Risk of Obstructive Sleep Apnea in Adult Patients with Asthma: A Population-Based Cohort Study in Taiwan

Te-Chun Shen¹,², Cheng-Li Lin³, Chang-Ching Wei⁴, Chia-Hung Chen¹,², Chih-Yen Tu², Te-Chun Hsia², Chuen-Ming Shih², Wu-Huei Hsu², Fung-Chang Sung¹,³, Chia-Hung Kao¹,⁵*

¹ Graduate Institute of Clinical Medicine Science, College of Medicine, China Medical University, Taichung, Taiwan, ² Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, ³ Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, ⁴ Division of Nephrology, Department of Pediatrics, China Medical University Hospital, Taichung, Taiwan, ⁵ Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

* d10040@mail.cmuh.org.tw

Abstract

Background

There are several publications reported that obstructive sleep apnea (OSA) was associated with asthma. However, large-scaled, population-based cohort study has been limited. We aimed to examine the risk of OSA among adult patients with asthma in an Asian population.

Methods

We conducted a retrospective cohort study using data from the National Health Insurance (NHI) of Taiwan. The asthma cohort included 38,840 newly diagnosed patients between 2000 and 2010. The date of diagnosis was defined as the index date. Each patient was randomly matched with four people without asthma according to gender, age, and the index year as the comparison cohort. The occurrence of OSA was followed up until the end of 2011. The risk of OSA was estimated using the Cox proportional hazard model after adjusting for gender, age, and comorbidities.

Results

The overall incidence of OSA was 2.51-fold greater in the asthma cohort than in the comparison cohort (12.1 versus 4.84 per 1000 person-years). Compared to non-asthma subjects, the adjusted hazard ratio (aHR) of OSA increased to 1.78 for asthma patients with one or less annual emergency room (ER) visit, and 23.8 for those who visited ER more than once per year. In addition, aHR in patients with inhaled steroid treatment compared to those without steroid treatment was 1.33 (95% CI = 1.01 – 1.76).
Conclusion
Patients with asthma have a significantly higher risk of developing OSA than the general population. The results suggest that the risk of OSA is proportional to asthma control and patients with inhaled steroid treatment have a higher risk for OSA than those without steroid treatment.

Introduction
Asthma is a serious global health problem affecting all age groups. It is a heterogeneous disease, usually characterized by chronic airway inflammation. The definition and diagnosis are based on the history of characteristic symptoms and evidence of variable airflow limitation [1]. Certain comorbidities are commonly present in patients with asthma, particularly those with difficult-to-treat asthma. The most common comorbid diseases include gastroesophageal reflux disease (GERD), rhinitis, sinusitis, anxiety, and depression [2–5]. In addition, patients with asthma often have poor sleep quality, which contributes to nocturnal deterioration of typical symptoms or other specific features [6].

Obstructive sleep apnea (OSA) is characterized by repeated episodes of upper airway obstruction that results in brief periods of breathing cessation or a marked reduction in airflow during sleep [7]. OSA is a common disorder with an estimated prevalence of 10%–20% [8]. Risk factors for OSA include male gender, age, obesity, and nasal diseases such as rhinitis [9]. Patients with OSA tend to have circular upper airways, whereas normal people have elliptical upper airways [10]. The most common type of upper airway obstruction is velopharyngeal narrowing, which accounts for about 80% of all cases [11]. Diagnosis of OSA is essential because of the subsequent cardiovascular comorbidities and the risk of sudden death [12].

Several publications have discussed relationships between asthma and OSA [13–17]. Salles et al. reported that OSA is prevalent in patients with asthma and is associated with disease severity. They considered OSA to be one of the most important pathophysiological mechanisms related to the worsening of asthma symptoms [13]. Treatment of OSA has been shown to improve asthma symptoms [18–19]. The National Asthma Education and Prevention Program’s Expert Panel Report 3 have recommend OSA evaluation in patients with asthma because OSA is a potential factor for asthma control [20]. However, large-scaled, population-based cohort study has been limited.

Taiwan’s National Health Insurance (NHI) database is a nationwide cohort dataset, which provides reliable data and has been used for various studies on either asthma or OSA [21–24]. In the present study, we aimed to determine whether asthma is associated with an increased risk of OSA.

Materials and Methods
Data source
The NHI program has been active in Taiwan since March 1, 1995. According to the NHI annual statistics report, the coverage rate of NHI in 2007 was nearly 99% of the entire population of Taiwan, and more than 25 million people were enrolled in this program (http://www.nhi.gov.tw/english/index.aspx). This population-based cohort study was conducted using registration and claims datasets from 2000 to 2011 obtained from the Longitudinal Health Insurance Database 2000 (LHID2000), a subset of the National Health Insurance Research Database.
(NHIRD), which is managed by Taiwan’s National Health Research Institutes (NHRI). The LHID2000 contains all ambulatory and inpatient claims data of one million beneficiaries who were randomly sampled from the 2000 registry for beneficiaries of the NHIRD. All personal information was encoded to protect privacy with surrogate identification before release for this research. Diagnostic codes were based on the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM). This study was exempted from full ethical review by the International Review Board, China Medical University and Hospital Research Ethics Committee (IRB permit number: CMU-REC-101-012).

Study participants
Using the LHID2000 from 2000–2010, we enrolled patients above 20 years, who had been diagnosed with asthma (ICD-9 code 493), as the asthma cohort. Exclusion criteria included those diagnosed with OSA (ICD-9 code 327.23, 780.51, 780.53, 780.57) [23, 24] before index date, and with incomplete gender or age information. The index date was defined as the date of asthma diagnosis. The comparison cohort was randomly selected from all NHI beneficiaries, non-asthma, above 20 years, and was frequency-matched for gender, age (every five years), and index year with a 1:4 ratio. The diagnosis of asthma was made based on a target history, and a comprehensive pulmonary function evaluation. Physicians usually follow the GINA guideline [1] for diagnosis. Similarly, the diagnosis of OSA always needs standard polysomnography [the common diagnostic criteria was apnea-hypopnea index (AHI) >5].

Outcome and relevant variables
All subjects were followed up until the occurrence of OSA; withdrawal from NHI; death; or December 31 2011; whichever came first. The OSA related co-morbidities included hypertension (ICD-9 code 401–405), diabetes (ICD-9 code 250), hyperlipidemia (ICD-9 code 272), chronic obstructive pulmonary disease (COPD) (ICD-9 code 496), coronary artery disease (CAD) (ICD-9 code 410–414), stroke (ICD-9 code 430–438), rhinitis (ICD-9 code 472–477), chronic sinusitis (ICD-9-CM 473), GERD (ICD-9 code 530.11, 530.81), and obesity (ICD-9 code 278). All diseases were confirmed only while those diagnostic codes that appeared at least twice within a year.

Statistical analysis
The differences in demographic characteristics, and comorbidities between the asthma, and comparison cohorts were examined using Chi-square test for categorical variables, and Student’s t-test for continuous variables. Incidence density rates were calculated by dividing the number of patients with OSA by total person years of follow-up. The asthma-to-comparison hazard ratios (HRs) and 95% confidence interval (CIs) for OSA by age-, sex-, and comorbidity-specific were calculated using univariable and multivariable Cox proportion hazard regression models. Only confounding variables that were found to be significant in the multivariable model were further analyzed. The combined effects of comorbidity and asthma were also assessed in the Cox models. We further analyzed the effect of the status of asthma control on the risk of OSA, based on the number of emergency room (ER) visits for asthma. In addition, we performed Cox proportional hazards regression analysis to measure hazard ratio of OSA among asthma patients by different treatments. We plotted the Kaplan–Meier curve to estimate the cumulative incidence of subsequent OSA between the asthma and comparison cohorts. Log-rank test was used to examine the significance of difference between the two cohorts. All statistical analyses were performed using SAS 9.3 statistical software (SAS Institute, Inc., Cary, NC, USA). A p value < 0.05 was considered to be significant.
We enrolled 38,840 patients with asthma from 2000–2010 as the asthma cohort, and 155,347 gender- and age-matched patients without asthma as the comparison cohort. Table 1 displays the difference in demographic characteristics, and comorbidities among the two cohorts. The mean age of the asthma cohort was 52.8 years (SD = 18.1), and the comparison cohort was 53.3 years (SD = 18.0). The asthma cohort had a significantly higher rate of hypertension, diabetes, hyperlipidemia, COPD, CAD, stroke, rhinitis, chronic sinusitis, GERD and obesity (all p < 0.001) than the comparison cohort. The mean follow-up period was 6.95 years (SD = 3.33) for the asthma cohort, and 6.51 years (SD = 3.44) for the comparison cohort. Fig 1 displays the results of Kaplan-Meier survival analysis between patients with or without asthma. The log-rank test showed that the asthma cohort had significantly higher cumulative incidence rates of OSA than the comparison cohort (p < 0.001, Fig 1).

The overall incidence of OSA was 2.51–fold higher in the asthma cohort than in the comparison cohort (12.1 vs. 4.84 per 1,000 person-years) (Table 2). After adjusting for gender, age, and comorbidities, the HR for developing OSA during the follow-up years was 1.87 (95% CI = 1.61–2.17) for the asthma cohort as compared to the comparison cohort. The incidence of

### Table 1. Comparisons in demographic characteristics and comorbidities between cohorts with and without asthma.

| Variables       | No (N = 155347) | Asthma (N = 38840) | p-value |
|-----------------|-----------------|-------------------|---------|
|                 | n               | %                 | n       | %                 |         |
| Sex             |                 |                   |         |                   |         |
| Female          | 84776           | 54.6              | 21194   | 54.6              | 0.99    |
| Male            | 70571           | 45.4              | 17646   | 45.4              |         |
| Age, years      |                 |                   |         |                   |         |
| 20–34           | 30004           | 19.3              | 7501    | 19.3              | 0.99    |
| 35–49           | 36868           | 23.7              | 9217    | 23.7              |         |
| 50–64           | 41204           | 26.5              | 10301   | 26.5              |         |
| > 65            | 47271           | 30.4              | 11821   | 30.4              |         |
| Mean (SD)†      | 52.8 (18.1)     |                   | 53.3 (18.0) |                   | <0.001  |
| Comorbidity     |                 |                   |         |                   |         |
| Hypertension    | 46377           | 29.9              | 15898   | 40.9              | <0.001  |
| Diabetes        | 12982           | 8.30              | 3672    | 9.45              |         |
| Hyperlipidemia  | 25921           | 16.7              | 8781    | 22.6              | <0.001  |
| COPD            | 2653            | 1.71              | 3786    | 9.75              | <0.001  |
| CAD             | 30901           | 19.9              | 11828   | 30.5              | <0.001  |
| Stroke          | 5740            | 3.69              | 2071    | 5.33              | <0.001  |
| Rhinitis        | 16262           | 10.5              | 13525   | 34.8              | <0.001  |
| Chronic sinusitis | 2171      | 1.40              | 1507    | 3.88              | <0.001  |
| GERD            | 1360            | 0.88              | 752     | 1.94              | <0.001  |
| Obesity         | 1269            | 0.82              | 675     | 1.74              | <0.001  |

COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; GERD, gastroesophageal reflex disease; Chi-square test; †Two sample t-test

doi:10.1371/journal.pone.0128461.t001
OSA was higher in men than in women in both cohorts. The adjusted HRs of OSA were 2.14 (95% CI = 1.77–2.59) and 1.50 (95% CI = 1.17–1.92) in men and women, respectively. The age-specific adjusted HRs of OSA for asthma cohort to comparison cohort were significant for all age subgroups. The incidence of OSA was higher in those with any comorbidity than in those without comorbidity in both cohorts. The adjusted HRs of OSA were 2.05 (95% CI = 1.74–2.41) and 1.90 (95% CI = 1.40–2.59) in those with and without comorbidity, respectively.

Table 3 shows the combined effects of asthma and comorbidities on the risk of OSA. When compared to subjects without asthma and GERD, the adjusted HR increased to 11.4 (95% CI = 6.68–19.4) for subjects with asthma and GERD. Co-existence with obesity (adjusted HR: 6.07, 95% CI = 3.24–11.4), hyperlipidemia (adjusted HR: 4.80, 95% CI = 3.88–5.94), rhinitis (adjusted HR: 4.29, 95% CI = 3.57–5.14), hypertension (adjusted HR: 4.11, 95% CI = 3.33–5.07) and CAD (adjusted HR: 4.10, 95% CI = 3.31–5.08) enhanced the risk of OSA in patients with asthma.

Table 4 shows that the adjusted HR of OSA increased to 1.78 (95% CI = 1.53–2.08) for patients with asthma with one or less ER visit per year, and 23.8 (95% CI = 14.5–39.0) for those who visited ER more than one times per year ($p$ for trend < 0.0001). Table 5 shows that incidence of OSA was highest in asthma patients with inhaled steroid treatment (15.3 per 1000

---

**Fig 1. Comparison of cumulative incidence of obstructive sleep apnea between patients with or without asthma.**

doi:10.1371/journal.pone.0128461.g001
Discussion

This population-based cohort study demonstrates an increased risk of OSA in patients with asthma as compared to the general population (12.1 versus 4.84 per 1000 person-years; crude HR: 2.51; 95% CI = 2.19–2.89; p < 0.001). This finding is compatible with the well-known concept that male participants, older subjects, and those with risk factors such as cardiovascular diseases, stroke, COPD, rhinitis, chronic sinusitis, GERD, and obesity may have a higher incidence of OSA. In the present study, we found adjusted HRs were greater in men than in women (2.14 vs. 1.54), in 50–64 years age group than in other age groups (2.00 vs. 1.63, 1.19 and 1.42), and in those with any comorbidities than in those without comorbidity (2.05 vs. 1.90). In addition, our study showed that the risk of developing OSA increased proportionately with the number of annual ER visits for asthma (adjusted HR from 1.78 to 23.8).

Several cross-sectional population-based studies have described the prevalence of OSA based on questionnaires submitted by people with asthma. Fitzpatrick MF et al. reported that people with asthma of all ages and body weights snored more often than the controls in a British population [25]. In the European Community Health Respiratory Survey (Iceland, Sweden, and Belgium), Janson et al. noticed that self-reported snoring and apnea were significantly more common in young adults with asthma versus controls (14% vs 9% and 3% vs 1%, respectively) [26]. Larsson LG et al. in a Swedish study found 17% snoring and 14% apnea in those...
with asthma, as compared to an overall prevalence of 10% and 7%, respectively [27]. Similarly, Ekici et al. conducted a study in Turkey involving 7469 adults; of which, 2713 had a history of asthma. They reported that snoring (OR = 1.7) and apnea (OR = 2.7) were more prevalent in patients with asthma than those without asthma [28]. However, these studies on association between asthma and OSA were cross-sectional studies, and the findings may not be a valid reflection of the true risk of OSA associated with asthma. In the present study, we identified that the overall incidence of OSA was 2.51-fold higher in the asthma cohort than in the comparison cohort, and a multivariable Cox method measured an adjusted HR of 1.87.

Table 3. Cox proportional hazard regression analysis for the risk of obstructive sleep apnea-associated asthma with combined effect of comorbidity.

| Variables | Event | Adjusted HR† (95% CI) | p-value# |
|-----------|-------|------------------------|----------|
|           | N     | n                      |          |
| Asthma    | 108970| 315                    | 1 (Reference) 0.13 |
| No        | 46377 | 206                    | 1.93 (1.58, 2.36)*** |
| Yes       | 22942 | 174                    | 2.56 (2.13, 3.09)*** |
| Yes       | 15898 | 154                    | 4.11 (3.33, 5.07)*** |
| Asthma    | 129426| 395                    | 1 (Reference) 0.45 |
| No        | 2592  | 126                    | 1.83 (1.49, 2.25)*** |
| Yes       | 30059 | 213                    | 2.32 (1.96, 2.74)*** |
| Yes       | 8781  | 115                    | 4.80 (3.88, 5.94)*** |
| Asthma    | 124446| 371                    | 1 (Reference) 0.14 |
| No        | 30901 | 150                    | 2.02 (1.65, 2.47)*** |
| Yes       | 27012 | 207                    | 2.53 (2.13, 3.00)*** |
| Yes       | 11828 | 121                    | 4.10 (3.31, 5.08)*** |
| Asthma    | 139085| 437                    | 1 (Reference) 0.96 |
| No        | 16262 | 84                     | 2.07 (1.64, 2.62)*** |
| Yes       | 25315 | 166                    | 2.03 (1.70, 2.43)*** |
| Yes       | 13525 | 162                    | 4.29 (3.57, 5.14)*** |
| Asthma    | 153987| 518                    | 1 (Reference) 0.06 |
| No        | 1360  | 3                      | 1.42 (0.46, 4.42) |
| Yes       | 38088 | 314                    | 2.44 (2.12, 2.80)*** |
| Yes       | 752   | 14                     | 11.4 (6.68, 19.4)*** |
| Asthma    | 154078| 511                    | 1 (Reference) 0.49 |
| No        | 1269  | 10                     | 3.25 (1.74, 6.07)*** |
| Yes       | 38165 | 318                    | 2.51 (2.18, 2.88)*** |
| Yes       | 675   | 10                     | 6.07 (3.24, 11.4)*** |

COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; GERD, gastroesophageal reflux disease; † Model was adjusted for age and sex; # p-value for interaction; ***p<0.001

doi:10.1371/journal.pone.0128461.t003
Several hypotheses have been postulated on the interactions between asthma and OSA. First, shared risks and comorbid conditions, such as GERD, rhinitis, and obesity, could play a very important role [13–16]. For example, Braido F et al. reported that 52.6% (1021/1941) of asthma subjects had OSA, including 47.3% (350/740) with asthma alone and 55.9% (671/1201) with asthma and allergic rhinitis [16]. In the present study, we also noticed strong combined effects of these comorbidities and asthma on the risk of OSA, particularly those with GERD (adjusted HR: 11.4) and with obesity (adjusted HR: 6.07). Second, systemic inflammation may contribute to both asthma and OSA. Asthma is associated with acute and chronic inflammation, which affects the strength or force generation of the respiratory muscles, including the upper airway dilator muscles [29]. The biological mechanism linking lower airway inflammation with sleep-related upper airway collapse may explain a unified airway hypothesis. Other theories include sleep architecture (neural), tracheal tug (mechanical), and respiratory phase interdependence (mechanical) [14]. In addition, corticosteroid usage for asthma control may also influence the incidence of OSA [30, 31]. In the present study, our findings also support the notion that asthma patients with inhaled steroid treatment have a higher risk for OSA development than patients without steroid treatment.

Some studies focused on the relationships between moderate to severe or difficult-to-treat asthma and OSA [7, 32–33]. Most of them suggested that OSA contributes to worsen asthma control. Recently, Teodorescu M et al. reported asthma was associated with an increased risk of new-onset OSA and they found asthma-OSA association was significantly dose-dependent on duration of asthma [17]. However, the correlation between asthma control and OSA incidence remains unknown. In the present study, the number of ER visits per year for asthma has been considered to reflect, at least in part, the asthma control status. The results related to ER visits also supported the hypothesis that poor control of asthma results in an increased risk of OSA. In addition, subjects with inhaled steroid control may also indicate a more difficult-to-control group of asthma (at least step 2 in GINA guideline). They do indeed have a higher risk for OSA development than patients without steroid treatment.

The strength of this study is in providing a longitudinal population-based evaluation of Asians with asthma, and their risks of developing OSA. It is generally very costly to conduct a population-based prospective cohort study, in which loss to follow-up is problematic after several years. Therefore, a retrospective cohort study using insurance or register data is an alternative, which meets the requirement but is economical. However, there are several limitations to be considered when interpreting the present findings. First, this study used the ICD-9-CM algorithm to define asthma, OSA, and comorbidities. The diagnosis depends on the performance

### Table 4. Hazard ratios of obstructive sleep apnea associated with the number of annual emergency room visits for patients with asthma.

| No. of Event | Crude HR^ (95% CI) | Adjusted HR^ (95% CI) |
|--------------|-------------------|----------------------|
| Non-asthma   | 521               | 1 (Reference)        | 1 (Reference)        |
| ≤1           | 311               | 2.39 (2.08, 2.76)**   | 1.78 (1.53, 2.08)**   |
| >1           | 17                | 30.9 (19.0, 50.2)**   | 23.8 (14.5, 39.0)**   |
| p for trend  | <0.001            | <0.001               |

Crude HR^, relative hazard ratio;  
^ Model was adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, COPD, CAD, stroke, rhinitis, chronic sinusitis, GERD and obesity;  
***p<0.001

doi:10.1371/journal.pone.0128461.t004
of clinical physicians. An ad hoc committee established by the insurance authority was in charge of evaluating the claims data to prevent errors and violation. In addition, we selected only those diagnoses that appeared at least twice within a year to increase the validity and accuracy of diagnosis. Second, NHRID does not provide detailed information on severity of asthma, socioeconomic status, environmental factors, occupation, smoking habits, alcohol consumption, abdominal adiposity indices, such as waist circumference (WC) or waist-to-height ratio, body mass index, diet preference, physical activity, and family history, although these are potential confounding factors for this study. In addition, relevant clinical variables, such as serum laboratory data, polysomnography, pulmonary function tests, or imaging results of patients were unavailable in our study.

Conclusion

Patients with asthma have a significantly higher risk of developing OSA than the general population. The results suggest that the risk of OSA is proportional to asthma control and patients with inhaled steroid treatment have a higher risk for OSA than patients without steroid treatment. Since evaluating OSA in patients with asthma has been included in the Guidelines for the Diagnosis and Management of Asthma [20], we suggest that periodic OSA evaluation in certain asthma patients may have a clinical benefit in the management of both asthma and OSA.

Author Contributions

Conceived and designed the experiments: TCS CCW CHK. Performed the experiments: TCS CLL CCW CHC CYT TCH CMS WHH FCS CHK. Analyzed the data: TCS CLL FCS CHK. Contributed reagents/materials/analysis tools: TCS CLL FCS CHK. Wrote the paper: TCS CLL CCW CHC CYT TCH CMS WHH FCS CHK. Supervision: CYT TCH CMS WHH FCS CHK.

References

1. Global strategy for asthma management and prevention. (2014) http://www.ginasthma.org.
2. Boulet LP. (2009) Influence of comorbid conditions on asthma. Eur Respir J 33: 897–906. doi: 10.1183/09031936.00121308 PMID: 19336592
3. Goodwin RD, Jacobi F, Thefeld W. (2003) Mental disorders and asthma in the community. Arch Gen Psychiatry 60: 1125–30. PMID: 14609888

Table 5. Cox proportional hazards regression analysis measured hazard ratio of obstructive sleep apnea among asthma patients by different treatments.

| Variables of asthma | N       | Event | PY     | Rate$ | Crude HR# (95% CI) | Adjusted HR† (95% CI) |
|--------------------|---------|-------|--------|-------|-------------------|----------------------|
| Non-steroid        | 13792   | 89    | 84271  | 10.6  | 1 (Reference)     | 1 (Reference)        |
| Inhaled steroid    | 11214   | 128   | 83602  | 15.3  | 1.46 (1.11, 1.92)** | 1.33 (1.01, 1.76)*   |
| Systemic steroid   | 13834   | 111   | 102003 | 10.9  | 1.04 (0.79, 1.37)  | 1.01 (0.76, 1.34)    |

Rate$ per 1000 person-year; Crude HR#, relative hazard ratio;
† Model was adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, COPD, CAD, stroke, rhinitis, chronic sinusitis, GERD and obesity;
*p<0.05,
**p<0.01

doi:10.1371/journal.pone.0128461.t005
4. Cruz AA, Popov T, Pawankar R, Annesi-Maesano I, Fokkens W, Kemp J, et al. (2007) Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2) LEN. Allergy 62 Suppl 84: 1–41. PMID: 17924930

5. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. (2012) EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 50: 1–12. doi: 10.4193/Rhino50E2 PMID: 22469599

6. Yamasaki A, Kawasaki Y, Takeda K, Harada T, Fukushima T, Takata M, et al. (2014) The relationships among sleep efficiency, pulmonary functions, and quality of life in patients with asthma. Int J Gen Med 7: 505–12. doi: 10.2147/IJGM.S27713 PMID: 25419157

7. Byun MK, Park SC, Chang YS, Kim YS, Kim SK, Kim HJ, et al. (2013) Associations of moderate to severe asthma with obstructive sleep apnea. Yonsei Med J 54: 942–8. doi: 10.3349/ymj.2013.54.4.942 PMID: 23709430

8. Tishler PV, Larkin EK, Schluchter MD, Redline S. (2003) Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. JAMA 289: 2230–40. PMID: 12734134

9. Young T, Peppard PE, Gottlieb DJ. (2002) Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 165: 1217–39. PMID: 11991871

10. Schwab RJ, Gefter WB, Hoffman EA, Gupta KB, Pack AI. (1993) Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. Am Rev Respir Dis 148: 1385–400. PMID: 8239180

11. Rabelo FA, Küpper DS, Sander HH, dos Santos Júnior V, Thuler E, Fernandes RM, et al. (2013) A comparison of the Fujita classification of awake and drug-induced sleep endoscopy patients. Braz J Otorhinolaryngol 79: 100–5. PMID: 23503915

12. Weiss JW, Launois SH, Anand A, Garpestad E. (1999) Cardiovascular morbidity in obstructive sleep apnea. Prog Cardiovasc Dis 41: 367–76. PMID: 10406330

13. Salles C, Terse-Ramos R, Souza-Machado A, Cruz AA. (2013) Obstructive sleep apnea and asthma. J Bras Pneumol 39: 604–12. doi: 10.1590/S1806-37132013000500011 PMID: 24310634

14. Prasad B, Nyenhuis SM, Weaver TE. (2014) Obstructive sleep apnea and asthma: associations and treatment implications. Sleep Med Rev 18: 165–71. doi: 10.1016/j.smrv.2013.04.004 PMID: 23890469

15. Puthalapattu S, Ioachimescu OC. (2014) Asthma and obstructive sleep apnea: clinical and pathogenic interactions. J Investig Med 62: 665–75. doi: 10.231/JIM.0000000000000065 PMID: 24583902

16. Braido F, Baiardini I, Lacedonia D, Facchini FM, Fanfulla F, Molinengo G, et al. (2014) Sleep apnea risk in subjects with asthma with or without comorbid rhinitis. Respir Care 59: 1851–6. doi: 10.4187/respcare.03084 PMID: 24917451

17. Teodorescu M, Barnet JH, Hagen EW, Palta M, Young TB, Peppard PE. (2015) Association between asthma and risk of developing obstructive sleep apnea. JAMA 313: 156–64. doi: 10.1001/jama.2014.17822 PMID: 25585327

18. Guilleminault C, Quera-Salva MA, Powell N, Riley R, Romaker A, Partinen M, et al. (1988) Nocturnal asthma: snoring, small pharynx and nasal CPAP. Eur Respir J 1: 902–7. PMID: 3066641

19. Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktas H. (2005) Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. Respir Med 99: 529–34. PMID: 15823448

20. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 120 (5 Suppl): S94–138. PMID: 17983880

21. Chung WS, Lin CL, Chen YF, Ho FM, Hsu WH, Kao CH. (2014) Increased stroke risk among adult asthmatic patients. Eur J Clin Invest 44: 1025–33. doi: 10.1111/eci.12336 PMID: 25207756

22. Chung WS, Shen TC, Lin CL, Chu YH, Hsu WH, Kao CH. (2014) Adult asthma increases the risk of acute coronary syndrome: A nationwide population-based cohort study. Eur J Intern Med 25: 941–5. doi: 10.1016/j.ejim.2014.10.023 PMID: 25468246

23. Kang JH, Keller JJ, Chen YK, Lin HC. (2012) Association between obstructive sleep apnea and urinary calculi: a population-based case-control study. Urology 79: 340–5. doi: 10.1016/j.urology.2011.08.040 PMID: 22000932

24. Chen YL, Weng SF, Shen YC, Chou CW, Yang CY, Wang JJ, et al. (2014) Obstructive sleep apnea and risk of osteoporosis: a population-based cohort study in Taiwan. J Clin Endocrinol Metab 99: 2441–7. doi: 10.1210/jc.2014-1718 PMID: 24735427

25. Fitzpatrick MF, Martin K, Fossey E, Shapiro CM, Elton RA, Douglas NJ, et al. (1993) Snoring, asthma and sleep disturbance in Britain: a community-based survey. Eur Respir J 6: 531–5. PMID: 8491303
26. Janson C, De Backer W, Gislason T, Plaschke P, Björnsson E, Hetta J, et al. (1996) Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. Eur Respir J 9: 2132–8. PMID: 8902479

27. Larsson LG, Lindberg A, Franklin KA, Lundbäck B. (2001) Symptoms related to obstructive sleep apnea are common in subjects with asthma, chronic bronchitis and rhinitis in a general population. Respir Med 95: 423–9. PMID: 11392586

28. Ekici A, Ekici M, Kurtipek E, Keles H, Kara T, Tunckol M, et al. (2005) Association of asthma-related symptoms with snoring and apnea and effect on health-related quality of life. Chest 128: 3358–63. PMID: 16304284

29. Reid MB, Lännergren J, Westerblad H. (2002) Respiratory and limb muscle weakness induced by tumor necrosis factor-alpha: involvement of muscle myofilaments. Am J Respir Crit Care Med 166: 479–84. PMID: 12186824

30. Shipley JE, Schtingart DE, Tandon R, Starkman MN. (1992) Sleep architecture and sleep apnea in patients with Cushing's disease. Sleep 15: 514–8. PMID: 1335612

31. Teodorescu M, Xie A, Sorkness CA, Robbins J, Reeder S, Gong Y, et al. (2014) Effects of inhaled fluticasone on upper airway during sleep and wakefulness in asthma: a pilot study. J Clin Sleep Med 10: 183–93. doi: 10.5664/jcsm.3450 PMID: 24533002

32. Yigla M, Tov N, Solomonov A, Rubin AH, Harlev D. (2003) Difficult-to-control asthma and obstructive sleep apnea. J Asthma 40: 865–71. PMID: 14736085

33. Teodorescu M, Polomis DA, Gangnon RE, Fedie JE, Consens FB, Chervin RD, et al. (2013) Chervin RD, Teodorescu MC. Asthma control and its relationship with obstructive sleep apnea in older adults. Sleep Disord 2013: 251567. doi: 10.1155/2013/251567 PMID: 24307949