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Association of Obstructive Sleep Apnea Risk or Diagnosis with Daytime Asthma in Adults

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Abstract

Objective—Obstructive sleep apnea (OSA) worsens nocturnal asthma, but its potential impact on daytime asthma remains largely unassessed. We investigated whether the sleep disorder is associated with daytime, in addition to nighttime asthma symptoms.

Methods—Asthma patients at tertiary-care centers completed the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ), and an asthma control questionnaire. SA-SDQ scores ≥36 for men and ≥32 for females defined high OSA risk. Medical records were reviewed for established diagnosis of OSA and continuous positive airway pressure (CPAP) use.

Results—Among 752 asthma patients, high OSA risk was associated similarly with persistent daytime and nighttime asthma symptoms ($p < 0.0001$ for each). A diagnosis of OSA was robustly associated with persistent daytime ($p < 0.0001$), in addition to nighttime ($p = 0.0008$) asthma

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symptoms. In regression models that included obesity and other known asthma aggravators, high OSA risk retained associations with persistent daytime (odds ratio =1.96 [95% confidence interval 1.31–2.94]) and nighttime asthma symptoms (1.97 [1.32–2.94]). Diagnosed OSA retained an association with persistent daytime (2.08 [1.13–3.82]) but not with nighttime (1.48 [0.82–2.69]) asthma symptoms. CPAP use was associated with lower likelihood of persistent daytime symptoms (0.46 [0.23–0.94]).

Conclusions—Questionnaire-defined OSA risk and historical diagnosis were each associated with persistent daytime asthma symptoms, to an extent that matched or exceeded associations with nighttime asthma symptoms. Unrecognized OSA may be a reason for persistent asthma symptoms during the day as well as the night.

Keywords

asthma; asthma control; sleep; obstructive sleep apnea; obstructive sleep apnea risk

Introduction

Asthma and obstructive sleep apnea (OSA) are both common disorders [1, 2]. Recent cross-sectional [3–6] and longitudinal [7] studies found an association of asthma with both OSA symptoms [4, 5, 7] and polysomnography (PSG)-established diagnoses [3, 6]. Bidirectional influences probably exist between the two conditions, and OSA appears to affect asthma control. Continuous positive airway pressure (CPAP) treatment for comorbid OSA improves asthma outcomes such as symptoms [8–10], rescue bronchodilator use [8], peak expiratory flow rates (PEFR) [8], and disease-specific quality of life [11]. OSA was found to be a risk factor for frequent exacerbations during the prior year in a large population of difficult-to-control asthma patients [12]. Additionally, in a cross-sectional manner, OSA risk is associated with poorly controlled asthma, as assessed on validated questionnaires [13].

However, the relationship between the nocturnal sleep disorder and asthma symptoms that occur specifically during daytime hours remains largely unstudied. The above interventional studies [8–10] focused on small numbers of patients enrolled for predominantly nocturnal asthma symptoms, and our previous study could not distinguish between daytime and nocturnal asthma control [13]. Some of the mechanisms that may link OSA with asthma include increased parasympathetic tone during apnea, hypoxemia-related reflex bronchoconstriction, irritation of upper airway (UAW) neural receptors, altered nocturnal neurohormonal secretion, and increased inflammatory mediators [14]. These mechanisms would be expected to affect daytime and nocturnal asthma manifestations differently. Neurally-mediated effects might have mainly nocturnal influence whereas other effects, from local airway and systemic inflammation for example, might have more daytime influence. Information on whether nocturnal OSA is also associated with daytime asthma symptoms could give important insight into mechanisms underlying this relationship.

In this context, we have assembled one of the largest existing cohorts of asthma patients, recruited at two tertiary care centers, to test for separate associations of OSA with daytime and nighttime asthma symptoms. Risk for OSA was assessed prospectively by a symptom inventory. Historical diagnosis of OSA and CPAP use for its treatment were ascertained from medical records. We hypothesized that OSA is associated with both daytime and nighttime asthma symptoms. Preliminary results of this analysis were presented at the May 2009 American Thoracic Society (ATS) meeting and published in abstract form [15]. This study expands on our previous work [4, 13, 16] with a dataset enhanced by subjects enrolled at an additional center, and focuses on relationships between OSA and timing of asthma symptoms that could not have been examined previously [13].

Methods

Study Subjects

The study population included asthma patients seen in routine follow-up at the Allergy and Pulmonary subspecialty clinics at the University of Michigan (UM)- Ann Arbor (May 2004 – April 2006) and the University of Wisconsin (UW)- Madison (July 2007– March 2009). Subjects were enrolled in an ongoing study of the relationship between OSA and asthma, which was approved by The University of Michigan Medical School Institutional Review Board for Human Subject Research and The University of Wisconsin Health Sciences Institutional Review Board. Written informed consent was obtained from each subject. Participants were 18–75 years old and had asthma diagnosed (based on ATS criteria [17]) and managed by an academic specialist. During visits, patients underwent history, physical examination, spirometry and asthma control assessment. Patients seen for urgent asthma visits and pregnant women were excluded.

Survey Instruments and Medical Records Review

Study assistants handed out and collected the questionnaires. The survey included two self-administered questionnaires and items regarding demographics.

The first instrument, the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ), assessed OSA risk [18]. Its eight symptom-items asked about loud snoring disruptive to the bed partner, pauses in breathing during sleep, sudden gasping arousals from sleep, worsening of snoring while supine or after alcohol, nocturnal sweating and nasal congestion, and history of hypertension. Responses were on a 5-point Likert scale (“never” to “always”). Data on weight, age, smoking, and body mass index (BMI) were rated on a 1 to 5 scale. The SA-SDQ has been validated with PSG in a large sample of sleep patients [18]. Scores range from 12–60, with cut-points of 36 for men and 32 for females used to define high OSA risk [18].

The second instrument asked about frequency of daytime and nighttime asthma symptoms following the National Asthma Education and Prevention Program (NAEPP) classification of asthma severity based on clinical features [19]. This allowed separation of daytime from nighttime asthma symptoms. There were four categories of daytime symptom frequency: 2 days/week, 3–6 days/ week, daily, and continuously. Similarly, nighttime symptom frequency included: 2 nights/ month, 3–4 nights/month, 5 nights/month (or > 1 night/ week), and frequently. Asthma symptoms occurring >2 days /week defined persistent daytime symptoms and those occurring >2 nights /month defined persistent nighttime symptoms.

Study physicians reviewed medical records for diagnosed comorbid lung diseases (such as allergic bronchopulmonary aspergillosis, chronic obstructive pulmonary disease and interstitial lung diseases), OSA diagnosis (which had been confirmed by polysomnography), and whether or not the patients were using CPAP— as documented in the clinic visit notes at the time of our survey. Data in regard to polysomnography indices or objective CPAP use were not collected in this study. Also noted from charts were established diagnoses of comorbidities known to worsen asthma (rhinitis, chronic sinusitis, nasal polyposis, gastroesophageal reflux disease [GERD], and psychiatric disease specifically depression, anxiety, panic or bipolar disorders) [1], and current asthma medications.

Statistical Analysis

Obesity was defined by BMI ≥ 30 kg/m², following Centers for Disease Control guidelines. Given the Caucasian predominance of our sample, African-Americans — a group with

particular susceptibility for worse asthma [1] — were compared to Caucasians and all other races combined. From the SA-SDQ, habitual snoring was identified by scores of 4 or 5 (“usually” or “always”). SAS statistical software Version 9.2 (SAS Institute, Cary, NC) was used for analyses. Two-sample t-tests and *chi*-squared tests were used to analyze group differences in continuous and categorical variables, respectively.

The main analysis was conducted on data from subjects without OSA and those with diagnosed OSA but not on CPAP treatment at the time of survey. Logistic regression models were constructed to test for univariate associations of persistent daytime or nighttime asthma symptoms with high OSA risk or diagnosed and untreated OSA, demographics, and other factors known to influence asthma control [1]. The same technique was then applied to explore associations of high OSA risk or diagnosed OSA with persistent asthma symptoms among subsets of subjects, ie those with sole persistent daytime, sole persistent nighttime and lastly, those with both daytime and nighttime persistent symptoms. Each of these subsets was compared to the subset of subjects without persistent asthma symptoms in any time period. In multivariate logistic regression models, persistent daytime or nighttime asthma symptoms were each regressed on high OSA risk or diagnosed OSA, while controlling for the above covariates and study site.

Data from subjects with diagnosed OSA were separately tested in logistic regression models for associations of CPAP use with persistent asthma symptoms. Due to the small sample size of CPAP users, multivariate models adjusted only for obesity. Two-sided p-values<0.05 indicated statistical significance.

Results

Among the 938 subjects approached, 873 (93%) agreed to complete the survey. However, 46 were excluded because of comorbid lung diseases including COPD. Among the remaining 828 subjects, 136 (16%) had an established diagnosis of OSA, and among these, 75 were on CPAP treatment at the time of survey and excluded from the main analysis, yielding a sample of n=752 subjects (80% of those approached). Among them, 244 were recruited at the UM and 508 at the UW.

Characteristics of the main study sample (n=752)

Demographic, physiologic and clinical characteristics of this sample (n=752) are presented in Table 1. Subjects at UM had increased representation of African-Americans (11% vs. 3%, $p<0.0001$), were more obese (51% vs. 32%, $p<0.0001$), had worse lung physiology (FEV_1 : 88 ± 20 vs. 94 ± 18 , $p<0.0001$; FEV_1/FVC : 72 ± 10 vs. 77 ± 9 , $p<0.0001$ and FEF_{25-75} : 63 ± 30 vs. 70 ± 30 , $p=0.005$), more frequent history of GERD (55% vs. 43%, $p=0.002$) and psychopathology (30% vs. 24%, $p=0.04$). They tended to use ICS more frequently (82% vs. 75%, $p=0.05$), and were more often on LABA (66% vs. 56%, $p=0.008$) and leukotriene modifiers (45% vs. 19%, $p<0.0001$).

Table 2 shows the prevalence of daytime and nighttime asthma symptoms: 260 (35%) of the subjects reported persistent daytime symptoms, 283 (38%) reported persistent nighttime asthma symptoms, and 210 (27%) reported both (persistent asthma symptoms daytime and nighttime subset). Among those with persistent daytime symptoms, 50 (19%) did not report nighttime symptoms (persistent asthma symptoms daytime only subset). Conversely, among those with persistent nighttime symptoms, 73 (26%) did not report daytime symptoms (persistent asthma symptoms nighttime only subset). As expected, when compared to subjects without, those with persistent daytime symptoms had worse lung physiology (mean $\pm$ standard deviation [s.d.]: FEV_1 predicted 87 ± 21 vs. 95 ± 18 , FEV_1/FVC 74 ± 10 vs. 77 ± 9 , FEF_{25-75} predicted 61 ± 29 vs. 71 ± 31 , all $p<0.0001$), as did those with persistent nighttime

symptoms (FEV₁% predicted 87±21 vs. 94±18, $p<0.0001$; FEV₁/FVC 75±10 vs. 77±9, $p=0.0009$; FEF₂₅₋₇₅% predicted 63±30 vs. 70±31, $p=0.003$).

Among self-reported OSA symptoms, snoring and witnessed apnea (with any frequency) were endorsed by 581 (77%) and 204 (27%) of the subjects, respectively, while habitual snoring was reported by 200 (27%). The mean (±s.d.) SA-SDQ score was 28±7, and 212 (28%) of the subjects met high OSA risk. In this sample, 60 subjects (8%) had diagnosed and untreated OSA, and their SA-SDQ scores were significantly worse on average than those of other subjects in the sample (37±6 vs. 28±7, $p<0.0001$).

Univariate associations of persistent daytime and nighttime asthma symptoms in n=752 subjects

The prevalence of persistent daytime and nighttime asthma symptoms were similar among subjects with high OSA risk, and both higher among these subjects than among those with lower OSA risk ($p<0.0001$ for each) (Figure 1). Likewise, among subjects with diagnosed and untreated OSA, the prevalence of persistent daytime and nighttime asthma symptoms were comparable, and each was significantly higher than it was among subjects without an established OSA diagnosis ($p<0.0001$ and $p=0.0006$, respectively) (Figure 2).

Univariate analyses (Table 3) showed similar relationships of high OSA risk with persistent daytime and nighttime asthma symptoms, with nearly overlapping confidence intervals. These associations were more robust when using the clinical diagnosis of OSA, particularly in relation to daytime symptoms.

Subjects with asthma symptoms that were persistent during both day and night, in comparison to those without any persistent symptoms, showed the strongest association between persistent asthma and high OSA risk or diagnosed OSA (Table 4), as opposed to subjects whose asthma symptoms persistent just during one of the time periods. Among subjects who had persistent asthma symptoms only during the daytime, as compared to subjects with no persistent symptoms, asthma symptoms were associated with diagnosed OSA and showed a trend toward association with high OSA risk. Among subjects whose asthma symptoms persisted only during the nighttime, as compared to those without persistent symptoms, no significant associations emerged between high OSA risk or diagnosed OSA and persistent asthma symptoms.

Multivariate associations of persistent daytime and nighttime asthma symptoms in n=752 subjects

In multivariate regression models (Table 5), high OSA risk was significantly associated with higher odds for both persistent daytime and nighttime asthma symptoms. These relationships again showed similar magnitudes: independent of the covariates, a high OSA risk predicted on average 96% higher odds for persistent daytime asthma symptoms (odds ratio=1.96 [95% confidence interval 1.31–2.94]) and a nearly identical 97% higher odds for persistent nighttime asthma symptoms (1.97 [1.32–2.94]). Analogous models with the diagnosed and untreated OSA as the predictor (Table 6), rather than OSA risk, showed a similar association with persistent daytime symptoms: a history of OSA was associated on average with 108% higher odds for persistent daytime asthma symptoms (2.08 [1.13–3.82]). However, the association with persistent nighttime symptoms was attenuated (1.48 (0.82–2.69)).

Analysis among n=136 asthma subjects with diagnosed OSA

Of these 136 subjects, 75 were using CPAP at the time of survey, as documented in their asthma clinic visit notes. CPAP users and non-users were of similar age (54±11 vs. 52±10, $p=0.27$), and had similar female gender (57% vs. 62%, $p=0.55$) and African-American race

(44% vs. 45%, $p=0.97$) predominance; however, their prevalence of obesity may have been slightly higher (83% vs. 72%, $p=0.14$). In univariate analyses CPAP use was associated with lower odds for persistent daytime asthma symptoms (0.50 [0.25–1.00], $p=0.049$) and but not nighttime symptoms (0.62 [0.31–1.22], $p=0.16$). These relationships seemed to strengthen when adjusted for obesity (Table 7), such that CPAP users were on average 54% less likely to report persistent daytime symptoms (0.46 [0.23–0.94]).

Discussion

Data from this large sample of asthma patients show that symptoms indicative of high OSA risk or diagnosed and untreated OSA are each associated with persistent asthma symptoms during the daytime. These associations were at least as strong as those found between OSA symptoms or history and persistent asthma symptoms at night, and were most robust among subjects who had both persistent daytime and nighttime symptoms. These relationships emerged independently of obesity and other contributors to poor asthma control. Furthermore, CPAP use attenuated the likelihood of persistent daytime symptoms. Although this cross-sectional study cannot prove causal relationships, our data strengthen available evidence for the relationship between OSA and asthma – specifically implicating a role for OSA in daytime asthma control – in a manner analogous to previously reported effects of this same nocturnal sleep disorder on daytime hypertension [20]. These results suggest that OSA may have carry-over effects during the day, possibly through inflammatory pathways that exacerbate asthma, and that CPAP treatment for OSA may improve asthma around the clock.

By testing associations of OSA separately with daytime and nighttime symptoms that could not be separated previously [13] and in a large sample of patients, the current findings represent a key advance which builds on knowledge generated by earlier reports [13] that used the Asthma Control Questionnaire (ACQ). The ACQ was validated to assess overall asthma control [21], and not to discriminate between daytime and nighttime asthma control, as most of its symptom-items do not specify timing. In this large sample of patients, we found significant independent associations of high OSA risk or diagnosed OSA with persistent daytime asthma symptoms that were at least as strong as those found with persistent nighttime symptoms (Table 5 and 6).

Additionally, we observed a reduced likelihood for persistent daytime asthma symptoms (Table 7) with CPAP use among previously diagnosed OSA patients. Previous interventional studies of CPAP therapy for OSA in asthma report improved outcomes, such as asthma symptoms [8–10], rescue bronchodilator use [8], PEFR [8], and disease-specific quality of life measured on validated questionnaires [11]; however, these studies have focused on patients with predominant nocturnal symptoms. In the only study which examined daytime and nighttime asthma symptoms separately in relation to OSA, Chan et al found that two weeks of CPAP in 9 subjects with OSA significantly improved asthma not only during the night but also during the day, and also improved morning and evening pre/postbronchodilator PEFR [8]. Cessation of CPAP returned the PEFR to pre-CPAP levels [8]. Our findings (Table 7) now add to this evidence and together suggest that treatment for OSA in patients with asthma could improve asthma symptoms day and night.

The mechanisms through which OSA worsens asthma still remain largely unstudied. Shared features or common comorbid conditions, such as obesity [22] and GERD [23], may link OSA with asthma. However, when we controlled for these variables in the multivariate models (Table 5 and 6), the associations of interest persisted, as another recent study has also found [24], suggesting that other links exist. Several mechanisms by which the events of airway obstruction in OSA might lead to immediate, but short lived effects on asthma

symptoms have also been proposed. Increased nocturnal bronchial reactivity [25] could be caused by vagal neural receptor activation that accompany the Muller maneuvers of obstructive events [26]. Hypoxia stimulates the carotid body, and enhances vagal activity and bronchial reactivity [27]. Additionally, short exposure to sustained hypoxia impairs defenses particularly important to asthmatics at night, such as cough [28] and arousal thresholds to resistive loading [29], and suppresses perception of asthma symptoms [30]. These effects are short lived in most cases and thus would be expected to affect primarily nighttime asthma.

In contrast, our observed associations of high OSA risk and diagnosed OSA with persistent daytime symptoms (Tables 5 and 6) and the “protective” association with CPAP use (Table 7), do suggest that nocturnal OSA events may have carryover effects on asthma during the daytime. Inflammatory changes present in the UAW of OSA patients (reviewed in [31]) may also be present in the lower airways. Compared with controls, OSA patients have elevated numbers of neutrophils, and higher concentrations of bradykinin and vasoactive intestinal peptide in nasal lavage fluid. Subepithelial edema, mucous gland hypertrophy, reduction of connective tissue and inflammatory cell infiltration were present on histology of surgical specimens from uvulopalatopharyngoplasty and tonsillectomy. In the uvula for example, although with a different cellular profile in each structural layer, this leukocyte-predominant inflammation is present at levels as deep as the musculature and may contribute to the UAW dysfunction. The snoring-related mechanical stress, and local and systemic effects of intermittent hypoxia have been implicated in the occurrence of UAW inflammation [31, 32]. These OSA features may have similar effects on the lower airways. Induced sputum, an established method to evaluate lower airway inflammation [33] confirms a neutrophilic profile in OSA patients [34, 35] and polymorphonuclear neutrophil cell numbers correlate with AHI [35]. Moreover, preliminary work in animal models shows neutrophilic lung inflammation arising from both apnea-related strenuous respiratory efforts and intermittent hypoxia [36, 37]. Additionally, one established feature of OSA is a sustained state of systemic inflammation, implicated in the associated cardiovascular morbidity [38], which also shares similarities with asthma-related systemic inflammation [39]. Thus OSA, through direct airway or systemic effects, may exacerbate a neutrophilic phenotype, one that is poorly characterized but increasingly recognized among subsets of asthmatics [40]. CPAP may have multiple beneficial effects on the mechanical and neuromechanical properties of the lower airway, it may ameliorate gastroesophageal reflux and also the systemic and local inflammation [41, 42]. It is also possible that CPAP, through sleep restoration, may help improve asthma control around the clock, as recent studies indicate that proper sleep is an important factor in the control of disease and quality of life of asthma patients [43, 44]. A robust univariate relationship of diagnosed and untreated OSA with persistent nocturnal asthma symptoms was noted (Table 4). Attenuation of this association in the final multivariate model (Table 6) does not negate its existence. Our subset of diagnosed but untreated OSA subjects was small (n=60), relative to much larger subsets of the other covariates included in the model, ie rhinitis (n=674), GERD (n=351), obesity (n=285). The small sample size limited statistical power to test for this specific association. Nevertheless, as our questionnaire suggests, there is likely a substantial burden of unrecognized and untreated OSA among asthmatics, a population which, as our data also put forth, could realize considerable benefit [8–11] by having their sleep disorder addressed.

Limitations of our study include use of a questionnaire-based approach (SA-SDQ) to evaluate OSA symptoms prospectively, in a large number of patients, and also reliance on established clinical diagnoses in only a small number of subjects. However, prospective polysomnography on all subjects would have been prohibitively expensive for this study. Additionally, in a large sample of sleep patients, the SA-SDQ demonstrated high internal validity, and good sensitivity and specificity [18]. This instrument has high diagnostic value

in comparison to other sleep apnea screening instruments [45]. Although the SA-SDQ has not been validated specifically in asthma patients, the scale does predict PSG-diagnosed OSA well in other samples [46, 47]. Our observation that the subset of subjects with diagnosed OSA had SA-SDQ scores nearly 10 points higher on average (37 ± 6 vs. 28 ± 7 , $p < 0.0001$) suggests that this instrument does have good utility in these patients; however, further studies aimed at its validation in asthmatics are needed.

The possibility of an overlap between OSA symptoms and nighttime asthma may also be raised. However, the symptoms included in the SA-SDQ primarily concern loud snoring and witnessed apneas specifically during sleep, and their worsening when supine or with alcohol. These sleep-related symptoms should be specific to upper rather than lower airway compromise. Further studies are necessary to validate the SA-SDQ specifically in patients with asthma.

Although asthma may contribute to OSA pathogenesis [7], the cross-sectional design of this study precludes conclusions about causality. In the context of data from interventional studies [8–11] and readily conceived underlying mechanisms as discussed above, our findings are suggestive of an effect of OSA on both daytime and nighttime asthma symptom control. Clearly, research on OSA and asthma is often complicated by shared comorbidities and potential for multidirectional causal pathways. For example, we cannot be certain whether obesity, GERD and psychopathology are more closely tied, etiologically, to asthma or OSA, or some may be intermediary variables in causal pathways between asthma and OSA. Finally, conducting this study in specialty-based clinic populations may have underestimated the true relationships of interest. The main breathing route during sleep is through the nose, and nasal congestion is a recognized risk factor for OSA [48]. The high prevalence of rhinitis corroborated with its “protective” association with asthma symptoms (most likely a treatment effect), may have attenuated the true OSA risk, because nasal steroid treatment improves nasal breathing and reduces AHI in patients with rhinitis [49]. This in turn may have attenuated the association of high OSA risk with asthma symptoms.

Conclusions/key findings

In summary, this sizeable study shows associations of at least equal magnitude between OSA, as assessed by symptoms or history, and both daytime and nighttime asthma symptoms. These associations occurred independently of obesity and traditional contributors to poor asthma control. Additionally, CPAP appeared to attenuate the likelihood of persistent daytime asthma symptoms. Our observations suggest that nocturnal OSA could contribute to daytime asthma control. Clinicians should consider OSA as a potential reason for poor asthma control, even in patients with daytime symptoms. Additionally, our data have important implications for local and systemic inflammatory pathways by which these diseases may be associated. Prospective studies with objective sleep and airway assessments of these putative mechanistic links are needed, to better understand and find means to intervene in the relationship of OSA with asthma.

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Abbreviations List

ACQ	Asthma Control Questionnaire
AHI	Apnea-Hypopnea Index
BMI	Body Mass Index (in kilograms per meter squared)
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
FEF₂₅₋₇₅	Forced Expiratory Flow between 25% and 75% of vital capacity
FEV₁	Forced Expiratory Volume in first second of the vital capacity
FVC	Forced Vital Capacity
GERD	Gastroesophageal Reflux Disease
ICS	Inhaled Corticosteroids
LABA	Long Acting β_2 -Agonist
LTM	Leukotriene Modifiers
NAEPP	National Asthma Education and Prevention Program
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PEFR	Peak Expiratory Flow Rate
PSG	Polysomnography (laboratory-based sleep study)

SA-SDQ	Sleep Apnea scale of the Sleep Disorders Questionnaire
s.d.	standard deviation of the mean
SDB	Sleep-Disordered Breathing
UAW	Upper Airway

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Figure 1.

Prevalence of persistent asthma symptoms in asthma subjects with (n=212) and without (n=540) high OSA risk.

[†] $p < 0.0001$ when compared to subjects without high OSA risk and with persistent daytime asthma symptoms; [‡] $p < 0.0001$ when compared to subjects without high OSA risk and with persistent nighttime asthma symptoms.

High OSA risk=scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥ 36 for men and ≥ 32 for females; OSA= obstructive sleep apnea.

Figure 2.

Prevalence of persistent asthma symptoms in asthma subjects without (n=692) and with (n=60) diagnosed and untreated OSA.

[†] $p < 0.0001$ when compared to subjects without OSA and with persistent daytime asthma symptoms; [‡] $p = 0.0006$ when compared to subjects without OSA and with persistent nighttime asthma symptoms.

OSA= obstructive sleep apnea.

Table 1

Demographic and clinical characteristics of n=752 asthma subjects.

Characteristic	Number (%), Mean $\pm$ s.d.
Gender (Female)	502 (67%)
Age	47 $\pm$ 14
BMI (kg/m ²)	29 $\pm$ 7
Obese (BMI $\geq$ 30)	285 (38%)
Race:	
African- Americans	42 (6%)
Caucasians	687 (91%)
Others ^a	23 (3%)
Current smokers	35 (5%)
FEV ₁ % predicted	92 $\pm$ 19
FEV ₁ /FVC	76 $\pm$ 9
FEF ₂₅₋₇₅ % predicted	68 $\pm$ 30
History of rhinitis	674 (90%)
History of chronic sinusitis	228 (30%)
History of nasal polyps	114 (15%)
History of GERD	351 (47%)
History of psychiatric disease	196 (26%)
Using inhaled corticosteroids (ICS)	588 (78%)
Using inhaled long acting β_2 -agonist (LABA)	447 (60%)
Using leukotriene modifiers (LTM)	204 (27%)

Abbreviations: s.d.= standard deviation; BMI= body mass index; FEV₁% = forced expiratory volume in first second; FVC%= forced vital capacity; FEF₂₅₋₇₅% = forced expiratory flow between 25% and 75% of vital capacity (all these physiologic variables are expressed as percentages of predicted values); GERD= gastroesophageal reflux disease.

^a. included Asians, Hawaiian/Pacific Islanders and American Indians/Alaskans

Table 2

Prevalence of self-reported asthma symptoms.

Type of Symptoms	Number (%)
Daytime Symptoms:	
2 days/week	492 (65%)
3–6 days/ week	116 (15%)
daily	94 (13%)
continuously	50 (7%)
Persistent Daytime Symptoms (>2 days/week)	260 (35%)
Nighttime Symptoms:	
2 nights/ month	469 (62%)
3–4 nights/month	94 (13%)
5 nights/month	85 (11%)
frequently	104 (14%)
Persistent Nighttime Symptoms (>2 nights/ month)	283 (38%)

Table 3

Univariate associations of persistent daytime or nighttime asthma symptoms with high OSA risk, diagnosed and untreated OSA, demographic variables, and other factors known to influence asthma control.

	Persistent Daytime Asthma Symptoms (n=260)		Persistent Nighttime Asthma Symptoms (n=283)	
	Odds Ratio (95% CI)	<i>p</i> -value	Odds Ratio (95% CI)	<i>p</i> -value
High OSA Risk *	2.88 (2.07–4.01)	<0.0001	2.63 (1.90–3.64)	<0.0001
OSA ‡	3.66 (2.11–6.33)	<0.0001	2.51 (1.47–4.28)	0.0008
Age	1.00 (0.99–1.01)	0.85	0.99 (0.98–1.00)	0.14
Gender (female vs. male)	1.07 (0.77–1.47)	0.69	0.98 (0.71–1.34)	0.88
Race (African-American vs. all others)	2.18 (1.17–4.08)	0.01	2.58 (1.37–4.86)	0.004
Obesity	2.52 (1.85–3.44)	<0.0001	2.35 (1.73–3.19)	<0.0001
Rhinitis	0.49 (0.30–0.78)	0.003	0.57 (0.35–0.91)	0.02
Chronic sinusitis	0.87 (0.63–1.22)	0.42	0.90 (0.65–1.25)	0.53
Nasal polyps	1.07 (0.71–1.63)	0.74	1.09 (0.73–1.65)	0.67
GERD	1.75 (1.29–2.37)	0.0003	1.65 (1.22–2.22)	0.001
Psychiatric disease	1.72 (1.23–2.40)	0.002	1.64 (1.18–2.29)	0.003

Abbreviations: CI= confidence interval; OSA= obstructive sleep apnea; GERD=gastroesophageal reflux disease.

* defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥36 for men and ≥32 for females;

‡ diagnosed and untreated OSA.

Table 4

Univariate associations of persistent daytime and/or nighttime asthma symptoms with high OSA risk or diagnosed and untreated OSA, among subsets of asthma subjects, compared in each case to subjects without persistent asthma symptoms during any time period.

	Persistent Asthma Symptoms Daytime Only (n=50) [†]		Persistent Asthma Symptoms Nighttime Only (n=73) [‡]		Persistent Asthma Symptoms Daytime AND Nighttime (n=210) [§]	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Persistent Daytime Symptoms						
High OSA risk [¥]	1.76 (0.92–3.38)	0.09	-	-	3.46 (2.41–4.98)	<0.0001
OSA [*]	3.62 (1.43–9.18)	0.007	-	-	3.86 (2.10–7.08)	<0.0001
Persistent Nighttime Symptoms						
High OSA risk [¥]	-	-	1.44 (0.81–2.57)	0.21	3.46 (2.41–4.98)	<0.0001
OSA [*]	-	-	1.29 (0.42–3.93)	0.65	3.86 (2.10–7.08)	<0.0001

Abbreviations: CI= confidence interval; OSA= obstructive sleep apnea.

[¥] defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥ 36 for men and ≥ 32 for females;

^{*} diagnosed and untreated OSA;

[†] Subjects who reported only persistent daytime but not nighttime asthma symptoms;

[‡] subjects who reported solely persistent nighttime but not daytime asthma symptoms;

[§] Subjects who reported persistent both, daytime and nighttime asthma symptoms; note, odds ratios and confidence intervals are identical for daytime and nighttime rows because each shows results for the same subjects (i.e., those who had persistent daytime and nighttime asthma symptoms, relative to no persistent asthma symptoms in any time period).

Table 5

Multivariate regression of persistent daytime or nighttime asthma symptoms on high OSA risk, with adjustment for other contributors to asthma control and study site.

	Persistent Daytime Asthma Symptoms (n=260)		Persistent Nighttime Asthma Symptoms (n=283)	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
High OSA Risk *	1.96 (1.31–2.94)	0.001	1.97 (1.32–2.94)	0.0009
Age	0.99 (0.98–1.01)	0.30	0.98 (0.97–0.99)	0.005
Gender (female vs. male)	0.80 (0.56–1.14)	0.22	0.72 (0.50–1.01)	0.06
Race (African-American vs. all others)	1.22 (0.60–2.45)	0.58	1.53 (0.76–3.07)	0.23
Obesity	1.57 (1.07–2.27)	0.02	1.54 (1.07–2.22)	0.02
Rhinitis	0.86 (0.51–1.44)	0.56	0.96 (0.57–1.62)	0.88
Chronic sinusitis	1.02 (0.69–1.53)	0.89	1.08 (0.74–1.60)	0.68
Nasal polyps	1.05 (0.64–1.74)	0.84	1.06 (0.65–1.73)	0.81
GERD	1.29 (0.92–1.82)	0.14	1.33 (0.95–1.86)	0.09
Psychiatric disease	1.46 (1.01–2.12)	0.05	1.38 (0.96–1.86)	0.08
Site (UW vs. UM)	0.34 (0.24–0.49)	<0.0001	0.39 (0.28–0.56)	<0.0001

Abbreviations: CI= confidence interval; OSA= obstructive sleep apnea; GERD=gastroesophageal reflux disease.

* defined as scores on Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) ≥ 36 for men and ≥ 32 for females.

Table 6

Multivariate regression of persistent daytime or nighttime asthma symptoms on diagnosed and untreated OSA, with adjustment for other contributors to asthma control and study site.

	Persistent Daytime Asthma Symptoms (n=260)		Persistent Nighttime Asthma Symptoms (n=283)	
	Odds Ratio (95% CI)	<i>p</i> -value	Odds Ratio (95% CI)	<i>p</i> -value
OSA *	2.08 (1.13–3.82)	0.02	1.48 (0.82–2.69)	0.19
Age	1.00 (0.98–1.01)	0.41	0.98 (0.97–1.00)	0.01
Gender (female vs. male)	1.12 (0.79–1.61)	0.52	1.27 (0.90–1.79)	0.18
Race (African-American vs. all others)	1.20 (0.59–2.41)	0.61	1.54 (0.77–3.08)	0.22
Obesity	1.90 (1.35–2.68)	0.0002	1.91 (1.36–2.67)	0.0002
Rhinitis	0.89 (0.53–1.51)	0.67	0.99 (0.59–1.67)	0.97
Chronic sinusitis	1.03 (0.69–1.53)	0.89	1.09 (0.74–1.60)	0.67
Nasal polyps	1.12 (0.68–1.85)	0.65	1.13 (0.69–1.84)	0.62
GERD	1.31 (0.93–1.84)	0.12	1.38 (0.99–1.92)	0.06
Psychiatric disease	1.46 (1.01–2.12)	0.05	1.41 (0.98–2.03)	0.07
Site (UW vs. UM)	0.34 (0.24–0.49)	<0.0001	0.38 (0.27–0.54)	<0.0001

Abbreviations: CI= confidence interval; OSA= obstructive sleep apnea; GERD=gastroesophageal reflux disease.

* diagnosed and untreated OSA.

Table 7

Multivariate regression of persistent daytime or nighttime asthma symptoms on CPAP use, with adjustment for obesity, among n=136 subjects with diagnosed OSA

	Persistent Daytime Asthma Symptoms (n=72)		Persistent Nighttime Asthma Symptoms (n=69)	
	Odds Ratio (95% CI)	<i>p</i> -value	Odds Ratio (95% CI)	<i>p</i> -value
CPAP use	0.46 (0.29–0.94)	0.03	0.57 (0.28–1.14)	0.11
Obesity	1.88 (0.81–4.38)	0.14	1.93 (0.83–4.47)	0.13

Abbreviations: CI= confidence interval; OSA= obstructive sleep apnea; CPAP=continuous positive airway pressure.