

Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma

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Background: Previous studies have suggested a link between obstructive sleep apnea and poor asthma control, which may be mediated through airway inflammation, obesity, and other mechanisms.

Objective: To test the hypothesis that the prevalence and severity of sleep apnea is greater among patients with severe compared with moderate asthma and controls without asthma.

Methods: Complete overnight home polysomnography was performed in 26 patients with severe asthma consecutively recruited to a difficult asthma program, 26 patients with moderate asthma, and 26 controls without asthma of similar age and body mass index. Flow rates and Juniper asthma control and quality of life questionnaires were also obtained.

Results: Obstructive sleep apnea-hypopnea, defined by an Apnea-Hypopnea Index ≥ 15 events/h of sleep scored using Chicago criteria, was present in 23 of 26 (88%) patients with severe asthma, 15 of 26 (58%) patients with moderate asthma, and 8 of 26 (31%) controls without asthma (χ^2 ; $P < .001$). Using the more restrictive scoring criteria applied in the Wisconsin cohort study, Apnea-Hypopnea Index ≥ 5 /h was present in 50% (severe), 23% (moderate), and 12% (control) of subjects ($P = .007$). Mean nocturnal arterial oxygen saturation was significantly lower in patients with severe asthma versus

controls, and apnea-hypopnea severity measures were significantly worse for both asthmatic groups compared with controls. Among subjects with asthma, no significant correlations were identified between the severity of sleep-disordered breathing and asthma severity or control measures (FEV₁, Juniper scores).

Conclusions: Obstructive sleep apnea-hypopnea was significantly more prevalent among patients with severe compared with moderate asthma, and more prevalent for both asthma groups than controls without asthma. These observations suggest potential pathophysiologic interactions between obstructive sleep apnea-hypopnea and asthma severity and control. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Sleep, sleep apnea, obstructive, dyspnea, paroxysmal, asthma

There is a subgroup of patients with asthma with severe disease characterized by dependence on corticosteroids, persistent symptoms, frequent hospitalizations, or fixed airflow obstruction.^{1,2} A diversity of mechanisms has been proposed to account for the refractory nature of disease in this subgroup, but this process remains poorly understood.

Obstructive sleep apnea-hypopnea (OSAH) is characterized by recurrent upper airway obstruction during sleep leading to hypoxemia and sleep fragmentation. There is growing experimental support for the concept that OSAH contributes to poor asthma control.³⁻⁷ Patients with asthma have a higher prevalence of reported snoring and witnessed apnea than subjects without asthma in questionnaire-based studies.^{4,8,9} Poor subjective sleep quality¹⁰ and OSAH are linked to poor asthma control.⁴ In addition, continuous positive airway pressure (CPAP) treatment of OSAH in subjects with asthma can improve flow rates and bronchodilator requirements³ and/or improve asthma symptoms,^{3,6,7,11} although these latter reports are limited by a lack of controls and small subject numbers.

There are few studies using current polysomnographic techniques to evaluate systematically the association between OSAH and asthma control.^{5,12} The establishment of a difficult-to-treat asthma program at our institutions,² with the recruitment of both subjects with severe asthma and matched subjects with moderate asthma, afforded us the opportunity to assess OSAH prevalence and severity among these 2 groups. We also studied a group of population controls without asthma. We hypothesized that the prevalence and severity of OSAH on overnight polysomnography would be greater among the severe group compared with the moderate asthmatic and nonasthmatic control groups. A secondary hypothesis was that there

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Abbreviations used

AHI: Apnea-Hypopnea Index
 BMI: Body mass index
 OSAH: Obstructive sleep apnea-hypopnea
 SaO₂: Arterial oxygen saturation
 TST: Total sleep time

would be significant correlations between OSAH severity and measures of asthma severity and control.

METHODS**Subjects**

Subjects with asthma were recruited from our Difficult Asthma Program.² Recruitment to the program was solely on the basis of asthma history. Severe asthma was defined according to American Thoracic Society criteria¹ and required at least 1 major criterion: daily oral steroids for >50% of the previous 12 months, or high-dose inhaled steroid: fluticasone ≥ 1000 $\mu\text{g}/\text{d}$ or equivalent, and at least 1 other add-on therapy continuously for ≥ 12 months; and ≥ 2 minor criteria: daily short-acting β -agonist, persistent FEV₁ <70% and FEV₁/forced vital capacity <80% predicted, ≥ 1 urgent visits or ≥ 3 steroid bursts in the last 12 months, prompt deterioration with <25% steroid dose reduction, or previous near-fatal asthma within 3 years.

Moderate asthma was defined as well controlled asthma symptoms (Juniper asthma control score¹³ <1), use of long acting β -agonist and fluticasone (or equivalent) ≥ 200 $\mu\text{g}/\text{d}$ and ≤ 1000 $\mu\text{g}/\text{d}$, ≤ 2 steroid bursts in the past year and none within 3 months, total days on oral steroids <30 in the previous 12 months, FEV₁ >70% predicted, and ≤ 1 unscheduled clinical visit in the previous 12 months.

Exclusion criteria for both groups included current smoking and other conditions which could lead to cardiorespiratory symptomatology. No sleep-related information was obtained from subjects before recruitment into the Difficult Asthma Program or the current study. Consecutive patients enrolled in the program were approached to participate in this study. Of the patients approached during the recruitment period, 26 of 27 patients with severe asthma and 26 of 31 patients with moderate asthma consented to participate.

Control subjects were recruited through community advertisements, which referred to a clinical study on "breathing patterns and asthma." Subjects were required to be generally healthy, to be nonsmoking for at least 1 year, and to have no previous history of asthma, respiratory problems, or prescription of inhalers. No sleep-related information was used in the recruitment or screening process. Potential recruits meeting eligibility criteria were included based on age, body mass index (BMI), and sex to match the asthmatic groups. Epworth sleepiness scores were obtained only after informed consent had been provided and the subjects were formally included in the study.

Written informed consent was obtained from all subjects. This study was approved by the Research Ethics Boards of the participating institutions.

Study protocol

Clinical history for patients with asthma included atopy, rhinitis and/or nasal polyps, and previous intensive care unit admission. Body weight, height, medications, flow rates, and Juniper Asthma Control Scores¹³ and Asthma Quality of Life¹⁴ questionnaires were recorded monthly for 1 year in the patients with severe asthma, and 5 times over 1 year in the patients with moderate asthma. For the current study, data from the visit closest to the polysomnographic recording were used. Subjects completed the Epworth sleepiness score at the time of recruitment for the sleep substudy after consent. The patients underwent polysomnography at a time of relative clinical stability, and at least 2 weeks after recovery from any exacerbation or intervention. Data collected on control subjects were the inclusion questions on respiratory symptoms, age, height, weight, medications, and Epworth sleepiness score, but no flow rates or asthma questionnaires.

Complete overnight polysomnography was performed in the subject's home using the Sandman Suzanne device (Tyco Inc, Ottawa, Ontario, Canada) as previously described.¹⁵ A technologist installed the device in the home on the evening of recording, verifying electrode impedance and signal quality. Signals included electroencephalogram (C3/A1, C4/A2), bilateral electro-oculograms, bipolar chin and tibialis anterior electromyograms, monitoring of airflow using both a thermistor and nasal pressure (which permits identification of both changes in flow amplitude and flow limitation typical of dynamic inspiratory upper airway collapse), rib cage and abdominal motion via piezoelectric belts (respiratory effort), snoring via tracheal microphone, body position, and arterial oxygen saturation (SaO₂).

Polysomnographic recordings were scored manually using the Sandman system (version 6.2) by a certified polysomnographic technologist, with physician review, both blind to patient status. The quality of recordings was assessed by using criteria similar to those described for the Sleep Heart Health Study.¹⁶ A total sleep time >4 hours was required, together with >5 hours of recording with a quality rating of very good to excellent, for a study to be included. Recordings in 3 subjects had to be repeated once to attain adequate study quality.

Sleep-wake state and periodic limb movements¹⁷ and microarousals¹⁸ were scored by using standard criteria. Respiratory events were scored by using the Chicago criteria.¹⁹ The primary respiratory signal was nasal pressure. Apnea was defined as cessation of airflow (>90% reduction in the nasal pressure flow signal) lasting >10 seconds. Hypopneas were defined as events lasting >10 seconds associated with a reduction in airflow >50% or with less than 50% reduction but either $\geq 4\%$ O₂ desaturation or arousal. Hypopneas associated with arousals versus desaturation were distinguished in the summary scoring. We also scored oxygen desaturation events, defined as apneas or hypopneas associated with $\geq 4\%$ O₂ desaturation.

Apneas and hypopneas were identified as either obstructive or central. For apneas, this was based on the presence or absence of respiratory effort during the event. For hypopneas, obstructive events included persistent and/or increasing effort and/or ribcage paradox or snoring during the event, with inspiratory flow limitation on the nasal pressure signal. Hypopneas were scored as central when there was an absence of these findings.

Three polysomnographic respiratory event indices were calculated. The total Apnea-Hypopnea Index (AHI) was calculated as all apneas and hypopneas divided by total sleep time (TST). The Wisconsin AHI was calculated as all apneas plus hypopneas associated with $\geq 4\%$ O₂ desaturation divided by TST, which were the criteria used in the Wisconsin Cohort Study.²⁰ The Oxygen Desaturation Index was calculated as apneas and hypopneas associated with $\geq 4\%$ O₂ desaturation divided by TST.

The primary definition of OSAH in this study was a total AHI value ≥ 15 events/h of sleep. We also calculated the prevalence of OSAH based on a Wisconsin AHI value ≥ 5 events/h of sleep, and based on a Wisconsin AHI value ≥ 5 events/h with excessive sleepiness,^{20,21} defined as an Epworth sleepiness score ≥ 11 .²²

Data analysis

Differences for 2 group comparisons were assessed using a nonpaired *t* test for normally distributed variables, and a Kruskal-Wallis rank-sum test for non-normally distributed data, whereas for 3-group comparisons, 1-way ANOVA was used for normally distributed variables, and 1-way ANOVA on ranks was used for nonnormally distributed data.²³ Proportions between groups were tested by using χ^2 analysis. Correlations between outcome measures were assessed by using Pearson product correlation, or for nonnormally distributed variables, Spearman rank-order correlation. The coefficient of variation for FEV₁ (% predicted) and Asthma Control Scores were also calculated as a measure of variability of asthma control. Statistical computations were conducted by using SigmaStat (v. 3.5; Systat Software, San Jose, Calif). A *P* value <.05 was required for statistical significance.

RESULTS

Subject characteristics are shown in Table I. The 3 groups were of similar age, sex distribution, and BMI. Flow rates were

TABLE I. Subject characteristics

	Severe (n = 26)	Moderate (n=26)	Control (n = 26)	P value
Age (y)	48.8 ± 2.0	47.9 ± 1.6	45.5 ± 1.7	.40
Sex (M/F)	12/14	14/12	13/13	.88
BMI (kg/m ²)	27.8 ± 1.1	27.8 ± 1.3	26.6 ± 0.7	.45
FEV ₁ (% predicted)	67.6 ± 4.4	83.4 ± 2.6	—	<.001
Inhaled corticosteroid dose (μg)*	1255.8 ± 73.0	502.3 ± 49.2	—	<.001
Asthma control score	1.6 ± 0.2	0.9 ± 0.1	—	.01
Quality of life score	5.0 ± 0.2	5.8 ± 0.2	—	.02
Epworth sleepiness score	11.3 ± 1.3	9.4 ± 0.9	6.6 ± 1.4	.28

Values are means ± SEs. *P* values for 3 groups from ANOVA or χ^2 analyses and for 2 groups from *t* test.

F, Female; M, male.

*Corticosteroid doses are expressed as fluticasone equivalents.

significantly lower and Juniper asthma control questionnaire scores significantly higher (poorer control) among the severe versus moderate asthma groups, as anticipated. Asthma quality of life scores were significantly lower (less favorable) for patients with severe asthma than for patients with moderate asthma. Eight patients with severe asthma (31%) and 2 patients with moderate asthma (8%) had previously been admitted to intensive care for asthma (χ^2 : *P* = .04). Four subjects with severe asthma but no subjects with moderate asthma had previously been intubated. Epworth sleepiness scores tended to be worse among patients with severe and moderate asthma than controls, but this did not achieve statistical significance.

There was a history of atopy in 15 of 26 (58%) patients with severe and 18 of 26 (69%) patients with moderate asthma (χ^2 : *P* = .39), and a history of rhinitis and/or nasal polyps in 54% of patients with severe and 27% of patients with moderate asthma (χ^2 : *P* = .048). All subjects with asthma underwent bronchoscopy as part of the Difficult Asthma Program,² and no gross upper airway abnormalities were noted. Subjects also underwent a clinical evaluation by a physician trained in sleep disorders. Mild-to-moderate reductions in upper airway dimensions typical of patients with sleep apnea were noted in some subjects, but no other craniofacial abnormalities were observed.

As shown in Table I, patients with severe asthma were using significantly higher doses of inhaled corticosteroid. Nasal steroids were being used by 10 (38%) patients with severe and 5 (19%) patients with moderate asthma at the time of polysomnography (χ^2 : *P* = .13). Oral prednisone was being used in 9 (35%) of the patients with severe asthma (mean dose, 13.6 ± 3.3 mg) but none of the subjects with moderate asthma. Long-acting β -agonists were being used by 100% of the subjects with severe and 19 (73%) of the subjects with moderate asthma (χ^2 : *P* = .01). Leukotriene antagonists were being used in 12 (46%) subjects with severe and 4 (15%) subjects with moderate asthma (χ^2 : *P* = .02).

The sleep quality data are shown in Table II. Although TST was similar for the 3 groups, sleep was more disrupted among patients with severe asthma, as evidenced by significantly lower sleep efficiency and higher microarousal index. As well, the proportion of slow-wave sleep was significantly less for patients with moderate asthma and tended to be less for patients with severe asthma than for control subjects.

The findings on OSAH prevalence in the 3 groups using different threshold criteria are shown in Table III. For the 3 groups, with each of the threshold definitions applied, there was a significant difference in OSAH prevalence. For all definitions, OSAH was strikingly prevalent, and significantly more so among

TABLE II. Polysomnography: sleep variables

	Severe	Moderate	Control	P value
TST (h)	5.9 ± 0.3	6.1 ± 0.2	6.3 ± 0.2	.55
Sleep efficiency (%)	73.6 ± 2.9*†	76.0 ± 2.4	84.0 ± 1.9	.008
No. of stage changes	159.2 ± 10.0	146.8 ± 9.5	159.2 ± 7.4	.54
No. of awakenings	31.2 ± 2.4	27.3 ± 2.3	23.9 ± 1.8	.06
Arousal index (events/h)	51.4 ± 2.9*†	43.1 ± 5.6	24.1 ± 1.5	<.001
S1 (%TST)	9.4 ± 1.0	7.5 ± 1.0	6.9 ± 0.7	.14
S2 (%TST)	70.3 ± 18.1	56.2 ± 2.3	44.6 ± 1.9	.29
S3&4 (%TST)	19.2 ± 2.5	16.4 ± 1.4†	24.1 ± 1.7	.020
REM (%TST)	19.0 ± 1.3	19.8 ± 1.7	22.3 ± 1.0	.22

Values are means ± SEs.

S1, Stage 1 non-REM sleep; S2, stage 2; S3&4, stages 3 and 4 combined; REM, rapid eye movement sleep

Post-ANOVA comparisons: **P* < .05 vs moderate; †*P* < .05 vs control.

patients with severe asthma than among both patients with moderate asthma and controls without asthma. The higher prevalence value among patients with moderate asthma compared with controls closely approached statistical significance for the primary study criterion (total AHI ≥ 15), but did not achieve statistical significance for the other OSAH criteria.

Group mean values for key respiratory variables are shown in Table IV. Respiratory events were predominantly obstructive hypopneas, identified by characteristic reductions in inspiratory flow, with flattening of the nasal pressure curve indicative of flow limitation, terminating in association with microarousal (the majority of events) and/or O₂ desaturation. Total AHI, Obstructive Hypopnea Index, and obstructive hypopnea with arousal values were significantly higher for both asthmatic groups than for controls without asthma, whereas the 2 asthma groups were not significantly different. Mean nocturnal SaO₂ was slightly but significantly lower for the severe asthma group. The mean duration of apneas and hypopneas did not differ between the groups.

Relationships between clinical features and symptom scores and OSAH severity

The presence of OSAH based on either total AHI or Wisconsin AHI was not significantly related in 2-by-2 analyses to the presence of atopy, rhinitis, or nasal polyps, or to the use of oral prednisone, high-dose inhaled corticosteroid (>1000 μg fluticasone equivalent per day), long-acting β -agonist, or leukotriene antagonist. Furthermore, there were no significant correlations between either daily inhaled corticosteroid dose or combined

TABLE III. Prevalence of OSAH

Threshold criterion	Severe	Moderate	Control	<i>P</i> (3 groups)	<i>P</i> (severe vs moderate)	<i>P</i> (severe vs control)	<i>P</i> (moderate vs control)
Total AHI ≥ 15 events/h	23/26 (88)	15/26 (58)	8/26 (31)	<.001	.012	<.001	.051
WAHI ≥ 5 events/h	13/26 (50)	6/26 (23)	3/26 (12)	.007	.044	.003	.303
WAHI ≥ 5 events/h with excessive sleepiness (Epworth sleepiness score ≥ 11)	11/26 (42)	4/26 (15)	1/26 (4)	.002	.032	.001	.158

Values are numbers (%) of subjects; *P* values are for χ^2 analyses.
WAHI, Wisconsin AHI.

dose of inhaled and nasal corticosteroid and any measure of OSAH severity (eg, $r = -0.07$, $P = .73$ for daily inhaled fluticasone dose vs total AHI, patients with severe asthma). In the severe group, OSAH severity correlated with body mass index (eg, $r = 0.52$, $P < .01$ for BMI vs total AHI), and with Epworth sleepiness scores for Wisconsin AHI ($r = 0.43$; $P = .03$), although not total AHI, whereas in the moderate group, these correlations did not achieve statistical significance.

Obstructive sleep apnea-hypopnea severity measures did not demonstrate significant correlations with asthma severity or control scores, including FEV₁ expressed as percent predicted, coefficient of variation of FEV₁ (% predicted), Juniper asthma control scores or coefficient of variation of asthma control scores, or the Juniper asthma quality of life scores (individual domain or total scores) in either the severe or moderate asthma group. In 2-by-2 analyses, OSAH was not significantly related to a history of intensive care unit admission, although the 4 subjects with severe asthma who had previously been mechanically ventilated were all positive for OSAH with total AHI values ranging from 21.3 to 34.7.

DISCUSSION

In this study, by using complete overnight polysomnography, we identified a strikingly high prevalence of OSAH among patients with severe asthma compared with age-matched and BMI-matched patients with moderate asthma and control subjects without asthma. OSAH also tended to be more prevalent among patients with moderate asthma than controls without asthma, although this did not achieve statistical significance. Mean nocturnal SaO₂ was significantly lower for the severe asthma group compared with controls, and OSAH severity measures were significantly greater for both groups than for controls without asthma. Despite the significantly higher OSAH prevalence among patients with severe compared with moderate asthma, no significant correlations were identified between OSAH severity and measures of asthma severity (FEV₁, Juniper asthma quality of life scores) or asthma control (Juniper control scores) for either asthma group.

We performed home rather than laboratory polysomnographic recordings. Although laboratory polysomnography is considered a gold standard, we are highly confident of our sleep study findings. The Sleep Heart Health Study has established that home polysomnography with careful attention to standardization yields reproducible findings that are closely comparable to conventional in-laboratory polysomnography, with minimal misclassification of cases.^{16,24,25} We applied similar quality assurance standards in this study. We have also previously demonstrated our ability to

TABLE IV. Polysomnography: respiratory variables

	Severe	Moderate	Control	<i>P</i> value
Respiratory events				
Central event index (n/h)	0.8 $\pm$ 0.3	0.8 $\pm$ 0.2	0.3 $\pm$ 0.1	.11
Obstructive apnea index (n/h)	6.7 $\pm$ 1.8	5.1 $\pm$ 1.7	2.4 $\pm$ 0.8	.13
Obstructive hypopnea index (n/h)	22.3 $\pm$ 1.8†	19.5 $\pm$ 3.3†	9.9 $\pm$ 1.07	<.001
OH with arousal (n/h)	21.5 $\pm$ 1.7†	18.9 $\pm$ 3.2†	8.9 $\pm$ 0.9	<.001
OH with SaO ₂ $\geq 4\%$ (n/h)	0.9 $\pm$ 0.3	0.6 $\pm$ 0.3	0.6 $\pm$ 0.2	.68
Wisconsin AHI (n/h)	7.6 $\pm$ 2.0	5.7 $\pm$ 1.9	3.0 $\pm$ 0.9	.15
Total AHI (n/h)	29.9 $\pm$ 2.9†	25.9 $\pm$ 4.0†	12.7 $\pm$ 1.4	<.001
Oximetry data				
ODI (n/h)	4.6 $\pm$ 2.0	2.8 $\pm$ 1.2	1.9 $\pm$ 1.0	.44
Mean sleep SaO ₂ (%)	94.7 $\pm$ 0.4†	95.5 $\pm$ 0.3	96.4 $\pm$ 0.3	.005
SaO ₂ <90% (% TST)	4.5 $\pm$ 2.7	1.5 $\pm$ 0.8	0.7 $\pm$ 0.6	.27
Nadir SaO ₂ (%)	85.7 $\pm$ 2.6	90.0 $\pm$ 0.9	90.0 $\pm$ 1.1	.14

Values are means $\pm$ SEs.

ODI, Oxygen desaturation index; OH, obstructive hypopnea.

Post-ANOVA comparisons: † $P < .05$ vs control.

apply this technology successfully.¹⁵ Furthermore, during the course of this study, we performed home and laboratory polysomnography in random order within 3 weeks of each other, in 6 sleep clinic patients with asthma and 8 sleep clinic patients without asthma, and obtained closely comparable findings for both sleep architecture and respiratory events with the 2 approaches. The sensitivity of home polysomnography for OSAH (total AHI ≥ 15) was 83% and the specificity 100%, using laboratory polysomnography as the standard. We believe these findings indicate that in our hands, home polysomnography is highly reliable for the evaluation of OSAH.

We are confident that the high prevalence of OSAH in our subjects was not a result of selection bias. The subjects were recruited to the Difficult Asthma Program entirely independently of symptoms of snoring, witnessed apneas, or daytime sleepiness, but rather solely on the basis of asthma characteristics as defined in Methods: Subjects, above.² Questions concerning sleepiness were asked only after recruitment for the OSAH substudy.

There have been few studies using current polysomnographic techniques to assess OSAH prevalence among patients with asthma. Catterall et al¹² noted irregular breathing and nocturnal hypoxemia in 10 subjects with asthma compared with 10 controls without asthma. In an uncontrolled study, Yigla et al⁵ found 21 of 22 (96%) of patients with severe asthma to be positive for OSAH on complete polysomnography by using scoring criteria similar to ours. Our study confirms the very high prevalence of OSAH

among patients with severe asthma and demonstrates that this is significantly greater than among patients with moderate asthma as well as substantially higher than among controls without asthma. These findings show at the least that the high OSAH prevalence among patients with severe asthma is not simply an artefact of the recording and/or analysis approaches used.

Values for AHI, and thus OSAH prevalence, depend greatly on the criteria used to score respiratory events.^{21,26} We scored respiratory events by using the criteria established for research by the Chicago task force,¹⁹ and calculated total AHI as the number of all apneas and hypopneas per hour of sleep, to provide a sensitive measure of OSAH for comparison with asthma severity. We also calculated Wisconsin AHI by including only those events that met the criteria described for the Wisconsin Cohort Study,²⁰ the most widely cited prevalence study, to allow comparison of our asthma and control groups to published population norms.^{20,21} The Wisconsin OSAH prevalence based on AHI ≥ 5 events/h was 24% for men and 9% for women age 30 to 60 years,^{20,21} which is comparable to the 12% prevalence (Table III) in our control group with equal male-female composition. Values for AHI ≥ 5 with daytime sleepiness were present in 4% of men and 2% of women in the Wisconsin cohort,²⁰ which is comparable to the 4% prevalence (Table III) among our controls. Thus, the recording and analysis techniques in this study applied to a general population sample yield similar findings, confirming the significantly increased prevalence of OSAH among patients with severe asthma.

The higher prevalence of OSAH among patients with severe versus moderate asthma, with the tendency to increased prevalence among patients with moderate asthma compared with controls (Table III), suggests a dose-response relationship. We had hypothesized that there would also be direct correlations between OSAH and asthma severity measures, but this was not observed. However, this does not preclude clinically significant interactions between OSA and asthma. Multiple pathophysiologic factors contribute to each of these conditions, so that direct correlation with individual factors may be difficult to identify. It could also be that our measures of asthma control were not sufficiently sensitive, in that flow rates and asthma control questionnaires were administered only once per month (severe) or at 4-month intervals (moderate). More detailed assessment such as daily peak flows, symptom scores, and rescue medication use, might be required to identify links between OSAH and asthma control.

There is a diversity of biological mechanisms by which OSAH could lead to worsening of asthma, and our study provides limited insight into some of these. Mechanical events during apneas and hypopneas (upper airway vibration, suction collapse, traction, and so forth) could lead to activation of vagal or other neural pathways, resulting in increased bronchoconstriction.^{11,27} Central respiratory control mechanisms that mediate normal sleep-related increases in bronchomotor tone could be influenced by neural changes related to OSAH and sleep fragmentation.^{28,29} Acid-pepsin reflux occurs frequently in patients with OSAH³⁰ and may worsen asthma.

Corticosteroids have been proposed as a contributing factor potentially acting through effects on upper airway caliber (increased adiposity) or dilator muscle function (steroid myopathy).^{5,31} One recent study³¹ identified a dose-response relationship between inhaled corticosteroid use and the risk of questionnaire-identified snoring and OSAH. However, in the current study, the use of neither oral prednisone nor high-dose

inhaled corticosteroid was significantly related to the presence of OSAH, and there was a complete absence of correlation between inhaled corticosteroid use at the time of polysomnography and measures of OSAH severity (eg, for inhaled corticosteroid dose vs AHI for patients with severe asthma, $r = -0.07$, $P = .73$). Thus, inhaled corticosteroid dose may be a surrogate for asthma severity in questionnaire-based studies, rather than a causative factor in the OSAH-asthma interaction.

We and others have demonstrated upper airway proinflammatory changes in OSAH that may contribute to upper airway neuromuscular dysfunction.^{30,32,33} Consistent with the united airway concept,³⁴ OSAH-related upper airway inflammation could lead to activation of inflammatory mechanisms in the lower respiratory tract. OSAH is also associated with systemic inflammation and increased oxidative stress,^{33,35} which could potentiate lower airway inflammation.

It could be that the interaction of OSAH and asthma is reciprocal—that is, that asthma-related factors could also contribute to worsening of OSAH. Nocturnal hypoxemia associated with respiratory events could be worsened by asthma-related decrements in lung function. Poor sleep quality, which has been associated with severe asthma^{10,12} and was observed in our severe group, could predispose to increased upper airway collapsibility or lowered arousal thresholds, leading to ventilatory instability and respiratory events.²⁹

Obesity and asthma may be linked through a diversity of mechanisms,^{36,37} and the obesity-OSA association is well established. In the current study, BMI correlated significantly with apnea severity in the severe asthma group, but morbid obesity was uncommon in our subjects, so this is a potentially important but not essential element.

Interventional data could provide insight into the asthma-OSA interaction, but to date these data are limited. Guilleminault et al¹¹ reported that CPAP decreased nocturnal but not diurnal asthma symptoms in a small group of subjects with OSAH. Chan et al³ reported that CPAP treatment of OSAH improved asthma symptoms and peak flow rates and decreased bronchodilator requirements in 9 patients with severe asthma. Ciftci et al⁶ reported that 2 months of CPAP treatment improved nocturnal asthma symptom scores in 16 patients with asthma and OSAH. Lafond et al⁷ found that CPAP treatment of OSAH improved disease-specific quality of life measures, although not flow rates or bronchial hyperreactivity, among patients with mild asthma. Although these studies support the concept of a causative link between OSAH and poor asthma control, most have methodologic limitations, including lack of appropriate controls and small subject numbers, which limit the impact of the findings. Larger-scale randomized controlled trials are required in this area.

In summary, in this study we observed a strikingly high prevalence of OSAH among a group of consecutively recruited patients with severe asthma compared with patients with moderate asthma and controls without asthma. Although it will be important to confirm these findings in larger cohorts of subjects with asthma, the results suggest a potentially important link between asthma control and OSAH. We believe that further studies are warranted to evaluate the mechanisms by which OSAH and asthma interact, and the clinical significance of this association. Interventional studies involving the treatment of OSAH in patients with moderate and severe asthma to determine the effects on asthma control could provide useful insights into this interaction.

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Clinical implications: The very high prevalence of obstructive sleep apnea-hypopnea among patients with severe asthma suggests that recognition and treatment of sleep apnea may be an important element in improving asthma control.

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