds ratio, $CI_1 - CI_2$ lower and upper 95 % confidence interval for OR, *p* value of Fisher's exact test

- **6.38** times higher for patients with low AI levels (< 27) than for those with AI levels ≥ 27; the proportions of patients with low scores in the psychological domain in these groups were 70.2 and 26.7 %, respectively ($p < 0.001$);
- **4.55** times higher for patients with at least one home visit of a doctor than for those without such a visit; the proportions of patients with low scores in the psychological domain in these groups were 78.3 and 44.3 %, respectively ($p = 0.003$).
- **3.57** times higher for patients with a high somatic index (> 0.4) than for those with a lower somatic index ≤ 0.4; the proportions of patients with low scores in the psychological domain in these groups were 65.1 and 33.7 %, respectively ($p < 0.001$);
- **3.45** times higher for patients with a higher number of comorbidities (≥ 2) than for those with fewer comorbidities < 2; the proportions of patients with low scores in the psychological domain in these groups were 63.6 and 33.3 %, respectively ($p = 0.001$);
- **3.30** times higher for patients aged over 58 years than for younger ones (18–58 years of age); the proportions of patients with low scores in the psychological domain in these groups were 63.9 and 34.1 %, respectively ($p = 0.001$);
- **2.20** times higher for widowed, separated, or divorced patients than for those who were single or married; the proportions of patients with low scores in the psychological domain in these groups were 62.7 and 43.0 %, respectively ($p = 0.02$);
- **2.13** times higher for patients with high health care service index (> 5.2) than for those with the index ≤ 5.2; the proportions of patients with low scores in the psychological domain in these groups were 58.1 and 39.5 %, respectively ($p = 0.02$);
- **1.96** times higher for patients with a high number of hospitalizations (≥ 2) in the past 3-year period than for those with < 2 hospital stays; the proportions of patients with low scores in the psychological domain in these groups were 56.5 and 40.0 %, respectively ($p = 0.03$).

3.3 Odds Ratio - Acceptance of Illness

The odds ratios in favor of a **low score** (below 27 points) in AI were as follows:

- **10.38** times higher for patients with low scores in the environmental domain (≤ 13.8) than for those with scores > 13.8 in this domain; the proportions of patients with low AI in these groups were 76.2 and 23.3 %, respectively ($p < 0.001$);
- **8.24** times higher for patients with low satisfaction with health state (≤ 3) than for those with the satisfaction > 3; the proportions of patients with low AI levels in these groups

were 78.8 and 30.8 %, respectively ($p < 0.001$);

- **7.69** times higher for patients with at least one district nurse intervention than for those without such interventions; the proportions of patients with low AI levels in these groups were 86.7 and 45.8 %, respectively ($p = 0.003$);
- **6.76** times higher for patients with low scores in the physical domain (≤ 13.1) than for those with scores > 13.1 in this domain; the proportions of patients with low AI levels in these groups were 71.8 and 27.1 %, respectively ($p < 0.001$).
- **6.38** times higher for patients with a low score in the psychological domain (≤ 14) than for those with scores > 14 in this domain; the proportions of patients with low AI in these groups were 72.0 and 28.4 %, respectively ($p < 0.001$);
- **4.17** times higher for patients with a higher number of concomitant chronic diseases (≥ 2) than for those with fewer than two diseases; the proportions of patients with low AI in these groups were 63.3 and 32.1 %, respectively ($p < 0.0001$).
- **4.35** times higher for patients with at least one home visit than for those without such visits; the proportions of patients with low AI levels in these groups were 78.3 and 44.9 %, respectively ($p = 0.003$);
- **4.33** times higher for patients with low satisfaction with QoL (≤ 4) than for those with the satisfaction > 4; the proportions of patients with low AI levels in these groups were 67.5 and 32.2 %, respectively ($p < 0.001$);
- **4.00** times higher for patients no somatic improvement than for those with such improvement; the proportions of patients with low AI levels in these groups were 71.4 and 38.7 %, respectively ($p = 0.008$);
- **4.39** times higher for patients with low scores in the social relationship domain (≤ 14.7) than for those with scores > 14.7 in this domain; the proportions of patients with low AI levels in these groups were 65.9 and 30.4 %, respectively ($p < 0.001$);
- **4.00** times higher for older patients ($\geq$ 58 years of age) than for those < 58 years old; the proportions of patients with low AI in these age groups were 66.3 and 32.6 %, respectively ($p = 0.001$);
- **2.86** times higher for patients living in the country than for city dwellers (OR = 0.35; 95%CI 0.12–0.96); the proportions of patients with low AI in these groups were 70.8 and 45.9 %, respectively ($p = 0.030$);
- **2.78** times higher for patients with numerous hospitalizations than for those with less frequent hospital stays (OR = 0.36, 95%CI 0.18–0.70); the proportions of patients with low AI levels in these groups were 60.9 and 35.9 %, respectively ($p = 0.001$);
- **2.70** times higher for patients with a high somatic index (≥ 0.4) than for those with the index < 0.4; the proportions of patients with low AI levels in these groups were 62.2 and 37.5 %, respectively ($p = 0.002$);
- **2.66** times higher for patients with chronic obstructive pulmonary disease (COPD) than for those without COPD; the proportions of patients with low AI levels in these groups were 69.0 and 45.4 %, respectively ($p = 0.025$);
- **2.44** times higher for patients who were widowed, separated, or divorced than for single and married patients; the proportions of patients with low AI in these groups were 64.7 and 42.9 %, respectively ($p = 0.01$);
- **2.33** times higher for patients with a high healthcare service index (≥ 5.2) than for those with the index < 5.2; the proportions of patients with low AI levels in these groups were 60.0 and 38.8 %, respectively ($p = 0.009$);

4 Discussion

Various aspects of life are of different significance for different people, depending on their social and cultural background. However, five domains: physical, psychological, social

(environmental), economic, and spiritual are commonly regarded as crucial for QoL, regardless of patients' life situation, health state, and other nonmedical aspects (Becerra 2016; Juniper et al. 1993). According to the Global Initiative for Asthma (GINA 2015), only every second person with bronchial asthma is treated properly, mainly because patients do not adhere to therapeutic recommendations. The factors that contribute to the lack of cooperation by the patient include non-acceptance of the illness, fear for life, anger, and insufficient social support (Moes-Wójtowicz 2012). For this reason, interest has grown in such psychological consequences of chronic conditions as depression and anxiety, which are the most common emotional reactions to the disease. Less numerous are reports on the impact of everyday symptoms associated with patients' fear for their health and life (Nowicka-Sauer et al. 2015). Attempts have also made to explain the relationship between psychological factors and asthma severity. The available findings indicate that psychological problems induced by dyspnea range from neuropsychological deficits (Schou et al. 2012) and depressive and anxiety disorders (Pumar et al. 2014) to a visible decline in the QoL level (Weldam et al. 2013). Currently, many researchers believe that not only does asthma have effects on mental health, but also that mental health contributes to the course of asthma (Baiardini et al. 2015).

In the present study, almost every sixth patient felt anxiety either very often or always, and every fourth felt it quite often, which might have translated into low QoL scores, as well as poor AI levels and worse health state. Panagioti et al. (2014) have found that anxiety and depression visibly lower health related QoL, and that low QoL is a predictor of mental health problems. What is more, anxiety and depression contribute to a higher utilization of healthcare services.

We found in this study that asthma severity of less than 60 % of predicted values for FEV_1 did not lower QoL in the psychological domain, and it had influence neither on the presence of anxiety nor on the AI level. Likewise, Rocco et al. (1998) have demonstrated that the severity of asthma is not related to psychological disorders. On the other hand, Oğuztürk et al. (2005), who analyzed the occurrence of anxiety and depression in regard to factors such as the duration of the disease, age, and the severity of asthma according to FEV_1, have found on the basis of multiple regression that asthma severity correlated negatively with anxiety in those who were ill for a shorter time, and that older patients did not experience enhanced anxiety. What is extremely important in the therapy of asthma patients is adaptation to life with the disease, since its acceptance gives the feeling of safety and reduces the intensity of negative mental reactions (Kurpas et al. 2014).

The physical and mental symptoms of asthma that are experienced daily by patients result in lower QoL levels and an increased demand for healthcare services, consequently leading to higher medical care expenses (Petrie et al. 2014; Bruusgaard et al. 2012; Dyer et al. 1998). Likewise, mental health was assessed in this study as considerably worse by patients with high indices of somatic symptoms, with at least two respiratory diseases aside from asthma, with high healthcare service indices, and with frequent hospitalization over a 3-year period. Moreover, we observed that QoL levels in the mental domain correlated positively with satisfaction with QoL and with satisfaction with health state. This justifies the conclusion that mental disorders significantly worsen health state and lower the QoL level. According to ten Brinke et al. (2005), asthma patients who report psychological problems visit family physicians and paramedics considerably more often, and significantly more often suffer from exacerbation of the disease and are hospitalized, compared to their counterparts without such health problems. Findings of those authors suggest that the severity of asthma strongly correlates with mental health state. This relationship has also been emphasized by van Lieshout and MacQeen (2008). Poor health state and low QoL among older asthma patients (58 years and more) result not only from the severity of the disease, but are also associated with patients' psychological state and adaptation to living with the disease (van der Meer et al. 2016; ten Brinke et al. 2005). In this

study we demonstrate that older age (over 58) is a factor that considerably lowers QoL in the psychological domain and reduces the AI level. Similar research conducted by Dyer et al. (1998) has shown that asthma patients aged 70 years or more have lower QoL, and that mental health is a vital contributor to a decline in QoL. Sex is not an important determinant of QoL in the mental domain.

Studies on health related QoL provide information that enables to evaluate the health state of a patient with regard to mental and social factors, and to assess the effects of psychological interventions. Such information is of prognostic value and helps plan and organize both emergency and long-term medical care. The idea of monitoring the somatic QoL of patients would entail the development of therapeutic programs that address patients' current physical, psychological, and social needs. For many years, bronchial asthma has attracted the attention of physicians and psychologists, resulting in studies conducted to gain a better understanding of the mechanisms underlying the disease development, and to identify factors that might influence its course. In spite of this, in some groups of patients, the effectiveness of treatment remains unsatisfactory. Considering the numerous psychological problems experienced by asthma patients, one way of improving the monitoring of pathological symptoms could be a close cooperation between clinicians and psychologists.

5 Conclusions

There is a substantial risk of low quality of life, poor mental health, and low acceptance of illness among older asthma patients, irrespective of sex. All these may be related to problems in the adaptation to the disease, as well as to psychological problems. Scoring of quality of life in the psychological domain and illness acceptance, and the presence of anxiety should be taken into account as part of a clinical assessment of patients with asthma, especially older ones. Treatment for asthma symptoms combined with alleviation of adverse psychological effects may improve the health related quality of life, and thus may reduce medical costs through a decrease in healthcare utilization.

Conflicts of Interest The authors have no financial or other relations that might lead to a conflict of interest.

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The Relationship Between Burnout Syndrome Among the Medical Staff and Work Conditions in the Polish Healthcare System

Alicja Głębocka

Abstract

Psychologists emphasize that people employed in social service organizations are vulnerable to chronic stress and burnout syndrome caused by a close and unsatisfied interpersonal relationship. However, emotional exhaustion, depersonalization, and a feeling of diminished personal accomplishment can be attributed to other external factors. One of them is poor living and occupational conditions. According to a report by OECD, the healthcare system in Poland is the worst among the member countries. The aim of the present study was to define the relationship between occupational burnout and the rating of the Polish healthcare system among the medical staff. The study included 224 participants. The Maslach Burnout Inventory and the Dehumanized Behavior and the Głębocka and Rużyczka scale of Behavioral Indicators of Patient's Dehumanization were applied. The evaluations of the healthcare system were also collected. The results demonstrate that physicians were the group of most emotionally exhausted and, simultaneously, most life-satisfied persons, while nurses presented the highest level of dehumanization and the lowest level of satisfaction from life achievements. Only did physicians evaluate the healthcare system as a relatively good one. They were also more tolerant of latent dehumanization. A relationship between the dimensions of burnout and the evaluation of healthcare system were observed. The emotionally exhausted or prone to dehumanization persons were more likely to evaluate the Polish healthcare system negatively.

Keywords

Depersonalization • Dehumanization • Emotional exhaustion • Mood contagion • Nurses • Physicians

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1 Introduction

Occupational burnout is a phenomenon that negatively affects the mental well-being of individuals and unsettles their functioning in the work environment. Burnout is attributed to a number of sources, including personality, interpersonal, and institutional factors (Alarcon et al. 2009; Dickinson-Bannack et al. 2007; Bakker et al. 2005). Workers who develop close professional relationships with others (physicians, nurses, or teachers) and hold high expectations of their own professional activity are at particularly high risk of burnout (Glebocka and Lisowska 2007).

Christine Maslach, a seminal researcher in occupational burnout, demonstrated that the burnout syndrome consisted of three dimensions: emotional exhaustion, depersonalization, and a feeling of diminished personal accomplishment (Maslach et al. 1996; Maslach 1982). Emotional exhaustion results from stress experienced in work settings, which may be caused by poor work conditions or organization, work overload, long working hours, lack of adequate gratification, or conflictual interpersonal relationships (Bakker et al. 2005; Shirom and Cooper 1989).

The Polish healthcare system, in general, meets the conditions determining that physicians and nurses are under heavy stress. According to the Euro Health Consumer Index (Björnberg 2015), the Polish healthcare system is one of the worst among 35 countries studied. Poland has been ranked thirty fourth, next to last place, scoring just 523 out of 1000 points. By contrast, the Netherlands, which is considered to have the model healthcare system, scored 916 points. Only have Montenegro and Albania fewer physicians than Poland per 100,000 population. Poland scores particularly low in terms of access to healthcare services, waiting times for treatment, on-line booking of appointments, e-prescriptions, and an autocratic top-down management culture. Unsurprisingly, Poland has been also ranked thirty second in terms of patient rights and information. Bureaucracy, which makes the medical staff focus on keeping medical records rather than actual care and interaction with patients, as well as dramatically low wages of interns, residents, nurses, and support staff further add to the inefficiency of healthcare in Poland. As a result, healthcare professionals seek additional sources of income, running several jobs at the same time. A feeling of diminished personal accomplishment, which is typical of burnout syndrome, may stem from social interactions with patients, particularly excessive expectations and demands of the latter and their lack of appreciation for physicians and nurses' efforts. It may also result from organizational inertia, which leads to wasting the potential, energy, and passion of the highly qualified medical staff. In terms of equity theory, the balance of rewards and costs is negative, while from the existential perspective, the loss of the meaning of life with respect to professional work occurs (Schaufeli and Enzmann 1998).

Due to the complex and difficult situation in the healthcare sector, workers may be expected to display high levels of emotional exhaustion and, consequently, seek remedies to cope with it. One of them is depersonalization, i.e., is heartless and demeaning attitude toward patients. Maslach (1982) has observed that reactions to burnout included excessive distancing from patients and a loss of concern for their problems. Zimbardo (1970) has pointed out to another phenomenon closely related to occupational burnout, which he termed defensive dehumanization. He defined it as a defensive mechanism of protecting oneself against strong negative feelings by treating other people as objects rather than persons.

Dehumanization in medicine is currently the subject of numerous studies. Treating patients as non-human individuals can manifest itself in various forms, such as judging, criticizing, taunting, disdaining, and stigmatizing patients as well as refusing them the right to decide. In practice, healthcare professionals' dehumanized behaviors include, e.g., talking about patients in their presence yet without their participation, speaking about "them", i.e., in the third person, asking for patients' opinion only to immediately discredit it as unimportant, irrelevant or wrong,

blocking any patients' attempts to negotiate, forcing patients to strictly adhere to hospital procedures, or routinizing the medical care provided (Salmon 2000).

Haque and Waytz (2012) have observed that dehumanization in medicine stems from the structural and organizational rules of functioning of healthcare facilities as well as functional psychological demands intrinsic to the medical profession. In medical settings, dehumanization does not necessarily result from workers' bad intentions, but more often from unintentional and unconscious actions, which are a by-product of specific interpersonal relationships and hospital demands. The authors identified the following major causes of dehumanization:

1. Deindividuating practices, i.e., denying the person's 'identity' – the self-perception as being an individual, independent, and distinguishable from others, capable of making choices. In the doctor's mind, patients stripped of individual characteristics melt into a mass of similarly and poorly dressed beings that expect their help. They become faceless bodies rather than persons worthy of empathic support. Empathy reduction, which is observed in medical workers, results from mechanistic attitude toward patients who are simply considered a collection of parts which are broken and should be fixed;
2. Impaired patients' sense of agency, which refers to treating hospitalized patients as incapable of planning or any intentional actions. Wounds and injuries, chronic pain, and medical procedures administered to patients all contribute to this incapacitation of sorts;
3. Dissimilarity, which manifests in perceiving patients, by their very nature of being ill, less similar to one's prototypical concept of human. Secondly, dissimilarity involves labeling patients as cases rather than humans suffering from a particular disease. A third aspect is related to the power asymmetry common to the doctor-patient dyad, i.e., a relationship between superior and subordinate, in which the physician always has more power, and power often contributes to dehumanization. A study by Lammers and Stapel (2011) has demonstrated that high-power senior surgeons administered a painful treatment or spoke about patients in a dehumanizing manner more frequently than low-power junior surgeons and nurses.

At present, the most desirable model of the doctor-patient relationship is centered on patients' needs, i.e., their emotions, values, goals, preferences, and expectations (Berghout et al. 2015). Individual approach toward patients brings about a number of benefits for both patients and medical workers themselves. However, in the literature there are also reports on the costs borne by physicians and nurses who involve too deeply in emotional relationships with patients. The relevant negative effects include secondary traumatic stress or emotional or mood contagion. Secondary traumatic stress, also known as compassion fatigue, occurs when the symptoms typical of post-traumatic stress disorder develop in witnesses, such as physicians, nurses or paramedics, rather than victims, in this case patients exposed to traumatic events. Emotional or mood contagion involves transfer of emotional states from either patients or peer workers. There have been reports confirming that occupational burnout can be emotionally contagious. Then, similar levels of emotional exhaustion, depersonalization and a feeling of diminished personal accomplishment are observed in persons closely co-operating with one another (Bakker et al. 2001; Pearlman and Saakvitne 1995).

An investigation by Vaes and Muratore (2013) has demonstrated that healthcare workers could adequately assess the mental functioning of their patients such as awareness of disease, suffering experienced, or burden of unfavorable prognosis. They do it on the basis of similar cases observed before. The more time they spend with severely or terminally ill patients, the more disappointment with work, mental and physical exhaustion, and a feeling of ineffectiveness they experience. Burnout symptoms reduce

commitment to work, become even more intensive when they attribute to patients the uniquely human emotions such as disappointment, resentment, pity, or sorrow. Paradoxically, conviction that patients experience non-uniquely human emotions such as anger, panic, irritation, or hostility, positively predict increased commitment to work and a stronger feeling of effectiveness. Thus, humanizing severely ill patients contributes to intensification of occupational burnout symptoms in healthcare workers who are in daily contact with such patients.

Decades-long investigation of burnout has led to a conclusion that this complex psychological phenomenon can stem from various sources, ranging from organizational shortcomings and interpersonal relationships with co-workers to the frequency and type of contacts with patients. These factors are interrelated, which intensifies burnout symptoms. It is fairly understandable that deficient work organization in healthcare facilities can result in general dissatisfaction among both medical staff and patients. Physicians and nurses might feel that they do the best they can under such unfavorable circumstances, whereas patients might negatively assess their work as they have to wait for hours or are sent from one hospital to another having been denied medical care due to some existing regulations. Although medical workers often face patients' justified irritation and annoyance, it is not them but government officials who are responsible for some absurd procedures hindering provision of healthcare services in state-owned facilities.

The present study seeks to measure occupational burnout indicators among physicians and nurses as compared with other professions. In addition to burnout indicators, several other dimensions were considered such as the subjective evaluation of the functioning of the healthcare system and factors underlying the general assessment thereof. Further, the ability to identify and adequately assess dehumanized behaviors was accounted for. The control groups consisted of teachers and entrepreneurs. Teachers, similar to medical staff, are at risk of occupational burnout due to the nature of their profession having to do with interpersonal relationships with those in their care. They also face organizational inertia in public educational institutions on a daily basis. Entrepreneurs, in contrast, operate in the private sector, so that they can ensure more efficient work organization in their firms.

The study hypotheses were the following: (i) occupational burnout indicators would be higher among the medical staff than in other groups; (ii) the indicators would point to a higher acceptance of dehumanized behavior; and (iii) the evaluation of the functioning of the healthcare system would come up better compared with teachers and entrepreneurs, who were deemed to represent recipients of medical services, i.e., former or future patients.

2 Methods

Subjects participated in the study on a voluntary and anonymous basis. The study protocol was approved by the Research Committee of the Faculty of Psychology and Humanities of the Andrzej Frycz Modrzewski University in Cracow, Poland.

The Maslach Burnout Inventory (MBI) and the scale of Behavioral Indicators of Patient's Dehumanization (BIPD) developed by Głębocka and Rużyczka were applied. The MBI addresses three general domains: emotional exhaustion, depersonalization, and personal accomplishment. The BIPD consists of two subscales: patent and latent dehumanization. The patent dehumanization subscale consists of nine short situations which provide obvious and clear evidence of either subjective or objective attitudes of medical staff toward patients. The second subscale, which consists of ten items, contains descriptions of situations with more hidden signs of dehumanization. All the situations were rated on a five-point scale, focusing on four areas: ethics, empathy, human approach, and professionalism. The total score for each subscale was composed of individual results for specific areas. The higher the score, the more positive evaluation of the situations presented for a given scale. The

assessments of the healthcare system were also collected. The subjects were asked to evaluate on a five-point scale the general situation in the healthcare sector and healthcare organization, access to healthcare services, waiting times for treatment, conditions offered to inpatients, physicians and nurses' attitude toward patients, and mutual relationships between healthcare professionals. Furthermore, they were asked to indicate to what degree the work organization, healthcare financing, physicians and nurses' working time and remuneration, workers' competence and personal characteristics, interpersonal relationships, and patients' expectations determined the assessment of the healthcare system.

2.1 Participants

The study involved 224 persons randomly chosen from different professional groups, namely 48 physicians, 68 nurses (all the staff worked in hospitals, and 40 % in medical treatment departments), 49 teachers and 59 persons running their own businesses. Owing to the nature of these professions, 74 % of nurses and teachers were women. The mean age was 36.1 ± 10.3 (SD) years. The oldest group was physicians (43.0 ± 11.1 years), followed by teachers (38.0 ± 8.0 years), entrepreneurs (35.0 ± 10.5 years), and nurses (31.0 ± 9.2 years).

3 Results

3.1 Occupational Burnout

Occupational burnout indicators were analyzed using the multivariate analysis of variance with respect to the professional group factor, which gave significant results (Wilks' lambda = 0.82; $F(9.512) = 3.23$, $p < 0.001$, $eta^2 = 0.08$). A *post-hoc* Scheffe's test indicates that the mean score (M) for emotional exhaustion was the highest among physicians (M = 2.4 ± 1.3), followed by nurses (M = 2.3 ± 1.8), teachers (2.0 ± 1.1) and, entrepreneurs (M = 1.5 ± 0.7) ($p < 0.05$). The study groups also differed in the degree of depersonalization. Here, the highest score was achieved by nurses (M = 1.8 ± 1.0), followed by physicians (M = 1.7 ± 0.9), entrepreneurs (M = 1.4 ± 1.0), and teachers (M = 1.3 ± 0.8). The difference between the two medical professions was insignificant. The highest level of satisfaction from personal achievements was observed in physicians (M = 4.3 ± 1.0), followed by teachers (M = 4.1 ± 1.0), entrepreneurs (M = 3.8 ± 1.2), and nurses (M = 3.5 ± 1.0); the nurses' score differed significantly from the other groups ($p < 0.05$). A high level of emotional exhaustion was found in 33.3 % of physicians, 28.3 % of nurses, 28.6 % of teachers, and just in 3.7 % of entrepreneurs. A high depersonalization level was found in 34.6 % of physicians, 41.5 % of nurses, 19.2 % of teachers, and in 23.1 % of entrepreneurs. Finally, high satisfaction from personal achievements was declared by 36.4 % of teachers, 24.0 % of entrepreneurs, 32.0 % of physicians, and just by 15.1 % of nurses. Out of the three dimensions of occupational burnout, i.e., emotional exhaustion, depersonalization, and personal accomplishment, only satisfaction from personal achievements correlated positively with the subject's age ($r = 0.27$, $p < 0.05$) and seniority ($r = 0.21$, $p < 0.05$).

3.2 Patent and Latent Dehumanization

The evaluation of patent dehumanization, i.e., factor I of the BIPD scale, which did not meet the normal distribution assumptions, was conducted using the Kruskal-Wallis non-parametric test by ranks. The results indicate no appreciable differences between the groups concerning the patent dehumanization behaviors depicted in the stories. However, differences at the trend level were identified with respect to factor II, i.e., latent dehumanization ($F(3.211) = 2.30$, $p = 0.07$). A *post-hoc* Scheffe's test revealed that the highest and lowest tolerance to this form of dehumanization behavior was

Table 1 Evaluation of healthcare and interpersonal relationships in healthcare facilities stratified by profession

Healthcare evaluation	Physicians	Nurses	Teachers	Entrepreneurs	p
Work organization in healthcare facilities	2.7 ± 0.9	2.5 ± 0.8	2.6 ± 0.8	2.5 ± 1.0	**ns;** ns.
Access to healthcare services	2.4 ± 0.8	2.2 ± 0.8	2.0 ± 0.8	1.7 ± 0.9	**0.05;** 0.05
Waiting time for treatment	2.5 ± 0.8	1.6 ± 0.7	1.5 ± 0.6	1.4 ± 0.7	**0.001;** 0.001
Conditions offered to inpatients	2.5 ± 0.7	2.8 ± 0.9	2.2 ± 1.0	2.4 ± 1.0	**ns;** 0.001
Physicians' attitude toward patients	3.1 ± 0.8	3.1 ± 0.8	2.7 ± 0.7	2.8 ± 0.9	**0.05;** 0.05
Patients' attitude toward physicians	3.1 ± 0.7	3.6 ± 0.8	3.0 ± 0.8	3.3 ± 0.8	**0.05;** 0.001
Nurses' attitude toward patients	3.0 ± 0.8	3.6 ± 0.8	3.1 ± 0.6	3.2 ± 0.7	**0.05;** 0.05
Patients' attitude towards nurses	3.1 ± 0.7	2.9 ± 0.9	3.2 ± 0.8	3.5 ± 0.7	**ns;** 0.05
Relationships between health care professionals	3.0 ± 0.9	3.2 ± 0.8	3.2 ± 0.7	3.3 ± 0.6	**ns;** ns.

Data are means ±SD; *Bold type*, significance differences between physicians *vs.* all other groups; *Underlining*, significance differences between nurses *vs.* all other groups; *ns,* non-significant

shown by physicians (M = 1.8 ± 0.5) and teachers (M = 1.5 ± 0.4), respectively ($p < 0.05$).

3.3 Evaluation of Healthcare

The evaluation of the healthcare sector regarding the profession factor revealed significant differences between the study groups ($F(3.214) = 2.64$, $p = 0.05$, $eta^2 = 0.04$). Healthcare was best assessed by physicians (M = 2.5 ± 0.9), in which they differed from non-medical professions: teachers (M = 2.2 ± 0.7) and entrepreneurs (M = 2.0 ± 0.8) ($p < 0.05$). However, despite the identified differences the general assessment of the situation in the healthcare sector was negative across all the test groups. When asked about the causes of the current situation, the subjects indicated deficient work organization (M = 3.9 ± 1.0), low healthcare financing (M = 4.4 ± 0.9), and the waiting time for treatment (M = 3.7 ± 1.2) as key reasons, while personal characteristics of patients was the least important (M = 2.7 ± 1.0) ($F(11.1584) = 27.33$, $p < 0.0001$, $eta^2 = 0.16$). In the subjects' opinion, interpersonal relationships between the medical staff and patients only moderately contributed to the poor condition of healthcare (M = 3.3 ± 1.0). Particularly, low importance was assigned to interpersonal relationships by physicians (M = 2.8 ± 0.9) and nurses (M = 3.0 ± 1.2), in which they significantly differed from non-medical professionals (M = 3.5 ± 0.9) ($p < 0.05$).

Fragmentary questions concerning the evaluation of healthcare functioning revealed some significant differences between the study groups ($F(3.221) = 3.33$, $p = 0.02$, $eta^2 = 0.06$). The evaluation was generally congruous regarding the work organization in healthcare facilities, as in the statistical terms all scores were significantly lower than the mean score ($p < 0.05$). Another dimension with no intergroup differences was the assessment of relationship between healthcare professionals. Physicians and nurses evaluated this relationship as average, while the other subjects considered them fairly good.

Physicians' attitude toward patients was evaluated as fairly good by nurses and physicians themselves, while teachers and entrepreneurs considered it fairly bad. Nurses' attitude toward patients was evaluated as fairly good by nurses themselves, while all other groups considered it average (neither good nor bad). Patients' attitude toward physicians was evaluated by all subjects as fairly good, which was particularly reflected among nurses. In contrast, nurses' assessment of patients' attitude toward them was the most negative compared with that of non-medical professions (Table 1).

Concerning the healthcare components, all subjects were the most critical about the waiting time for treatment (M = 1.7 ± 0.8), access to healthcare services (M = 2.1 ± 0.8), and conditions offered to inpatients (M = 2.5 ± 0.9)

Table 2 Occupational burnout symptoms – multiple regression analysis

Predictors	Emotional exhaustion	Depersonalization	Satisfaction from personal achievements
	b-coefficient	b-coefficient	b-coefficient
General assessment of healthcare	−0.34**	−0.21*	0.20*
Work organization in healthcare facilities	−0.03	0.02	−0.05
Access to healthcare services	0.01	−0.04	−0.02
Waiting time for treatment	0.03	−0.03	0.09
Conditions offered to inpatients	0.22*	0.16	−0.07
Physicians' attitude towards patients	−0.02	0.01	0.12
Patients' attitude toward physicians	0.01	0.15*	−0.16*
Nurses' attitude toward patients	0.01	−0.01	0.06
Patients' attitude toward nurses	−0.10	−0.17*	0.08
Relationships between healthcare professionals	−0.15*	−0.13	0.23*
	$R^2 = 0.12$, $F(10.212) = 3.67$, $p < 0.001$, SE of estimate: 9.5	$R^2 = 0.09$, $F(10.218) = 2.89$, $p < 0.001$, SE of estimate: 4.6	$R^2 = 0.13$, $F(10.217) = 3.85$, $p < 0.001$, SE of estimate: 7.6

*$p < 0.05$ and **$p < 0.001$ for the burnout syndrome predictor's significance

Table 3 Depersonalization in the context of the evaluation of dehumanization behavior – multiple regression analysis

	b-coefficient	b-SE	b-coefficient	b-SE	t(218)	P -value
Absolute term			5.27	1.63	3.23	<0.002
Factor I – Patent dehumanization	−0.14	0.08	−1.85	1.08	−1.72	0.088
Factor II – Latent dehumanization	0.28	0.08	3.31	0.92	3.60	0.001

$R^2 = 0.06$, $F(2.218) = 6.49$, $p < 0.001$, SE of estimate: 4.7

($p < 0.001$), whereas patients' attitude toward physicians ($M = 3.3 \pm 0.8$), nurses' attitude toward patients ($M = 3.3 \pm 0.7$), patients' attitude toward nurses ($M = 3.2 \pm 0.8$), and the relationship between healthcare professionals ($M = 3.2 \pm 0.8$) had the highest scores. Differences in the interpersonal relationships were insignificant, except for the physicians' attitude toward patients ($M = 2.9 \pm 0.8$) ($p < 0.001$).

3.4 Predictors of Occupational Burnout

The occupational burnout predictors were determined in the context of the evaluation of the functioning of the healthcare system and of interpersonal relationships. Three dimensions, namely a negative assessment of healthcare, a poor relationship between healthcare professionals, and a positive assessment of conditions offered to inpatients appeared to predict emotional exhaustion. Depersonalization predictors included a negative general assessment of healthcare, positive patients' attitude toward physicians, and a negative patients' attitude toward nurses. Finally, a positive general assessment of healthcare, a negative assessment of patients' attitude toward physicians, and proper relationships between healthcare professionals were all predictors of satisfaction with personal achievements (Table 2).

The tolerance for latent dehumanization behavior appeared a significant predictor of depersonalization (Table 3).

4 Discussion

The findings of the present study demonstrate that the predictors of occupational burnout were higher among the medical staff than in other professions. These findings are congruous with those of earlier studies on the subject conducted in Poland (Jabłkowska and Borkowska 2005). Physicians demonstrate the highest level of emotional exhaustion and nurses closely followed, while both groups differed significantly from the control group of entrepreneurs. As for depersonalization, healthcare professionals achieved higher scores than their non-medical counterparts did. In terms of satisfaction with personal achievements, nurses were definitely dissatisfied, in which they significantly differed from the other groups, while physicians achieved the highest score. It may be concluded that a consistent picture of workers demonstrating occupational burnout syndrome emerges in the group of nurses, whereas physicians show a relatively high tendency toward emotional exhaustion and depersonalization, accompanied by dissatisfaction from personal achievements. These differences can be likely attributed to broader opportunities for professional development and career as well as social recognition and prestige enjoyed by the medical profession in Poland. For the general public, physician is a respectable authority. Unfortunately, nursing profession is not viewed in the same way (Włodarczyk and Tobolska 2011). Nurses are not treated as healthcare team members in their own rights, with physicians being specialists in treatment and nurses being specialists in patient care. According to a popular notion, nurses, being inferior to physicians in terms of qualifications, should strictly follow the physicians' instructions. In addition, professional development and career opportunities are much broader for physicians than for nurses. A high disproportion in wages between both groups also weighs in on the satisfaction from personal achievements.

To explain the mechanisms of occupational burnout among the medical staff, it was assumed that depersonalization of patients would be accompanied by a higher acceptance of dehumanization behavior. However, the hypothesis that physicians and nurses would evaluate dehumanized behavior more positively was only partially confirmed. A highly critical assessment of patents' dehumanization was uniform across all the study groups. Differences were revealed in the evaluation of latent dehumanization, but only between physicians and teachers. A critical assessment of latent dehumanization by nurses and teachers might stem from their education, centered to a greater extent, on humanities. The curriculum for nursing education includes courses on psychology of somatic disorders and on professional burnout, whereas physicians' education focuses, almost exclusively, on medical knowledge. A relatively high level of tolerance for dehumanization behavior among physicians may stem from the defensive strategy against emotional exhaustion; belittling patients may help carry out medical procedures more effectively, as it is easier to cause pain to someone who has been dehumanized (Haque and Waytz 2012). Alternatively, tolerance for dehumanization might be a reflection of the perception of power (Lammers and Stapel 2011). Being an authority and feeling responsible for the life and health of patients, physicians may tend to neglect their feelings, values, rights, or habits in the name of higher values. However, when a positive evaluation of latent dehumanization is taken as a predictor of depersonalization, a question arises to what extent the ability to recognize and adequately evaluate latent dehumanization behavior can effectively reduce dehumanization behavior. A number of studies demonstrate that including patients into the treatment-related decision-making processes, departing from strict hospital routines, and listening to patients, not questioning their opinions, not only positively affect the doctor-patient interactions and the mental well-being of patients, but also accelerate healing. Hence, it seems reasonable to make physicians aware what behaviors reflect latent dehumanization and how to effectively reduce such behaviors. That is important since the depersonalizing frame of mind toward patients

may move onto other medical workers in the mood contagion process (Bakker et al. 2001).

Another factor that increases the risk of occupational burnout among the medical staff is a subjective perception of how the healthcare system functions. Physicians offered the most optimistic vision of healthcare, access to healthcare services, treatment waiting time, physicians and nurses' attitude toward patients, and patients' attitude toward physicians compared with the other study groups. Although the physicians scored higher than the other professionals did, in most cases, the result oscillated around the middle point of the scale. Only was the score on the lower side concerning access to healthcare services, which implies certain limitations. Scores in the control groups also made it clear that the perception of access to healthcare services was far from being satisfactory. Notably, rather poor perception of this aspect by former or potential patients is in line with other results on the functioning of the healthcare system in Poland (Björnberg 2015). OECD (2015) has assumed waiting times for cataract surgery and hip replacement as a measure of waiting time in the healthcare system. In Poland, these times are the longest among all the countries studied, namely over 400 days and 350 days for cataract surgery and hip replacement, respectively.

The general assessment of the healthcare system was identified as one of a key predictors of occupational burnout. Poor relationships between healthcare professionals were a predictor of emotional exhaustion, while positive ones were a predictor of satisfaction from personal achievements. These relations are consistent with those found in earlier studies. In addition, emotional exhaustion was dependent on the positive evaluation of conditions offered to inpatients. Most likely, emotionally exhausted persons believe that the relevant complaints of patients are groundless or unfair. It could hardly be assumed that the lack of complaints reflects a high quality of hospital services, as shared rooms and bathrooms, as well as hospital diets of sorts are rather common in the Polish healthcare system. A plausible explanation is that physicians accuse patients of focusing on less important aspects of hospital care, namely the living conditions. Thus, patients' complaints about the lack of privacy and poor living conditions may be considered as unfair, because the medical staff should not be blamed for them. In fact, Polish patients' expectations in this area are growing. According to the surveys conducted by the Public Opinion Research Center, 66 % of patients were satisfied with hospital conditions in 2009 compared with 52 % in 2014 (CBOS 2014).

Depersonalization is determined by a negative attitude of patients toward nurses, which is understandable, as well as by a positive attitude of patients toward physicians, which is rather surprising. These discrepancies are difficult to explain. Perhaps a positive attitude toward physicians is understood by as a form of patients' subordination, obedience, or even submissiveness toward physicians. Such patients do not articulate their demands or expectations, so they are more prone to deindividuation, melting into a mass of other individuals, and becoming cases rather than persons who suffer. They are more easily dehumanized (Haque and Waytz 2012). If the subjects did understand a positive attitude of patients toward physicians in this way, then a negative attitude does not necessarily indicate improper or disturbed relationships, but might simply be the opposite of the superior-subordinate relationship and reflect more partnership-like type of relationship, which is currently much promoted in the patient-centered model of healthcare (Berghout et al. 2015). Such explanation is further supported by another relation identified in the present study: the more negative assessment of patients' attitude toward physicians, the higher physician's satisfaction from personal achievements.

To sum up, the healthcare system in Poland contributes to occupational burnout and patient dehumanization. The factors enhancing such processes are of both organizational and interpersonal nature (Bakker et al. 2005; Shirom and Cooper 1989). In addition to reducing waiting time for treatment, increasing access to healthcare services, and improving hospital conditions, efforts should be made to enhance

the quality of interpersonal relationships. Both medical workers and patients would benefit from a psychological attempt to explain the causes and mechanisms of dehumanization behavior and to specify the effective ways to mitigate this process.

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Association of Estrogen-Related Traits with Allergic Rhinitis

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Abstract

Estrogen's role in allergic diseases has recently been of considerable interest. The present article seeks to determine the relationship between estrogen-dependent traits and allergic rhinitis. The following traits were considered: digit ratio, age at menarche, regularity of menstrual cycles, and the waist to hip ratio. The study consisted of surveys and measurement data collected from 768 female university undergraduates. One hundred and sixty eight undergraduates (21.9%) had been diagnosed with allergic rhinitis. The results of logistic regression show that in women with a high digit ratio, indicating exposure to a higher estrogen level in the prenatal period, the risk of allergic rhinitis was almost twice as high as that in those with an average value of the ratio. The difference in the digit ratio was greater for the right than left hand. A significantly higher risk of allergic rhinitis was also observed in women who experienced first menstruation at a younger age. No differences in risk of allergic rhinitis were noted due to general obesity, abdominal obesity, or irregularity of menstrual cycles. We conclude that a higher digit ratio is suggestive of a propensity to allergies in adulthood plausibly having to do with greater exposure to estrogen at early stages of ontogenetic development.

Keywords

Digit ratio • Estrogen • Menarche • Obesity • Prenatal period • Respiratory allergy • Rhinitis

1 Introdution

In recent years, more and more studies focus on the effect of sex hormones on respiratory and immune functions (Macsali et al. 2009, 2011, 2012 Melgert and Postma 2009; Real et al.

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2005, 2007, 2008; Svanes et al. 2005). Evidence for such relationship includes, among others, gender differences in the prevalence and severity of asthma and allergic diseases. In childhood, such diseases are more common in males, whereas after puberty in females (Caracta 2003). Clinical tests and tests performed in animal models suggest that sex hormones play a major role in the differences (Keselman and Heller 2015). The significance of sex hormones in respiratory function is also indicated by changes in the severity asthma and respiratory allergies symptoms as well as lung function during the menstrual cycle (Matteis et al. 2014; Chen et al. 2003; Becklake and Kauffmann 1999; Prescott et al. 1997; Pauli et al. 1989; Settipane and Simon 1989; Eliasson et al. 1986). In addition, a link between the time of puberty appearance and asthma and allergies, both in childhood and in adulthood, is well documented. Girls with asthma and allergy, regardless of their body mass index (BMI), experience the first menstruation at younger age (Hong et al. 2015) and the early age at menarche increases the risk of asthma and allergies in adulthood (Gnatiuc et al. 2013; Macsali et al. 2012; Al-Sahab et al. 2011; Zheng et al. 2011). Not only has the first but also last menstruation in life an effect on respiratory health. It is demonstrated that menopause is related to a decrease in spirometric parameters, whereas the risk of asthma and wheeze after menopause drops significantly.

The literature also contains studies connecting respiratory function, asthma, and atopic sensitization with irregular menstrual cycles, polycystic ovary syndrome (PCOS), contraceptives and hormone replacement therapy (Real et al. 2007; Salam et al. 2006; Svanes et al. 2005). Studies indicate that the incidence of allergic diseases in childhood may be related to hormone levels as early as in the prenatal period. It has been reported that mother's early age at menarche, a marker of mother's endogenous estrogen status, increases the risk of atopy in her offspring (Xu et al. 2003). Hormones, mainly progesterone, influence mother's immune system, which during pregnancy shifts to Th2 immunity to protect the fetus against the toxic effect of Th1. Progesterone promotes the development of Th2-type immunity and down regulates Th1 cells and production of pro-inflammatory cytokines (Rangaraj and Doull 2003; Whitacre et al. 1999). Estradiol also plays an important role in this process. According to the recent reports, estrogen receptors are found on numerous immunoregulatory cells and estrogen's actions skew immune responses toward allergy (Bonds and Midoro-Horiuti 2013).

The effect of sex hormones on respiratory and immune function is one of currently explored and relevant research subjects due to the increased exposure to estrogens and a rapid increase in the prevalence of respiratory and atopic diseases. Nowadays, women remain under the influence of estrogens for a longer period in their lives, a phenomenon caused by the lowered age at menarche, later menopause, and fewer pregnancies. Frequent obesity, use of oral contraceptives, and exposure to environmental estrogens, all contribute to a heightened amount of estrogens in the body. Published data point to certain trends, but the determination of direction of relationships and developmental periods in which high estrogen level raises the risk of respiratory diseases, as well as the explanation of the mechanism of such dependency, require further research.

Digit ratio, i.e., a proportion of the length of finger 2 to finger 4, is determined early on in the prenatal period and remains unchanged throughout the later ontogenetic phases. The ratio is influenced by prenatal sex hormones, mainly testosterone and estrogens. A high testosterone or low estrogen level results in 'male' finger proportions, which leads to a lower ratio values, i.e., finger 4 longer than finger 2. In contrast, a high estrogen or low testosterone level determines 'female' finger proportions, which leads to a high ratio values, i.e., finger 2 longer than finger 4 (Manning 2002). As regards the early age at menarche, its connection with the level of estrogens has repeatedly been demonstrated. Hormonal disorders may manifest in irregular menstrual cycles. Also adiposity, especially located in the abdominal region, has a considerable influence on hormonal activity. It

has been proved that females with a low waist to hip ration are characterized by low levels of male and high levels of female sex hormones (Jasienska et al. 2004; Evans et al. 1983).

The present work seeks to determine the relationship between estrogen level-dependent traits and self-reported, confirmed by a physician, allergic rhinitis. The following traits were considered: digit ratio, age at menarche, regularity of menstrual cycles, and waist to hip ratio.

2 Methods

The study protocol was approved by a local Ethics Committee. Data were collected following the ethical principles as stated in the Declaration of Helsinki. The material consisted of survey and measurement data collected from 768 female students of Cracow universities. The mean age of the subjects was 20.3 ± 1.5 years (range 19–25 years), with inappreciable age differences between women with and without allergy.

Questions in the survey concerned the occurrence of allergy, socio-economic status, age at menarche, and the regularity of menstrual cycles. Age at menarche was reported using in a retrospective method. Socio-economic status was determined by standard variables commonly used in anthropological research: place of residence before the higher education period (possible categories: country, town up to 100,000 inhabitants, and town above 100,000 inhabitants), mother and father's education level (categories: occupational, secondary, and higher), and the number offspring (0, 1, 2, 3+). A complex indicator of socio-economic status was created on the basis of all of the above factors. The subjects were divided into three groups of low, medium and high status. The above division was made on the basis of the value of the first component calculated in the principal component analysis.

The occurrence of allergy was determined using the response to the question Have you been diagnosed with an allergy on the basis of medical tests; and if yes, what allergens are you allergic to?' Allergic rhinitis was defined by a positive response to the question: 'Do you get attacks of 'hay fever' (i.e., sneezing, running or blocked nose, sometimes with itchy eyes or nose)?'

Anthropometric measurements included body height, body weight, waist circumference, hip circumference, and the length of finger 2 and finger 4. All measurements were taken by the authors of the present study according to current anthropometric methodology. On the basis of the measurements, the following indicators were calculated: body mass index (BMI), waist to hip ratio (WHR), waits to height ratio (WHtR), and 2D:4D digit ratio.

The above factors were considered as categorical variables. Women were divided into three groups based on the hand-specific tertiles of 2D:4D. The first tertile had the lowest 2D:4D (<0.979 for the right hand and <0.980 for the left hand) and the third tertile had the highest 2D:4D (>1.019 for the right hand and >1.020 for the left hand). Classification was made as that in works by other authors. On the basis of subjects' age at menarche, division was applied into early puberty (age at menarche below the 25th percentile, i.e., 12 years of age), average puberty (age at menarche from the 25th to 75th percentile), and late puberty (age at menarche above the 75th percentile, i.e., 13 years of age). BMI was used to qualify women as having below normal body mass (BMI <18.5), normal body mass (BMI from 18.5 to 24.99), and overweight (BMI 25.0–29.99) or obese (BMI ≥ 30.0).

On the basis of WHR, women were divided into two groups: with normal value of the indicator (WHR <0.8) and with abdominal obesity (WHR ≥ 0.8). WHtR was divided into three categories: below 0.4, 0.4–0.5, and above 0.5. The frequency of each category's occurrence is shown in Table 1.

2.1 Statistical Elaboration

Logistic regression was applied to determine the risk of allergic rhinitis depending on markers of estrogen levels: digit ratio, age at menarche,

Table 1 Characteristics of subjects

		Number of subjects n (%)	Nonallergic subjects n (%)	Allergic subjects n (%)	p
SES	Low	162 (25.1)	135 (27.8)	27 (16.8)	**0.001**
	Average	247 (38.2)	192 (39.5)	55 (34.4)	
	High	237 (36.7)	159 (32.7)	78 (48.8)	
Digit ratio – right hand	Low	251 (32.6)	206 (34.3)	45 (26.80	0.133
	Middle	247 (32.2)	192 (32.0)	55 (32.7)	
	High	270 (35.2)	202 (33.7)	68 (40.5)	
Digit ratio – left hand	Low	231 (30.1)	187 (31.2)	44 (26.2)	0.297
	Middle	262 (34.1)	206 (34.3)	56 (33.3)	
	High	275 (35.8)	207 (34.5)	68 (40.5)	
BMI (kg/m^2)	Underweight	110 (14.3)	79 (13.2)	31 (18.4)	**0.030**
	Normal	560 (72.9)	451 (75.2)	109 (64.9)	
	Overweight	98 (12.8)	70 (11.6)	28 (16.7)	
WC (cm)	<80	658 (85.7)	514 (85.7)	114 (85.7)	0.908
	≥80	110 (14.3)	86 (14.3)	24 (14.3)	
WHR	<0.8	610 (79.4)	467 (77.8)	143 (85.1)	0.039
	≥0.8	158 (20.6)	133 (22.2)	25 (14.9)	
WHtR	<0.4	157 (20.4)	116 (19.3)	41 (24.4)	0.251
	0.4–0.5	497 (67.5)	397 (66.2)	100 (59.5)	
	>0.5	114 (14.8)	87 (14.5)	27 (16.7)	

SES socio-economic status, *BMI* body mass index, *WC* waist circumference, *WHR* waist-to-hip-ratio, *WHtR* waist-to-height ratio, ***Bold typed p-values*** statistically significant differences between non-allergic and allergic women based on Chi^2 test ($p < 0.05$)

menstrual cycle regularity, and WHR. These factors were considered as categorical variables. Secondly, the analyses were performed with 2D:4D, age at menarche, BMI, and WHR as continuous variables. Relationships between allergic rhinitis and markers of estrogen level were tested by analysis of variance. Due to the relationship between socio-economic factors and the prevalence of allergies, maturity rate, and anthropological parameters, socio-economic status was included in each analysis as a potential confounder. A p-values <0.05 was used to define statistically significant differences.

3 Results

Medically diagnosed allergy was reported by 205 women (26.7% of all subjects), of which 168 women were diagnosed with allergic rhinitis (21.9% of all subjects). The results of logistic regression are shown in Table 2. In women with a high digit ratio, indicating exposure to a high estrogen level in the prenatal period, the risk of allergic rhinitis was almost twice as high as that in women with middle values of the ratio ($p<0.05$). The difference was greater for the right than left hand. A significantly higher risk of allergic rhinitis was also observed in women who experienced first menstruation at younger age. No differences in the odds ratio of allergic rhinitis due to obesity, abdominal obesity, or irregular menstrual cycles were found.

Women with allergic rhinitis were characterized by a significantly higher digit ratio for both right and left hand, and the earlier age at menarche. They also tended to have higher BMI and WHR, although the differences here failed to reach statistical significance in comparison with non-allergic women (Table 3). The inclusion of SES as a covariate remained without an effect on the results (p-values ranged from 0.166 to 0.978).

Table 2 Allergy risk in relation to markers of estrogen exposure

		Crude		Adjusted for SES	
Factor	Category	OR	95 %CI	OR	95 %CI
Digit ratio – right hand	Low	0.98	0.51–1.92	0.95	0.37–2.45
	Middle	1.00	Ref	1.00	Ref.
	High	**2.36**	**1.16–4.25**	**2.12**	**0.96–4.01**
Digit ratio – left hand	Low	1.01	0.46–1.47	1.02	0.17–1.26
	Middle	1.00	Ref.	1.00	Ref
	High	**2.13**	**1.01–3.39**	**2.03**	**0.62–4.10**
Age at menarche (years)	Early	**2.01**	**0.41–3.18**	**1.98**	**0.31–3.43**
	Average	1.00	Ref.	1.00	Ref.
	Late	0.91	0.55–1.54	0.86	0.22–1.61
Menstrual cycle regularity	Yes	1.00	Ref	1.00	Ref.
	No	1.12	0.74–1.69	1.09	0.56–2.03
BMI (kg/m^2)	Underweight	0.87	0.28–1.19	0.72	0.12–1.52
	Normal	1.00	Ref.	1.00	Ref.
	Overweight	0.91	0.42–1.39	0.95	0.42–1.40
WC (cm)	< 80	1.00	Ref.	1.00	Ref.
	≥ 80	1.02	0.42–2.48	1.05	0.46–2.22
WHR	< 0.8	1.00	Ref.	1.00	Ref.
	≥ 0.8	1.32	0.90–3.00	1.26	0.79–2.88
WHtR	<0.4	0.88	0.36–2.17	0.89	0.37–2.20
	0.4–0.5	1.00	Ref.	1.00	Ref.
	> 0.5	1.17	0.43–3.14	1.15	0.36–3.16

SES socio-economic status, *BMI* body mass index, *WC* waist circumference, *WHR* waist-to-hip-ratio, *WHtR* waist-to-height ratio, *OR* odds ratio, *CI* confidence interval, *Ref,* reference category; ***Bold type*** statistically significant differences within categories of a given factor ($p<0.05$)

Table 3 Markers of estrogen exposure in non-allergic and allergic subjects

	Non-allergic subjects	Allergic subjects	p
Digit ratio – right hand	0.98 ±0.07	1.01 ±0.04	**0.001**
Digit ratio – left hand	1.00 ±0.05	1.02 ±0.03	**0.044**
Age at menarche (years)	12.7 ±1.1	12.4 ±1.3	**0.030**
BMI (kg/m^2)	21.5 ±3.0	21.8 ±3.6	0.340
WC (cm)	71.2 ±9.0	71.3 ±9.2	0.463
WHR	0.75 ±0.07	0.76 ±0.06	0.611
WHtR	0.43 ±0.05	0.43 ±0.06	0.808

Data are means ±SD; *BMI* body mass index, *WC* waist circumference, *WHR* waist-to-hip-ratio, *WHtR* waist-to-height ratio, ***Bold typed p-values*** statistically significant differences between non-allergic and allergic women based on MANOVA

4 Discussion

The influence of sex hormones on respiratory function in women is noticeable at different stages of the ontogenetic development. However, results obtained by various authors are not conclusive. There also are reports that not substantiate the presence of such a relation.

It has been demonstrated that the allergy development in an offspring is negatively correlated to the maternal age at menarche. The underlying reason of this correlation may have to do with the age at menarche-dependent

differences in the mother's estrogen level in the prenatal period, which determines the development of the child's immune system and increases the risk of allergy in later life (Xu et al. 2000). Other studies demonstrate that high progesterone and estrogen levels in the fetal period are connected with a higher risk of asthma and allergic diseases (Rangaraj and Doull 2003; Karmaus and Botezan 2002; Holt and Macaubas 1997; Wjst and Dold 1997). The notion outlined above has not been confirmed in the research by Xu et al. (2003) on the correlation between the mean progesterone and estradiol levels in pregnant mothers and the prevalence of allergy in children aged 5–6. Yet the authors point out that allergic diseases, especially rhinitis, may not manifest themselves in some children, and the possible future effect of mother's sex hormones on the children's tendency to develop atopic conditions after puberty cannot be entirely excluded.

In the present study we investigated the relation between the digit ratio, a marker of prenatal sex hormone levels, and the prevalence of allergic rhinitis. The results demonstrate that a high digit ratio was associated with a higher odd ratio for allergy. The literature abounds in studies on the correlation between the finger length proportions and anthropometric and physiological traits, as well as the prevalence of certain diseases. However, none of such reports have dealt with respiratory health. Of note also is that although the digit ratio strongly depends on the level of sex hormones in the fetal period, it is not related to their level in adulthood (Klimek et al. 2015).

Age at menarche is a marker of sex hormone levels in adolescence and adulthood. Early maturing women have a higher level of estrogen, a lower serum estrogen binding globulin, and they are exposed to a greater cumulative estrogen and progesterone doses than late maturing women (Apter et al. 1989). Several studies have reported a negative correlation between age at menarche and the risk of allergic rhinitis, asthma, and atopy after puberty, irrespective of BMI (Westergaard et al. 2003; Xu et al. 2000). The present study reported similar results.

Both puberty time and allergic diseases are related to the amount of adipose tissue. Estrogen is strongly connected with abdominal obesity. Nonetheless, the present results failed to reveal an appreciable relation between obesity/abdominal obesity and allergic rhinitis.

Finally, another characteristic related to the level of sex hormones in the present study was the regularity of the menstrual cycle. Other studies have indicated a more frequent occurrence of irregular menstrual cycles in women with atopic conditions, notably asthma and rhinitis (Bonds and Midoro-Horiuti 2013; Galobardes et al. 2012; Svanes et al. 2005). Again we failed to confirm these findings.

Summing up, this investigation supports the notion that sex hormones play a considerable role in the development of allergic conditions. The risk of rhinitis was increased by exposure to a high estrogen level in the prenatal period, as indicated by the digit ratio, and by early age at menarche. Conditions, having to do with female sex hormones in adulthood such as irregular menstruation or abdominal adiposity, were not associated with allergic rhinitis.

The results of this study are in line with the literature reports that demonstrate a considerable effect of estrogens on immunological processes. It has been shown that estrogens enhance antigen-presenting cell function, which facilitates allergic diseases, polarize T cells to type 2 responses of T helper cells, promote the class switching of B cells to immunoglobulin E synthesis, and promote degranulation of mast cell/basophils. Additionally, estrogens affect lung function and mechanics (Bonds and Midoro-Horiuti 2013).

The study has limitations. One cannot unequivocally determine if the indicators applied are a valid representation of the differences in hormone levels measured directly in blood or saliva. However, due to a retrospective nature of the study, we were able to perform direct measurements only in the period of adulthood.

In conclusion, this work demonstrates that allergy in adulthood may be associated with elevated estrogen level at an early stage of the ontogenetic development. Markers of estrogen

level in adulthood are unrelated to allergic rhinitis.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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Alpha Wavelet Power as a Biomarker of Antidepressant Treatment Response in Bipolar Depression

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Abstract

There is mounting evidence of a link between the properties of electroencephalograms (EEGs) of depressive patients and the outcome of pharmacotherapy. The goal of this study was to develop an EEG biomarker of antidepressant treatment response which would require only a single EEG measurement. We recorded resting 21-channel EEG in 17 in-patients suffering from bipolar depression in eyes-closed and eyes-open conditions. The EEG measurement was performed at the end of a short washout period which followed previous unsuccessful pharmacotherapy. We calculated the normalized wavelet power of alpha rhythm using two referential montages and an average reference montage. The difference in the normalized alpha wavelet power between 10 responders and 7 non-responders was most strongly pronounced in link mastoid montage in the eyes-closed condition. In particular, in the occipital (O1, O2, Oz) channels the wavelet power of responders was up to 84 % higher than that of non-responders. Using a novel classification algorithm we were able to correctly predict the outcome of treatment with 90 % sensitivity and

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100 % specificity. The proposed biomarker requires only a single EEG measurement and consequently is intrinsically different from biomarkers which exploit the changes in prefrontal EEG induced by pharmacotherapy over a given time.

Keywords
Alpha waves • Antidepressant • Bipolar depression • Pharmacotherapy • Treatment outcome • Wavelet

1 Introduction

Bipolar depression remains a major unresolved challenge for psychiatric therapeutics. Several longitudinal studies indicate that the proportion of total time in the depressive component of bipolar depression is far greater than in manic or hypomanic phases (Frye et al. 2014). A recent study (Tundo et al. 2014) and meta-analysis (Vázquez et al. 2013) have demonstrated that the overall efficacy of pharmacotherapy for bipolar depression was significantly greater with antidepressants than with placebo treatment and was not less than that of unipolar depression. Moreover, the risk of non-spontaneous mood-switching induced by antidepressant treatment seems to have been overestimated.

However, low remission rate and long response time are two fundamental difficulties associated with antidepressant treatment. These difficulties are documented in the STAR*D study in which 47 % of the 2876 major depressive disorder out-patients responded to citalopram but only 28 % achieved full remission (Trivedi et al. 2006). Taking into account that clinical improvement may occur as long as 8 weeks after the onset of treatment (Bauer et al. 2007), it is not surprising that the selection of an antidepressant is often based on lengthy trial-and-error. This difficulty has driven the search for treatment response biomarkers for several decades.

Biomarkers rooted in electroencephalography (EEG) are particularly appealing, since this technique is both cost effective and readily available in clinical practice (Baskaran et al. 2012; Iosifescu 2011). The efficacy of such biomarkers was almost exclusively investigated in pharmacotherapy of major depressive disorder. The very first qualitative analysis of EEG in patients with major depressive disorder has suggested the possibility that the Fourier spectrum of pre-treatment EEG may in fact reflect patients' propensity for pharmacological treatment (Ulrich et al. 1984, 1986). During the pharmacotherapy, the alpha power decreased in responders and increased in non-responders. However, the observed differences were not statistically significant. In the later studies of Knott et al. (1996, 2000) and Bruder et al. (2001) there has been no significant difference in the baseline alpha power between responders and non-responders. Interestingly enough, Bruder et al. (2001) have found a gender-specific effect: the alpha power asymmetry in the open-eyes condition strongly differentiated female responders from female non-responders. In a more recent work, comparison of the natural logarithm of alpha power in the occipital region (O1, O2) in the mixed (open- and closed-eyes) conditions has yielded a slightly greater $p = 0.06$ than the conventional threshold of significance (Bruder et al. 2008). However, the responders' log power asymmetry was greater than that of non-responders ($p = 0.02$). That study has rekindled the interest in alpha waves measures in major depressive disorder by predicting the treatment response using the log alpha power (72.7 % sensitivity and 57.5 % specificity) and alpha asymmetry (63.6 % sensitivity and 71.4 % specificity).

In the eyes-closed condition, the prominent alpha wave spindles are the hallmark of the non-stationarity of EEG signals (Shaw 2003). Nevertheless, the Fourier analysis, whose applicability requires the signal to be stationary, is predominantly used in quantitative EEG. In healthy individuals, the alpha power spectrum is usually stable but like other EEG traits it must not be considered as unchangeable. The inter-subject differences are high, which was demonstrated as early as in 1934 by Adrian and Matthews (Niedermeyer 2005). As long as the prediction of treatment response is based upon the changes in a patient's spectrum which are manifested shortly after the initiation of pharmacotherapy, the inter-subject variability is irrelevant (Leuchter et al. 2009b, c). However, the effectiveness of any prediction algorithm based on a single EEG measurement may be degraded by the inter-subject variability of alpha rhythm. In this work we test the hypothesis that in bipolar depression the differences in alpha power topography between responders and non-responders may be used to develop a clinically efficient biomarker of antidepressant treatment response once non-stationarity and inter-subject variability are taken into account.

Routine in-patient psychiatric care encompasses both patients who did not take an antidepressant for an extended period of time and those who were admitted because of a failure of ongoing pharmacotherapy. In the latter group, in sharp contrast to research trials, the length of the washout which precedes the change of antidepressant should be as short as possible. In the patient's interest, the washout period is determined only by the properties of the drugs involved in the treatment. Herein, we present a way to predict the outcome of pharmacotherapy in a diverse cohort of bipolar depression patients using EEG measured at the end of a washout period which is so short that the influence of unsuccessful pharmacotherapy on alpha rhythm may not be excluded *a priori*. We hypothesize that the prediction is also effective in this case.

2 Methods

2.1 Patients

The study protocol was approved by the Bioethical Commission of the Institute of Psychiatry and Neurology in Warsaw, Poland. The study comprised 26 depressive bipolar in-patients. All of them were right-handed, aged between 18 and 75 years, and met the International Classification of Diseases (ICD-10) criteria of bipolar depression. All patients received a written description of the protocol and signed the informed consent form. Subjects were excluded if they were substance abusers, pregnant, had psychotic depression, organic brain pathology (confirmed by MRI or CT scan), a history of chronic benzodiazepine use, and suffered from severe neurological disorders (e.g., epilepsy, Alzheimer's or Parkinson's disease). We enrolled only patients with a history of unchanged normothymic treatment during 4 weeks before the trial. Drug selection was based on the initial psychiatric status, previous treatment history, and patient preference. Antidepressive monotherapy was preceded by a short washout of an average length of 55 ± 31 h. The study was scheduled for 4 weeks of active treatment.

Out of the 26 subjects who entered the study, 17 reached completion and 9 patients left the trial due to: worsening of the depressive symptoms ($n = 2$), hypomania ($n = 2$), medication intolerance ($n = 1$), or other reasons ($n = 1$). Three subjects requested a discharge from the hospital before the end of the trial. Out of the 17 subjects, 10 responded to treatment. There was no difference in pre-treatment severity of depression on the Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) between responders and non-responders. The clinical characteristics of both groups are presented in Table 1.

The length of the wash-out period did not differ significantly in both groups (53 ± 31 h for responders and 61 ± 37 h for non-responders). For the patients who completed

Table 1 Clinical characteristics of responders and non-responders

	Responders (n = 10)	Non-responders (n = 7)
Gender (F/M)	8/2	6/1
Age (yr)	44.4 ± 20.1	50.0 ± 13.3
Wash-out period (h)	53.2 ± 31.2	60.7 ± 36.7
MADRS pre-treatment	28.6 ± 6.4	29.6 ± 8.5
MADRS post-treatment	6.4 ± 5.4	22.4 ± 6.9
BDI pre-treatment	37.6 ± 11.7	34.1 ± 11.7
BDI post-treatment	7.0 ± 5.6	25.7 ± 11.7

the study the antidepressant selection was as follows: venlafaxine (n = 6), bupropion (n = 4), citalopram (n = 3), reboxetine (n = 2), fluoxetine (n = 1), and mirtazapine (n = 1). Doses of the antidepressants were consistent with the official product characteristics (SPC). In the responders group (n = 10), patients received treatment with: bupropion (n = 3), venlafaxine (n = 3), reboxetine (n = 2), citalopram (n = 1), fluoxetine (n = 1). In the non-responders group they received venlafaxine (n = 3), citalopram (n = 2), bupropion (n = 1) and mirtazapine (n = 1).

Normothymic treatment was unchanged during the trial. In the responders group, five subjects received monotherapy: lamotrigine (n = 3), olanzapine (n = 1), lithium (n = 1) and another five received a combination of normothymics: lithium + lamotrigine (n = 2), lithium + quetiapine (n = 1), lithium + lamotrigine + quetiapine (n = 1), lamotrigine + carbamazepine + olanzapine (n = 1). In the non-responders group, two subjects were treated with monotherapy consisting of olanzapine and quetiapine. Five subjects received a combination of normothymics: lithium + olanzapine (n = 1), lithium + lamotrigine (n = 1), lithium + valproate (n = 1), lithium + carbamazepine + olanzapine (n = 1), lamotrigine + olanzapine (n = 1).

2.2 Assessment of Depressive Symptoms

Depressive symptoms were quantified by the MADRS, administered by the attending physician, and the BDI which was completed by patients. The assessment of depressive symptoms was done at baseline and Day 28 of the trial. The response to treatment was defined as a reduction of the final MADRS score by more than 50 %. A final MADRS score less than, or equal to, 10 corresponded to remission.

2.3 EEG Recording

The EEG recording was done at baseline and Days 7 and 28 of the trial. In this work we analyzed the baseline recording. The 10–20 international standard was used to position 21 Ag/AgCl electrodes (impedance below 5 kΩ). The ground electrode was placed between Fpz and Fz. Two referential montages were used: the conventional linked mastoid (LM) and the referential (REF) montage for which the reference electrode was mounted between Fz and Cz. The EEG was recorded through a Grass Telefactor Comet data acquisition system with the sampling frequency of 200 Hz and bandpass of 0.3–70 Hz (Natus Medical Inc., Pleasanton, CA). The EEG waveforms corresponding to two referential montages were recorded simultaneously. We also generated the average reference (ARE) montage using the instantaneous average of all 21 electrodes as a common reference. The subjects remained in the supine position in a quiet room. The measurement consisted of three 5-min intervals. During the first interval, subjects had the eyes-open. The eyes-closed intervals were separated by a short (approximately 10 s) blinking interval.

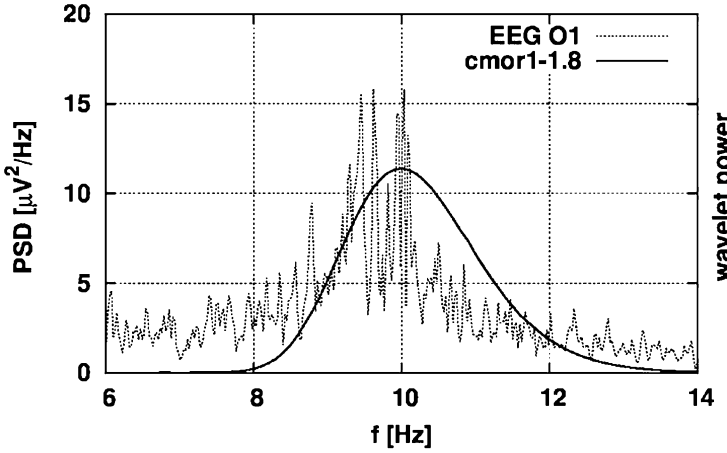

Fig. 1 The wavelet power of the monochromatic signal with frequency 10 Hz (*solid line*). The power was calculated using Morlet mother function ($f_c = 1.8$ and $f_b = 1$). The example of power spectral density of patient's EEG (channel O1) is shown with the *dotted line*

2.4 Data Analyses

The continuous wavelet transform of signal $s(t)$, such as EEG record, was defined as:

$$W_s(a, t_0) = \frac{1}{\sqrt{a}} s(t) \psi^* \left(\frac{t - t_0}{a} \right) dt \qquad (1)$$

(Latka et al. 2003, 2005). In the above formula, a is the scale and t_0 indicates the localization of the wavelet. We refer to the square of the complex modulus of *Ws* as the wavelet power. In this work we will use the wavelet power averaged over time interval:

$$w(f) = \left\langle \left| W_s(f, t_0)^2 \right| \right\rangle_{t_0}. \qquad (2)$$

The dual localization of wavelets in time and frequency enables us to associate a pseudo-frequency f_a with the scale a

$$f_a = \frac{f_c}{a \delta t} \qquad (3)$$

where f_c is the center frequency and δt is the sampling period of the signal $s(t)$. Thus, the value of wavelet coefficient reflects the local properties of the signal at a given scale (pseudo-frequency). From the plethora of existing mother functions one should judiciously choose one that is effective in extracting the features of a signal that are important for the problem to be resolved. Herein, we employ the complex Morlet

$$\Psi(t) = \frac{1}{\sqrt{\pi f_b}} e^{i 2 \pi f_c t} e^{-t^2 / f_b} \qquad (4)$$

where center frequency f_c and bandwidth parameter f_b may be independently adjusted. In Fig. 1, we present the time averaged wavelet power *w(f)* of a monochromatic wave with frequency 10 Hz (value close to the average frequency of alpha waves in healthy adult subjects) plotted as a function of wavelet transform pseudofrequency f_a. It is apparent that for $f_c = 1.8$ and $f_b = 1$ the width of the wavelet power distribution essentially covers the alpha band (8–13 Hz). For this choice of the complex Morlet parameters and pseudo-frequency $f_a = 10$ Hz, the wavelet power is just the weighted average of power in the entire alpha band. In other words, wavelet smooths out the alpha band spectrum. The use of a just single pseudo-frequency to characterize the power in the alpha range is not by all means obvious. In this work we were interested in the topography of the alpha wave power. Therefore, we normalize power *w(f;i)* in the *i-th* EEG channel by the total power

$$n(f; i) = \frac{w(f; i)}{\sum_{i=1}^{21} w(f; i)}. \qquad (5)$$

Even if the dominant alpha frequency of the subject is different than the chosen value of 10 Hz, the wavelet power is approximately proportionally reduced in all channels, preserving the topography of the normalized wavelet power. The dominant alpha frequency, averaged over all channels and patients, was equal to 9.7 Hz for responders and 9.3 Hz for non-responders. Moreover, there were no statistically significant differences between responders and non-responders in any of the analyzed channels.

Many authors advocate the use of a narrow Fourier band cantered around the dominant alpha frequency to characterize the resting state or task-related changes in alpha rhythm (Klimesch 1997, 1999). In Fig. 1, we provide an example of Fourier spectrum of a depressive patient with broad distribution of alpha power without a distinctive dominant frequency. These traits of Fourier spectrum are common in patients and motivated us to use a broad analysing wavelet.

Log transformation is frequently used in analysis of physiological data. The question arises as to whether logarithm of wavelet power should be used in Eq. (5). The justification of such transformation is the assumption that susceptibility to antidepressant treatment is multiplicatively related to EEG alpha wavelet power. Although there is no *a priori* justification of such relation, the application of log transformation is a viable modification of the presented prediction algorithm.

In the eyes-open condition, we calculated alpha wavelet power for contiguous EEG data segments without manual or software excising of eye blinks. Therefore, it is worth mentioning that the average number of blinks per minute in the eyes-open interval was similar for responders and non-responders (28 ± 15 vs. 25 ± 21).

A neurophysiologist selected a 2 min data segment from the eyes-open interval which, apart from eye blinks, was free from artefacts. The 2 min artefact-free EEG segment was also extracted from the first eyes-closed interval. Until the end of study, neither the neurophysiologist nor the persons who performed data analyses had access to patients' treatment records. For both referential montages (LM and REF) and average reference, we calculated the continuous wavelet transform using the Morlet mother function with parameters $f_c = 1$ and $f_b = 1.8$. The calculations were performed for the pseudo-frequency 10 Hz. The wavelet power over the entire data segment was averaged for each EEG channel. Finally, the averaged wavelet power in each channel was normalized for the total averaged wavelet power from all 21 channels. Consequently, the normalized wavelet power was independent of the subject's EEG amplitude. Wavelet transforms, in stark contrast to traditional Fourier methods, are intrinsically more robust with respect to eye movement or blink artefacts. This property enabled to calculate the alpha wavelet power for continuous EEG data segments without manual or software excising of eye blinks.

The frequency of a peak value of wavelet power in the interval 8–13 Hz is referred to as a dominant alpha wave frequency. We defined the alpha power ratio as a ratio of the sum of alpha wavelet power at frontal (Fp1, Fp2, Fpz) sites to the sum of alpha power at occipital (O1, O2, Oz) sites.

The Mann–Whitney U test was used to assess the statistical significance of differences in normalized wavelet power $n(10\ \text{Hz})$ and response index between responders and non-responders. In all cases, the traditional $p = 0.05$ was chosen as a threshold of statistical significance.

2.5 Prediction of Antidepressant Treatment Response

From the mathematical point of view, prediction of treatment response is equivalent to binary classification based upon a single criterion (such as normalized alpha wavelet power or alpha power ratio). The receiver operating characteristic (ROC) provides a rigorous framework

for such classification (Hanley 1989). This framework enables to determine an optimal classification threshold and a qualitative assessment of statistical significance. The area under the receiver operating characteristic curve (AUC) was used to quantify the performance of the binary classifier. When the classification was feasible we calculated the optimal threshold value (cut-off point) as well as the sensitivity, specificity, and accuracy.

It turns out that regardless of the chosen montage prediction of antidepressant treatment, the response is usually possible at several EGG sites. Therefore, we elected to test the prediction algorithm based on a response index, i.e., the percentage of channels in which the patient was classified as a responder. In other words, the patient is classified as a responder when this index is greater than 50 %; otherwise he is assigned to the non-responder category. The proposed classification scheme may seem arbitrary, but it is reminiscent of the nearest neighbor pattern classification introduced by Cover and Hart (1967). The existence of two classes (responders and non-responders) leads to the classification threshold equal to 50 %. Ideally, such an index should assume the value of 100 % for responders and 0 % for non-responders.

3 Results

3.1 Average Reference Electrode (ARE) Montage

In Fig. 2, we present the topography of alpha wavelet power for non-responders (a and d) and responders (b and e) in the eyes-open (EO) and eyes-closed (EC) conditions. Panels c and f of Fig. 2 show the relative difference in the wavelet power between responders and non-responders (relative to non-responders) for the open and closed-eyes conditions, respectively. In these two figures, the red thick circles around the EEG site labels indicate channels for which the AUC was significantly greater than 0.5.

For the open-eyes condition, the AUC was significantly greater than 0.5 in five channels listed in Table 2. The largest value of 0.84 occurred at C3 site. The wavelet power of responders $nR(10\ \text{Hz}; C3) = 0.021 \pm 0.005$ was smaller than that of non-responders $nN(10\ \text{Hz}; C3) = 0.029 \pm 0.007$; the difference was significant ($p = 0.02$). For the cut-off threshold 0.024, the prediction of antidepressant treatment response had 82 % accuracy, 80 % sensitivity, and 86 % specificity.

For the closed-eyes condition, the classification was feasible in eight channels (Table 2). The AUC assumed the highest value of 0.87 in the Fpz channel. The classification for this channel had 82 % accuracy, 80 % sensitivity, and 86 % specificity. The wavelet power of responders $nR(10\ \text{Hz}; Fpz) = 0.037 \pm 0.006$ was smaller than that of non-responders $nN(10\ \text{Hz}; Fpz) = 0.05 \pm 0.02$ ($p = 0.001$).

The response index of responders was notably higher than that of non-responders for both open (76 ± 26 % *vs.* 20 ± 20 %, $p = 0.0005$) and closed (76 ± 22 % *vs.* 23 ± 19 %, $p = 0.001$) eyes conditions (Table 5). The value of the index averaged over both conditions was equal to 76 ± 20 % and 21 ± 17 % for responders and non-responders, respectively ($p = 0.0004$). For the closed-eyes condition, the alpha power ratio for responders of 0.30 ± 0.06 was smaller than that of non-responders 0.41 ± 0.13 ($p = 0.03$). For the open-eyes condition, the difference was insignificant.

3.2 Link Mastoids (LM) Montage

For the open-eyes condition, AUC was significantly greater than 0.5 in five channels listed in Table 3. The largest value of 0.79 occurred at Fz site. The wavelet power of responders $nR(10\ \text{Hz}; Fz) = 0.059 \pm 0.008$ was smaller than that of non-responders $nN(10\ \text{Hz}; Fz) = 0.064 \pm 0.007$, although the difference did not reach statistical significance ($p = 0.06$). For the cut-off threshold of 0.056, the prediction of antidepressant treatment response had the accuracy of 82 %, sensitivity of 70 %, and specificity of 100 %.

For the closed-eyes condition, the classification was feasible in 9 channels (Table 3). The

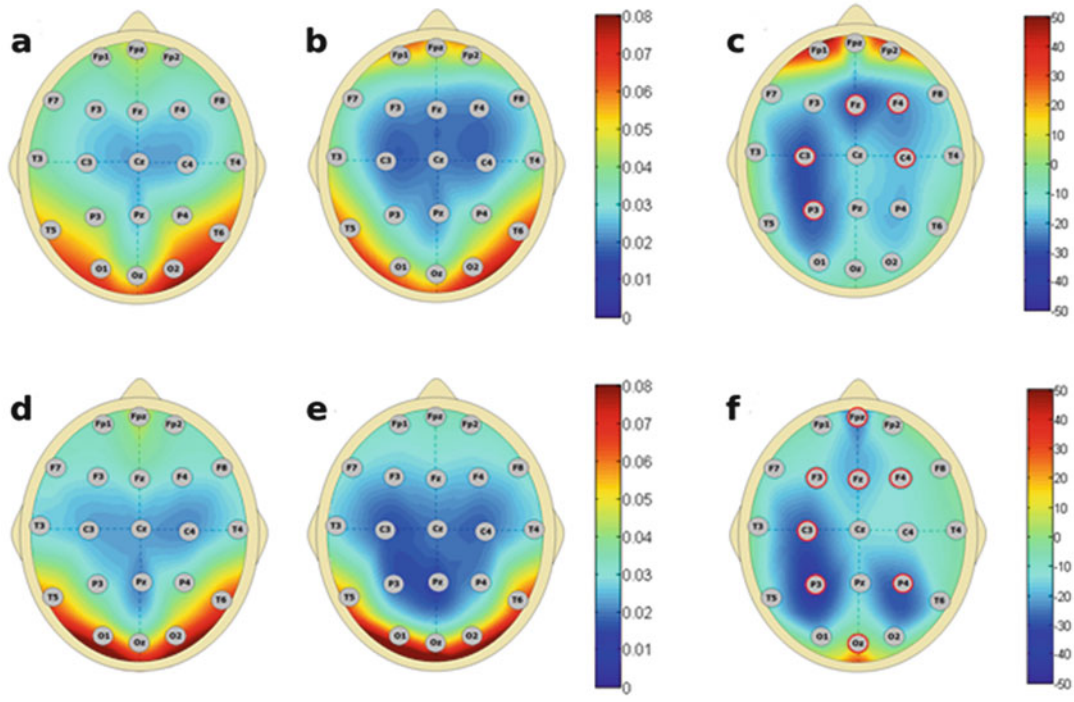

Fig. 2 Topography of alpha wavelet power for non-responders (**a** and **d**) and responders (**b** and **e**) in eyes-open (*first row*) and eyes-closed conditions (*second row*). Panels (**c**) and (**f**) show the relative difference of the wavelet power between responders and non-responders (relative to non-responders) for open and closed-eyes, respectively. The *red thick circles* around EEG site labels indicate channels for which the AUC was significantly greater than 0.5

AUC took on the highest value of 0.86 in O1 channel. The wavelet power of responders *nR* (10 Hz; O1) = 0.07 ± 0.03 was significantly greater than that of non-responders *nN*(10 Hz; O1) = 0.039 ± 0.013 (p = 0.001). The classification for this channel had the accuracy of 82 %, sensitivity of 80 %, and specificity of 86 %.

The response index of responders was notably higher than that of non-responders for both eyes-open (80 ± 23 % *vs*. 20 ± 28 %, p = 0.002) and eyes-closed (76 ± 22 % *vs*. 23 ± 20 %, p = 0.001) conditions (Table 5). The value of the index averaged over both conditions was equal to 76 ± 20 % and 21 % ± 17 % for responders and non-responders, respectively (p = 0.0004). These values of indices averaged over both conditions were exactly the same as those for the ARE montage. For the eyes-closed condition, the alpha power ratio for responders of 0.85 ± 0.42 was smaller than that of non-responders of 1.81 ± 1.3 (p = 0.04). As in the case of the ARE montage, for the eyes-open condition, the difference was insignificant.

3.3 Referential (REF) Montage

For this montage, the AUC was significantly greater than 0.5 in only three channels in the eyes-open condition: F4, C4, and C3 (Table 4). The highest value of AUC of 0.76 was observed in channel F4. The wavelet power of responders *nR*(10 Hz; F4) = 0.03 ± 0.01 was smaller than that of non-responders *nN*(10 Hz; F4) = 0.04 ± 0.01; the difference was insignificant (p = 0.08). The classification for this channel had the accuracy of 88 %, sensitivity of 100 %, and specificity of 71 %. The response index of responders was higher than that of non-responders: 83 ± 18 % *vs*. 23 ± 25 %,

Table 2 The outcome of binary classification (prediction of treatment response) based on the normalized alpha wavelet power for the eyes-open (EO) and eyes-closed (EC) conditions

	EO						EC						
Channel	Fz	F4	C3	C4	P3	F4	Fpz	Fz	F3	C3	P3	P4	Oz
AUC	0.74	0.83	0.84	0.74	0.84	0.76	0.87	0.79	0.74	0.73	0.76	0.76	0.79
p-value	0.11	0.03	0.02	0.11	0.02	0.09	0.001	0.06	0.11	0.13	0.09	0.09	0.06
Cut-off point	0.029	0.03	0.024	0.024	0.041	0.029	0.041	0.029	0.031	0.017	0.039	0.0319	0.095
Δ (%)	−26	−20	−29	−18	−26	−11	−29	−20	−13	−29	−31	−28	39
Sensitivity (%)	70	90	80	70	70	70	80	70	90	60	90	60	90
Specificity (%)	71	71	86	71	100	85	86	90.9	57	86	71	86	71
Accuracy (%)	71	82	82	71	82	77	82	71	77	71	82	71	82

The power was calculated for the average reference (ARE) montage. Only are the channels presented for which the AUC was significantly greater than 0.5. Δ is the relative percentage difference of the wavelet power between responders and non-responders (relative to non-responders), p-values correspond to the Mann-Whitney U test

Table 3 The outcome of binary classification (prediction of treatment response) based on the normalized alpha wavelet power for the eyes-open (EO) and eyes-closed (EC) conditions

	EO					EC								
Channel	Fz	T3	C3	T4	T6	Fp1	Fpz	F3	Fz	T3	C3	O1	O2	Oz
AUC	0.79	0.76	0.76	0.77	0.74	0.76	0.74	0.83	0.80	0.83	0.83	0.86	0.80	0.81
p-value	0.06	0.09	0.07	0.07	0.10	0.09	0.11	0.03	0.04	0.03	0.03	0.01	0.04	0.03
Cut-off point	0.056	0.029	0.047	0.027	0.024	0.049	0.054	0.056	0.056	0.030	0.054	0.054	0.050	0.049
Δ (%)	−9	−23	−18	−22	−23	−16	−14	−16	−15	−24	−18	77	61	84
Sensitivity (%)	70	90	70	90	80	70	60	80	60	90	90	80	70	80
Specificity (%)	100	71	86	71	71	71	71	71	86	71	71	86	86	71
Accuracy (%)	82	82	76	82	76	71	65	76	71	82	82	82	77	76

The power was calculated for the LM montage. Only are the channels presented for which the AUC was significantly greater than 0.5. Δ is the relative difference of the wavelet power between responders and non-responders (relative to non-responders), p-values correspond to the Mann-Whitney U test

Table 4 The outcome of binary classification (prediction of treatment response) based on the normalized alpha wavelet power for the eyes-open condition

Channel	F4	C3	C4
AUC	0.76	0.73	0.73
p-value	0.08	0.13	0.13
Cut-off point	0.043	0.017	0.025
Δ (%)	−25	−36	−23
Sensitivity (%)	100	80	70
Specificity (%)	71	71	86
Accuracy (%)	88	76	76

The power was calculated for REF montage. Only are the channels presented for which the AUC was significantly greater than 0.5. Δ is the relative difference of the wavelet power between responders and non-responders (relative to non-responders), p-values correspond to the Mann-Whitney U test

respectively ($p = 0.0006$). In both open-eyes and closed-eyes conditions there was no difference in the alpha power ratio between the responders and non-responders.

3.4 Prediction of Treatment Response

The values of the response index for all patients are collected in Table 5. The index was calculated for the open-eyes and closed-eyes conditions for both ARE and LM montages. Figure 3 visualizes the application of these indices to the prediction of antidepressant treatment response (white and black boxes represent the assignment to responders (R) and non-responders (N), respectively). For both ARE and LM montages, the prediction based on the response index averaged over the eyes-open and eyes-closed conditions resulted in only one misclassification (90 % sensitivity, 100 % selectivity, and 94 % accuracy). However, it was not the same subject that was misclassified. The prediction based on the eye-open response index for the REF montage resulted also in one misclassification (100 % sensitivity, 86 % selectivity, and 94 % accuracy).

4 Discussion

With the exception of the pilot study of Bares et al. (2012), the efficacy of EEG biomarkers of antidepressant response was exclusively investigated in the pharmacotherapy of major depressive disorder. Unipolar depression is considered to be a disorder of right hemispheric functions, particularly those associated with the temporoparietal region, or of interaction between the hemispheres with relative right-sided or non-dominant impairment (Small 2005). In the broader perspective, the dominant and non-dominant hemispheres subserve positive and negative affect, respectively (Debener et al. 2000). Therefore, EEG asymmetry indices seem a natural choice for the prediction of the outcome of antidepressant treatment (Ulrich et al. 1984). A study of 50 patients with major depressive disorder treated with fluoxentine has demonstrated that in the eyes-open condition the difference in overall alpha asymmetry (averaging was done over homologous sites of the anterior, central, and posterior regions) between responders and non-responders was significant only for female but not for male patients (Bruder et al. 2001). In a later work, Bruder et al. (2008), using the occipital alpha asymmetry of resting EEG (mixed open and closed-eyes scenarios), have predicted the outcome of a 12-week fluoxentine treatment with 63.6 % sensitivity and 71.4 % specificity. Tenke et al. (2011) established that responders had a greater alpha power compared with non-responders and with healthy control subjects in major depressive disorder, with the largest differences at occipital sites O1 and O2, where the alpha rhythm was most strongly pronounced. Bruder et al. (2008), using alpha rhythm power, have achieved 72.7 % sensitivity and 57.5 % specificity in prediction of antidepressant treatment response. By combing two metrics: asymmetry and power of alpha waves, they have improved the prediction performance to 83.3 % sensitivity and 67.7 % specificity. Tenke et al. (2011) have reported 92 % specificity, accompanied by 50 % sensitivity.

Table 5 The response index (the percentage of channels in which a patient is classified as responder) for the average reference (ARE) and conventional linked mastoid (LM) montages

Responders				Non-responders			
	Response (%)				Response (%)		
ID	EO	EC	EO+EC	ID	EO	EC	EO+EC
ARE							
R1	100	87.5	93.75	N1	0	0	0
R2	100	87.5	93.75	N2	0	12.5	6.25
R3	60	75	67.5	N3	0	25	12.5
R4	80	100	90	N4	40	12.5	26.25
R5	100	100	100	N5	20	12.5	16.25
R6	20	50	35	N6	40	50	45
R7	60	50	55	N7	40	50	45
R8	60	87.5	73.75				
R9	80	87.5	83.75				
R10	100	37.5	68.75				
LM							
R1	100	89	94	N1	20	22	21
R2	100	100	100	N2	0	0	0
R3	40	33	37	N3	60	11	35
R4	60	100	80	N4	60	0	30
R5	100	100	100	N5	0	33	17
R6	80	22	51	N6	0	11	6
R7	100	67	83	N7	0	89	44
R8	60	100	80				
R9	60	100	80				
R10	100	44	72				

The index was calculated for the eyes-open (EO) and eyes-closed (EC) conditions. The average value of the index for both conditions (EO+EC) is also presented

In the present study, the difference in the normalized alpha wavelet power between responders and non-responders was most strongly pronounced in LM montage in the closed-eyes condition. In particular, in the occipital (O1, O2, Oz) channels the wavelet power of responders was up to 84 % higher than that of non-responders (Table 3), which is in accord with the results of previous studies (Tenke et al. 2011; Bruder et al. 2008). Moreover, the ratio of the wavelet power in the frontal channels (Fp1, Fp2, Fz) to that of the occipital channels was significantly higher in non-responders (1.8 ± 1.2) than in responders (0.9 ± 0.4) ($p = 0.04$). The same trait of alpha wavelet power topography was observed in ARE montage in the closed-eyes condition. It is worth pointing out that for both LM and ARE montages for closed-eyes, the wavelet power of responders in frontal, central, and parietal electrodes was smaller in responders.

The performance of a single-channel prediction based on the normalized alpha wavelet power matched or exceeded those of previous studies. For example, for ARE montage (Table 2) in the eyes-open condition, for three out of the five channels for which discrimination between responders and non-responders was possible (AUC statistically greater than 0.5) the classification accuracy was equal to 82 %. For the eyes-closed condition, the accuracy was equal to 82 % for three out of the eight channels. The performance of classification for the LM montage (Table 3) was comparable to the above outlined. For REF montage (Table 4), the prediction of treatment response was possible only in

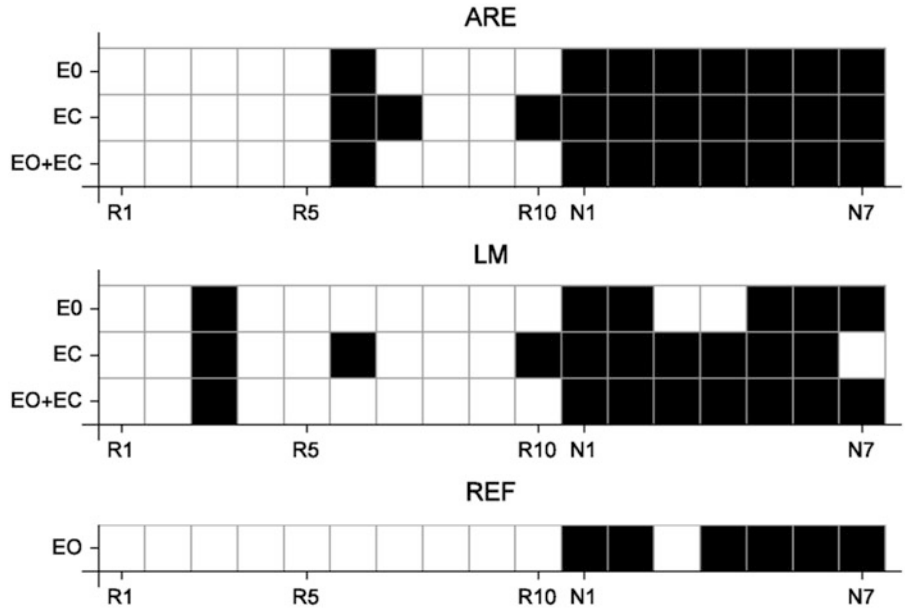

Fig. 3 Outcome of the prediction of antidepressant treatment response for three different montages: ARE (*top*), LM (*middle*), and REF (*bottom*). For ARE and LM montages, the prediction was based on the value of the response index for the *open*- (EO) and *closed*-eyes (EC) conditions, and on the average over both conditions. For REF montage, the prediction was possible only for the *open*-eyes condition. *White* and *black boxes* represent assignment to responders (R) and non-responders (N), respectively

the eyes-open condition at three EEG sites. The classification based on alpha power ratio was possible in the closed-eyes condition for both the ARE (82 % accuracy, 80 % sensitivity, and 85 % specificity) and LM (76 % accuracy, 70 % sensitivity, and 85 % specificity) mintages.

We elected to test the prediction algorithm in which the classification of a patient is based on the response index, i.e., on the percentage of channels for which the patient is classified as a responder. The prediction for the open-eyes condition is more accurate than that for the closed-eyes condition, for both ARE (94 % *vs*. 82 %) and LM (82 % *vs*. 76 %, respectively) montages (Fig. 3; Table 5). Averaging of the response index over both conditions led to only one misclassification (94 % accuracy, 90 % sensitivity 90 %, and 100 % selectivity) for both montages. While ARE montage seems to be the most suitable for the prediction of treatment response, the prevalent link mastoids also leads to an acceptable classification performance. It should be emphasized that the influence of a choice of reference and montage on the outcome of antidepressant treatment prediction in unipolar depression has not yet been thoroughly investigated. We believe that the present results would facilitate the development of effective EEG biomarkers of antidepressant response in bipolar depression. Wavelet alpha power may be used to define three potential biomarkers of antidepressant treatment response: normalized power at a given site, response index, and ratio of frontal to occipital power. The evaluation of their efficacy and the selection of the best biomarker requires further clinical studies.

To our knowledge, this is only the second study that has explored the possibility of predicting the response to antidepressant intervention in bipolar affective disorder. In the other study, Bares et al. (2012) have found that the treatment response in bipolar depression patients is associated with a reduction of prefrontal theta cordance one week after administration of a new antidepressant. Such a reduction was first observed in unipolar depression (Bares et al.

2007, 2008, 2010; Leuchter et al. 2009a; Cook et al. 1999, 2002, 2005, 2009).

As we pointed out in the introduction, previous attempts to employ alpha waves for predicting the outcome of pharmacotherapy of unipolar depression have met with limited success. Nevertheless, properties of this EEG band have been incorporated into the antidepressant treatment response index (ATR) that combines the baseline prefrontal EEG theta and alpha power with that after a week of pharmacotherapy (Leuchter et al. 2009b). The algorithm behind the ATR is proprietary and cannot be independently verified. In a recent study Leuchter et al. (2009c) have forecast the response to escitalopram with 58 % sensitivity and 91 % specificity.

Nearly half of depressive patients do not respond to initial antidepressant treatment. Cipriani et al. (2009) have performed multiple-treatment meta-analysis of 117 randomized controlled trials, consisting of 25,928 participants, to assess the efficacy of 12 new-generation antidepressants. Mirtazapine, escitalopram, venlafaxine, and sertraline turned out the most efficacious. With the exception of reboxetine, the reported differences have been rather moderate; the odds ratios in binary comparisons were of the order of 1.3. The usual strategy is either to switch medications or add a drug with a different mechanism of action such as monoamine oxidase (MOA) inhibition (Stahl and Grady 2003). However, it has never been proven that MOA enhances the effectiveness of switching or combining antidepressants (Thase and Rush 1997). On the contrary, the results of level II treatment in STAR*D indicate that response or remission is independent of MOA (Rush et al. 2006). In the present study, we demonstrate that a highly effective prediction of the response to antidepressants in bipolar depression was not affected by ongoing pharmacotherapy, which is in line with previous studies with and without a short wash-out period (Cook et al. 2005). In other words, the prediction can be based on a single EEG measurement that can be taken either prior to the onset of pharmacotherapy or during the washout period that precedes a change in medication. The approach presented is intrinsically different from the prediction based on changes in prefrontal EEG induced by pharmacotherapy over a given time (usually a week) and quantified by either ATR index (Iosifescu et al. 2009; Leuchter et al. 2009b, c) or theta band cordance.

The nature of differences of alpha waves observed between responders and non-responders is not fully understood. Bruder et al. (2005, 2008) have argued that in unipolar depression these differences reflect endophenotypic vulnerability to depression, while others support the hypothesis of time-dependent susceptibility of depressive patients to pharmacotherapy. The latter hypothesis has been expressed in the literature in a variety of implicit forms. Either of the two hypotheses can be ultimately verified only with a QEEG metric that proves highly successful in the prediction of antidepressant treatment response. We strongly believe that any such metric should take into account at least two fundamental features of human EEG time series: non-stationarity and inter-subject variability. In the present study, we pointed to the mathematical framework of continuous wavelet transform as a possible source of such metrics. The limitations of this and similar studies (Iosifescu 2011) are related to open, non-randomized treatment with a variety of medications. A rigorous testing of the presented approach to the prediction of antidepressant treatment response on a much larger cohort of depressive patients is required before a definitive assessment of its applicability can be made.

Relatively little is known about the differences between the properties of brain oscillations in unipolar and bipolar depression. (Tas et al. 2014; Lee et al. 2010; Lieber 1988). The question arises as to whether the presented algorithm is applicable to unipolar depression and whether it can be modified to predict antidepressant response in a cohort of unipolar and bipolar patients. The latter question is particularly significant, since previous studies demonstrated that 60 % of bipolar depresssion cases have been incorrectly diagnosed as unipolar depression and consequently were inappropriately treated (Goodwin and Jamison 2007;

Dunner 2003). These questions should be addressed in alternative study designs.

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