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Polysomnographic variables in Alternate overlap syndrome: data from sleep heart health study

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ABSTRACT

Objective: To evaluate influence of asthma on polysomnographic variables of patients with obstructive sleep apnea (OSA).

Methods: A longitudinal retrospective study using data collected from the Sleep Heart Health Study (SHHS).

Results: All 2822 patients included had OSA, 2599 were non-asthmatic whereas 223 were asthmatics. Average BMI for non-asthmatics was 28.8 kg/m^2 whereas asthmatics had 29.5 kg/m^2. Median pack-years of smoking was 1.42 vs. 1.98 in non-asthmatic and asthmatic groups, respectively. Sex distribution, age (in years), BMI, FEV_1, FVC, AHI ≥ 4% (all apneas, hypopneas with ≥4% oxygen desaturation or arousal per hour of sleep), RDI ≥ 3% (overall respiratory distribution index at ≥3% oxygen desaturation or arousal), sleep latency, percentage of sleep time in apnea/hypopnea and Epworth sleep scale score were all statistically significant. Non-asthmatics had greater AHI (12.63/hr) compared to asthmatics (11.34/hour), $p = 0.0015$. RDI in non-asthmatics and asthmatics was (23.07 vs 20.53; $p = 0.009$). Sleep latency was found to be longer in asthmatics 19.8 minutes vs. 16 minutes ($p = 0.008$). Epworth sleepiness scale score was high in asthmatics (9 vs. 8, $p = 0.002$).

Conclusion: OSA was found more severe in non-asthmatic subgroup, but asthmatics had statistically significant higher Epworth sleepiness scale score and sleep latency. Clinicians should be vigilant and keep low threshold to rule out OSA particularly on patients with difficult to control asthma, smoker, GERD, obese and nasal disease.

1. Introduction

The estimated global asthma burden is 235 million individuals, contributing to 180,000 yearly mortality and the prevalence has been increasing [1]. Asthma spares no race, age, socioeconomic status, geographic or ethnicity but its burden is specifically high in the urban areas [2]. Airway obstructive diseases, like asthma and chronic obstructive pulmonary disease (COPD), have a common basis of local and systemic inflammation. Also, they have been classically associated with nocturnal mortality and morbidity [3,4].

Interestingly, nocturnal asthma and obstructive sleep apnea (OSA) share similar features, and this has led to multiple studies on asthma relating to nocturnal sleep and OSA [5–7]. A clear association between OSA and asthma has not been established yet but has been on speculation for decades as seen in one classic study done by Shu Chan C. et al. [8]. Correlation between poor asthma-related symptoms and sleep-disordered breathing (S) have been described in the literature [9]. OSA in COPD patients is termed 'Overlap syndrome' which is common in

literature, but there is a relative lack of study of OSA and asthma. Emerging evidence of an association between OSA and asthma have led some scholars to coin the term sole syndrome 'Alternate overlap syndrome.'

2. Patients and methods

2.1. Study design

We conducted a longitudinal retrospective study using data collected from the Sleep Heart Health Study (SHHS) [10–13].

2.2. Data source

Data were compiled from the SHHS which is a large multi-center cohort study implemented by the National Heart Lung & Blood Institute to determine the cardiovascular and other consequences of SDB. It tested whether sleep-related breathing was associated with an increased risk of coronary heart disease, stroke, all-cause mortality, and hypertension. The

SHHS1 dataset represents data from the baseline and first follow-up visit, collected on 6,441 individuals between 1995 and 1998. All patients in this database are de-identified to protect their privacy. Therefore, informed consent was waived to conduct our study.

2.3. Patient selection

In the SHHS1 dataset, 6,441 participants aged 40 years and older were enrolled between November 1st, 1995 and January 31st, 1998 to take part in SHHS Visit 1. We identified participants diagnosed with OSA, defined as an apnea-hypopnea index (AHI) ≥ 5 based on polysomnographic data [10–12]. We then divided the participants into two cohorts based on a history of asthma. Patients with missing data were then excluded from this study. This left a total of 2,861 records for final analysis.

2.4. Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were provided for all study variables. Continuous variables were not normally distributed and presented as median and IQ range. Categorical variables were presented as count and percentage. Statistical tests of significance (Mann-Whitney U test for continuous variables and Chi-Square test or Fischer's Exact test for categorical variables) were conducted to assess differences between the cohorts. A two-tailed p-value ≤0 .05 was regarded as statistically significant.

3. Results

Baseline demographic, clinical, spirometry and polysomnographic characteristics of the study population are summarized in Table 1.

The total number of patients included in the study was 2,822. All enrolled patients had OSA, defined as AHI ≥ 5 with ≥ 4% desaturation or arousals per hour of sleep. Of all the included patients, only 223 were asthmatics whereas 2,599 were non-asthmatics. The male-to-female ratio was 1.46 with the median age of

Table 1. Baseline demographic, clinical, spirometry and polysomnographic characteristics of the study population.

Characteristics	All patient (N = 2822) Count (Percent) Median (IQ range)	Total	Non-Asthmatics (n = 2599)	Asthmatics (n = 223)	p Value
Gender		2822			0.003*
Male	1675 (59.4)		1564 (60.2)	111 (49.8)	
Female	1147 (40.6)		1035 (39.8)	112 (50.2)	
Age (Years)	66 (58–74)	2822	66 (58–74)	64 (54–71)	0.001*
Race		2822			0.925
Black	228 (8.1)		209 (8.0)	19 (8.5)	
White	2429 (86.1)		2239 (86.1)	190 (85.2)	
Others	165 (5.8)		151 (5.8)	14 (6.3)	
BMI (Kg/m^2)	28.8 (25.8–32.3)	2809	28.8 (25.8–32.2)	29.5 (26.5–33.7)	0.013*
Comorbidities					
Diabetes	252 (9.3)	2712	226 (9.0)	26 (12.4)	0.073
Hypertension	1383 (49.0)	2822	1280 (49.2)	103 (46.2)	0.210
Previous MI	59 (15.0)	393	51 (15.2)	8 (13.8)	0.480
Stroke	22 (5.6)	392	18 (5.4)	4 (6.9)	0.415
Smoking (pack-years)	1.47 (0–25)	2686	1.42 (0–25)	1.98 (0–24)	0.809
Spirometric Parameters					
FEV$_1$	2.66 (2.11–3.27)	2721	2.68 (2.14–3.29)	2.44 (1.87–3.09)	< 0.001*
FVC	3.53 (2.78–4.31)	2678	3.54 (2.79–4.32)	3.42 (2.72–4.21)	0.046*
PSG Parameters					
AHI ≥ 4%	12.52 (7.86–21.14)	2822	12.63 (7.92–21.26)	11.34 (7.27–19.65)	0.015*
Arousal index	20 (14.63–27.65)	2738	20.1 (14.7–27.77)	18.93 (14.0–26.18)	0.131
Average SaO2% during NREM sleep	94.18 (92.94–95.30)	2822	94.2 (92.94–95.32)	93.89 (92.97–95.13)	0.162
Average SaO2% during REM sleep	93.89 (92.23–95.15)	2738	93.94 (92.23–95.16)	93.6 (92.26–94.93)	0.272
Minimum SaO2 in non-REM sleep	86 (83–88)	2732	86 (83–88)	86 (82–88)	0.995
Minimum SaO2 in REM sleep	85 (81–88)	2719	85 (81–88)	84 (81–88)	0.378
RDI ≥ 3%	22.89 (16.42–34.38)	2738	23.07 (16.52–34.67)	20.53 (15.04–30.94)	0.009*
Time in REM sleep	77 (57–96)	1288	77 (57–96)	78 (56.5–97.0)	0.780
Percent of sleep time with SaO2 < 85%	0.019 (0–0.310)	2818	0.018 (0–0.318)	0.039 (0–0.276)	0.449
Percent of sleep time with SaO2 < 90%	1.236 (0.255–4.965)	2818	1.212 (0.253–4.974)	1.397 (0.352–4.825)	0.452
Percent of sleep time in Apnea	2.66 (0.8–6.87)	2822	2.80 (0.84–7.03)	1.66 (0.49–4.84)	< 0.001*
Percent of sleep time in Hypopnea	20.29 (15.4–26.43)	2822	20.38 (15.61–26.52)	19.07 (13.49–26.14)	0.011*
REM Latency	74 (55–106.5)	2552	74 (54.5–106.5)	76 (58.5–106)	0.477
Sleep efficiency	82.79 (75.06–88.01)	1652	82.85 (75.17–88.08)	82.46 (73.84–87.92)	0.679
Sleep latency	16.5 (9.5–28)	1652	16.0 (9.5–28.0)	19.8 (12.6–31.4)	0.008*
Epworth Sleepiness Scale score (Sleep Heart Health Study Visit One (SHHS1))	8 (5–11)	2731	8 (5–11)	9 (5–12)	0.002*

IQ range, interquartile range; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; PSG, polysomnography; AHI, apnea-hypopnea index; RDI, respiratory disturbance index; REM, rapid eye movement; SaO$_2$, Oxygen saturation.

66 years (58–74 years). The majority included cases were whites (86%), whereas black and other races only represented 8.1% and 5.8%, respectively. Median BMI was higher for asthmatics when compared to non-asthmatics (29.5 vs. 28.8 Kg/m^2, respectively). Median pack-years of smoking was 1.42 in non-asthmatics vs. 1.98 in asthmatics. Sex distribution, age (in years), BMI, history of COPD, FEV_1, FVC, AHI ≥ 4% (all apneas, hypopneas with ≥ 4% oxygen desaturation or arousal per hour of sleep), RDI ≥ 3% (overall respiratory distribution index at ≥ 3% oxygen desaturation or arousal), percent sleep time in apnea, sleep latency, percentage of sleep time in Apnea/Hypopnea and Epworth sleep scale score were all statistically significant. Non-asthmatics had greater AHI (12.63/hour) as compared to asthmatics (11.34/hour, $p = 0.015$). RDI was significantly higher in non-asthmatics when compared to asthmatics (23.07 vs. 20.53; $p = 0.009$). Sleep latency was found to be longer in asthmatics (19.8 minutes vs. 16 minutes, $p = 0.008$). Epworth sleepiness scale score was significantly higher in asthmatics (9 vs. 8, $p - = 0.001$). Percent of sleep time with saturation less than 85% and 90% were both more in asthmatics than non-asthmatics, (0.039 vs. 0.018 and 1.397 vs 1.212, respectively).

4. Discussion

OSA and asthma are both highly prevalent conditions. Epidemiologic data show the prevalence of OSA as high as 70% among asthmatics [14,15]. Asthma and OSA share several risk factors together like obesity, smoking, gastroesophageal reflux, sinoatrial disease and systemic inflammation [16]. OSA and asthma exhibit very similar obstructive characteristics and also both have diurnal and nocturnal variations [17]. Current guidelines recommend testing for OSA in overweight and or obese patients with poorly controlled asthma. Since its introduction by Sullivan in 1981, CPAP has been the main line of treatment for OSA [18]. Growing evidence suggests bidirectional effects of OSA with asthma and better outcomes of asthma treated with CPAP in patients with concomitant OSA [14,19–21].

Effects of asthma on OSA involves mechanical factors (increased airway resistance during REM sleep due to reduction in Functional Residual capacity and End Expiratory Lung Volume leading to upper airway collapse and worsening of apnea), Smoking (directly increasing airway edema and resistance), Corticosteroids use (causing airway myopathy, obesity and airway fat deposition) and increased nasal resistance due to rhinitis or polyps. Similarly, recent animal and human studies have shown OSA could influence lower airway inflammation and remodeling [22]. Effects of OSA on asthma includes

increasing vagal tone during apneic episodes triggering muscarinic receptors induced bronchoconstriction, intermittent hypoxic oxidative stress causing endothelial dysfunction, increased inflammation, Vascular Endothelial Growth Factor (VEGF-hypoxia-sensitive glycoprotein which may contribute to bronchial inflammation), Leptin-related airway changes (pro-inflammatory effects), Sleep fragmentation (causing increased cholinergic outflow during REM sleep), GERD (asthma triggered form micro-aspirations and respiratory mucosal injury and reflex bronchospasm) and cardiac dysfunction (OSA leads to cardiac dysfunction and CHF itself has been known to worsen asthma) [23–26]. The majority of patients with asthma have rhinitis and nasal obstruction which causes changes in airway velocity and resistance promoting upper airway collapse and thus symptoms of SDB [27]. OSA is an under-recognized condition, and failure to diagnose OSA may result in initiating standard treatment of asthma in OSA-asthma overlap syndrome. Nasal disease and corticosteroids use in such cases could probably promote OSA based on the mechanisms mentioned above. This leads to a vicious cycle of difficult to control symptoms. OSA, on the other hand, in itself is also an independent risk factor for asthma exacerbation [28–30]. Hypothetical mechanisms by which sleep fragmentation may worsen asthma control include left ventricular dysfunction, impaired immunological function, and weight gain [27]. Also, the prevalence of SDB increases with increasing asthma severity [31]. There appears to be a bidirectional synergistic effect between asthma and OSA [16]. However, there are some conflicting reports regarding the use of CPAP in patients with concomitant asthma and OSA (Alternate overlap syndrome). Ballard et al. found that the functional residual capacity of the asthmatics fell during sleep, which might partly contribute to the nocturnal increase in airway resistance and induce airway collapse which might contribute to SDB symptoms [32,33]. Some studies have reported symptomatic improvement, asthma control, decreased nocturnal attacks and alleviation of FEV_1 decline by CPAP in asthmatics with OSA [8,20,34–36]. While other studies, for instance, Lafond C. et al. demonstrated that in newly diagnosed OSA patients with mild to moderate asthma had no improvements in airway responsiveness or FEV_1 with nocturnal CPAP [37]. Similarly, Devouassoux G. et al. suggested a long-term follow up for CPAP induced airway hyper-responsiveness in OSA patients [38]. Frequent use of steroids in asthma might further worsen OSA by mechanisms explained above. Increased airway collapsibility secondary to steroid-induced airway myopathy can potentially contribute to this scenario [39]. Exact mechanisms are yet to be elucidated. Two widely recognized pathophysiological hypotheses are

systemic inflammation in obesity and mechanical effects of obesity on lung and airway function. Neither of them fully clarifies the pathogenesis and unlikely that single mechanism will explain all.

As noticed in the general population, in our study, asthma was more prevalent in the females [40]. Relatively higher pack-years of smoking was seen in asthmatics than non-asthmatics which is also consistent with data demonstrating a higher risk of OSA and asthma with increasing pack-years. Asthmatic subgroup consisted of a relatively younger population and had higher BMI as compared to the non-asthmatic subgroup. This demonstrates increasing trends towards smoking and unhealthy lifestyles among the younger generation. As BMI increases (particularly in morbidly obese individuals) there is evidence of a reduction in expiratory flow and a decrease in FEV_1 and FVC which could be seen in our study especially in asthmatic subgroup [41]. FEV_1 has been noted to be significantly lower in the asthmatic group which is expected, as asthma and obesity both contribute independently to a reduction of FEV_1. It remains to be answered if there is additive or synergistic or no difference in decline if the two factors act together. Similar to meta-analysis by De-Lei Kong et al., our study has demonstrated asthma patients with OSA have higher BMI than non-asthmatic OSA patients, (28.8 vs. 29.5, p = 0.013) [19]. Despite the factors mentioned above, more severe OSA was observed in the non-asthma group, AHI (12.63 vs. 11.34, $P = 0.015$). The severity of the OSA in asthmatics demonstrated in this study was probably due to the gender and age factor. Non-asthmatic population consisted of greater number of male patients (60.2% vs 49.8%) and also consisted of an older population compared to asthmatic population (mean age 66 years vs. 64 years). Older age and male gender both are established risk factors of OSA which reflected in AHI and RDI; probably resulting in significant severe OSA in the non asthmatic population. The difference of the population in both subgroups might have contributed in the difference noticed. Furthermore, sleep latency was seen significantly longer in asthmatics (19.8 vs. 16 min, p = 0.008), and the Epworth score was also significantly higher in the asthmatic subgroup (9 vs. 8, p = 0.02). This reflects data from cross-sectional and experimental studies which link OSA with worse clinical outcomes in patients with asthma, across the healthcare continuum [22]. Kwon et al. have labeled inhalers as 'doubled aged sword' while Teodorescu et al. have demonstrated a linear dose-dependent increase in OSA risk and habitual snoring with inhaled corticosteroids [42,43]. Fluticasone inhalers in asthmatics have shown variable effects on OSA depending upon the baseline characteristics of the patient [44]. Much work remains to understand the implications of asthma treatment on OSA. Asthma-OSA overlap could potentially be managed as a separate entity where care is tailored to the individual patient.

5. Conclusion

There is an urgent need for early and periodic detection of OSA in asthma. Clinicians should also keep a low threshold to rule out OSA particularly on elderly obese male patients with difficult to control asthma. Immediate and long-term implications of asthma treatment on the OSA remains unclear but current consensus is to manage both diseases simultaneously. A further prospective randomized control trial is needed to understand the effects of asthma on OSA

6. Limitations

This study is subject to the limitations inherent in its retrospective cross-sectional design. The study population majority was white and patients aged 40 or older were only included. Unwilling patients, healthy patients and patients whose social, physical or mental conditions preclude a home polysomnogram were not included. History of asthma was reported by a doctor of medicine. Disparities among the subgroup number of patients were included. Data obtained from the SHHS visit one and was not followed up with the visit 2.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Ferkol T, Schraufnagel D. The global burden of respiratory disease. Ann Am Thorac Soc. 2014;11 (3):404–406.
[2] World Health Organization. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Geneva, Switzerland: World Health Organization; 2013.
[3] Cochrane G, Clark J. A survey of asthma mortality in patients between ages 35 and 64 in the greater London hospitals in 1971. Thorax. 1975;30(3):300–305.
[4] McNicholas WT, Fitzgerald MX. Nocturnal deaths among patients with chronic bronchitis and emphysema. Br Med J (Clin Res Ed). 1984;289 (6449):878.

[5] Clark T, Hetzel M. Diurnal variation of asthma. Br j dis chest. 1977;71:87–92.

[6] Soutar, C., Costello, J., Ijaduola, O.,et al. Nocturnal and morning asthma. Relationship to plasma corticosteroids and response to cortisol infusion. Thorax. 1975;30(4):436–440.

[7] Turner-Warwick M. Epidemiology of nocturnal asthma. Am J Med. 1988;85(1):6–8.

[8] Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: role of snoring and obstructive sleep apnea. Am Rev Respir Dis. 1988;137(6):1502–1504.

[9] Julien, J.Y., Martin, J. G., Ernst, P.,et al. Prevalence of obstructive sleep apnea–hypopnea in severe versus moderate asthma. J Allergy Clin Immunol. 2009;124 (2):371–376.

[10] Quan, S.F., Howard, B. V., Iber, C.,et al. The sleep heart health study: design, rationale, and methods. Sleep. 1997;20(12):1077–1085.

[11] S.H.H.R.G.R.S.s.p.c.e.S.M.H.L.B.K.Q.S.F.I.C.G.D.J.B. W., Bonekat WH, Rapoport DM, Smith PL, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep. 1998;21(7):759–767.

[12] Dean, D.A., Goldberger, A.L., Mueller, R., et al. Scaling up scientific discovery in sleep medicine: the national sleep research resource. Sleep. 2016;39(5):1151–1164.

[13] Zhang, G.-Q., Cui, L., Mueller, R., et al. The national sleep research resource: towards a sleep data commons. J Am Med Inform Assoc. 2018 ;25(10):1351–1358. doi: 10.1093/jamia/ocy064.

[14] Lu, H., Fu, C., Li, W., et al. Screening for obstructive sleep apnea syndrome in asthma patients: a prospective study based on Berlin and STOP-bang questionnaires. J Thorac Dis. 2017;9(7):1945.

[15] Alharbi, M., Almutairi, A., Alotaibi, D.,et al. The prevalence of asthma in patients with obstructive sleep apnoea. Prim Care Respir J. 2009;18(4):328–330.

[16] Puthalapattu S, Ioachimescu OC. Asthma and obstructive sleep apnea: clinical and pathogenic interactions. J Invest Med. 2014;62(4):665–675.

[17] Schechter MS. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2002;109(4):e69–e69.

[18] Sullivan, C., Berthon-Jones, M., Issa, F., et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet. 1981;317(8225):862–865.

[19] Kong, D.-L., Qin Z., Shen H., et al. Association of obstructive sleep apnea with asthma: a meta-analysis. Sci Rep. 2017;7(1):4088.

[20] Kauppi, P., Bachour, P., Maasilta, P., et al. Long-term CPAP treatment improves asthma control in patients with asthma and obstructive sleep apnoea. Sleep Breathing. 2016;20(4):1217–1224.

[21] Serrano-Pariente, J., Plaza V., Soriano JB., et al. Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea. Allergy. 2017;72(5):802–812.

[22] Owens RL, Macrea MM, Teodorescu M. The overlaps of asthma or COPD with OSA: A focused review. Respirology. 2017;22(6):1073–1083.

[23] Razak MRA, Chirakalwasan N. Obstructive sleep apnea and asthma. Asian Pac J Allergy Immunol. 2016;34(4):265–271.

[24] Qiao Y.-X, Xiao Y. Asthma and obstructive sleep apnea. Chin Med J (Engl). 2015;128(20):2798.

[25] Alkhalil M, Schulman E, Getsy J. Obstructive sleep apnea syndrome and asthma: what are the links? J Clin Sleep Med. 2009;5(1):71.

[26] Holguin F, Fitzpatrick A. Obesity, asthma, and oxidative stress. J Appl Physiol. 2009;108(3):754–759.

[27] Prasad B, Nyenhuis SM, Weaver TE. Obstructive sleep apnea and asthma: associations and treatment implications. Sleep Med Rev. 2014;18(2):165–171.

[28] Ten Brinke, A., Sterk PJ, Masclee AA., et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J. 2005;26(5):812–818.

[29] Umashankar, N., et al. Association of OSA risk in asthma. Chest. 2016;150(4):845A.

[30] Davies S, Cachada N, Turner A, et al. P202 obstructive sleep apnoea (osa) and non-eosinophilic asthma: an important phenotype in the severe asthma population. Thorax 2017;72:A192–A193.

[31] Goldstein, NA., Aronin C., Kantrowitz B., et al. The prevalence of sleep-disordered breathing in children with asthma and its behavioral effects. Pediatr Pulmonol. 2015;50(11):1128–1136.

[32] Ballard, RD., Irvin CG., Martin RJ., et al. Influence of sleep on lung volume in asthmatic patients and normal subjects. J Appl Physiol. 1990;68 (5):2034–2041.

[33] Van de Graaff WB. Thoracic influence on upper airway patency. J Appl Physiol. 1988;65(5):2124–2131.

[34] Wang T.-Y, Lo Y.-L, Kuo H.-P. Obstructive sleep apnea accelerates decline in FEV1 in asthmatic patients. Eur Respir J. 2014;44(Suppl 58):2935.

[35] Teodorescu, M., Polomis DA., Gangnon RE., et al. Asthma control and its relationship with obstructive sleep apnea (OSA) in older adults. Sleep Disord. 2013;2013:251567.

[36] Wang, T.-Y., Lo YL, Lin SM, et al. Obstructive sleep apnoea accelerates FEV 1 decline in asthmatic patients. BMC Pulm Med. 2017;17(1):55.

[37] Lafond C, Series F, Lemiere C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. Eur Respir J. 2007;29(2):307–311.

[38] Devouassoux, G., Lévy P., Rossini E., et al. Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure–induced airway hyperresponsiveness. J Allergy Clin Immunol. 2007;119 (3):597–603.

[39] Yigla, M., Tov N., Solomonov A., et al. Difficult-to-control asthma and obstructive sleep apnea. J Asthma. 2003;40(8):865–871.

[40] Greenblatt, R., Mansour O., Zhao E., et al. Gender-specific determinants of asthma among US adults. Asthma Res Pract. 2017;3(1):2.

[41] Ray, C.S., Sue DY., Bray G., Hansen JE., et al. Effects of obesity on respiratory function. Amer Rev Respir Dis. 1983;128(3):501–506.

[42] Kwon M, Arunthari V, Lee AS, et al. Inhalers in a patient with obstructive sleep apnea: a double-edged sword. Am J Respir Crit Care Med.2018;197(1):New York: American Thoracic Society.

[43] Teodorescu, M., Consens FB., Bria WF., et al. Predictors of habitual snoring and obstructive sleep apnea risk in patients with asthma. Chest. 2009;135 (5):1125–1132.

[44] Teodorescu, M., Xie A., Sorkness CA., et al. Effects of inhaled fluticasone on upper airway during sleep and wakefulness in asthma: a pilot study. J Clin Sleep Med. 2014;10(2):183–193.