

SCIENTIFIC INVESTIGATIONS

Effects of Coexisting Asthma and Obstructive Sleep Apnea on Sleep Architecture, Oxygen Saturation, and Systemic Inflammation in Women

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Study Objectives: Both asthma and obstructive sleep apnea (OSA) are strongly associated with poor sleep. Asthma and OSA also have several features in common, including airway obstruction, systemic inflammation, and an association with obesity. The aim was to analyze the effect of asthma, OSA, and the combination of asthma and OSA on objectively measured sleep quality and systemic inflammation.

Methods: Sleep and health in women is an ongoing community-based study in Uppsala, Sweden. Three hundred eighty-four women ages 20 to 70 years underwent overnight polysomnography and completed questionnaires on airway diseases and sleep complaints. C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor α were analyzed.

Results: The group with both asthma and OSA had higher CRP, higher IL-6, a longer sleeping time in stage N1 sleep and stage N2 sleep, and less time in stage R sleep than the control group with no asthma or OSA. The group with both asthma and OSA had lower mean oxygen saturation (93.4% versus 94.7%, $P = .04$) than the group with OSA alone. The results were consistent after adjusting for age, body mass index, and smoking status. Asthma was independently associated with lower oxygen saturation, whereas OSA was not.

Conclusions: Our data indicate that coexisting asthma and OSA are associated with poorer sleep quality and more profound nocturnal hypoxemia than either of the conditions alone. The results are similar to earlier findings related to OSA and chronic obstructive pulmonary disease, but they have not previously been described for asthma.

Keywords: asthma, inflammation, OSA, polysomnography

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Both asthma and obstructive sleep apnea (OSA) are strongly associated with poor sleep. The aim was to analyze the effect of asthma, OSA, and the combination of asthma and OSA on objectively measured sleep quality and systemic inflammation.

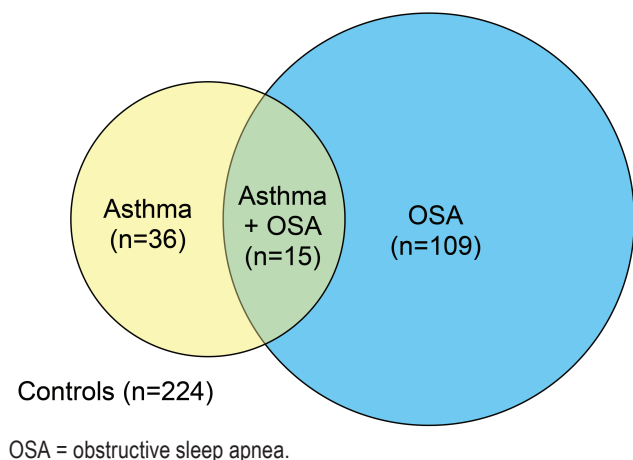
Study Impact: Coexisting asthma and OSA is associated with poorer sleep quality and more profound nocturnal hypoxemia than either of the conditions alone. Asthma was independently associated with lower oxygen saturation, whereas OSA was not.

INTRODUCTION

Asthma is strongly associated with poor sleep quality.¹ This can be explained in part as a result of nocturnal asthma symptoms and frequent coexisting rhinitis,^{2,3} but these factors may not fully explain the increased prevalence of insomnia in asthma. Associations between asthma and obstructive sleep apnea (OSA) have been described in recent years and several studies have shown a considerably higher prevalence of OSA in individuals with compared with individuals without asthma.^{4,5} Although OSA and asthma are conditions with a different pathophysiological background, they have several features in common. First, obesity, which is strongly associated with OSA, has also been identified as a major risk factor for asthma,⁶ in particular, nonallergic, difficult-to-treat asthma.⁷ Second, both asthma and OSA are associated with local inflammation in the upper airway, nasal obstruction, and snoring.⁸ Third, there are similarities in the systemic inflammatory

patterns in OSA and certain asthma phenotypes. For example, inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor α (TNF- α), and interleukin 6 (IL-6), are elevated in nonallergic, neutrophilic asthma phenotypes and also in obesity and OSA.^{9–13}

An overlap syndrome between chronic obstructive pulmonary disease (COPD) and OSA has previously been described¹⁴ and it is known that coexisting COPD and OSA result in more profound nocturnal hypoxemia than either of the conditions alone.¹⁵ Further, treatment with continuous positive airway pressure (CPAP) has been shown to reduce airway reactivity among individuals with asthma without OSA¹⁶ and to improve asthma-related quality of life among individuals with asthma and OSA.¹⁷ However, corresponding community-based polysomnography studies of asthma and OSA have not been performed to the same extent and our knowledge of objectively measured sleep in patients with asthma is limited.

Figure 1—The study population.

The aim of the current study was to analyze the effect of asthma and OSA and the combination of asthma and OSA on objectively measured sleep quality and systemic inflammation in a community-based sample of women.

METHODS

Study Population

Sleep and health in women is an ongoing, population-based study in Uppsala, Sweden. From a total study population of 7,051 women who had responded to a postal questionnaire, 400 participants ages 20 to 70 years underwent full-night polysomnography in their homes.^{18,19} Subjects were randomly selected from the study population, with oversampling of habitual snorers (230 snorers, 170 nonsnorers) to obtain a wider range of sleep-disordered breathing. Preceding the polysomnography, all participants completed new questionnaires that included questions on airway diseases, allergies, sleep disturbances, comorbidity in other diseases, and current medication. In the morning after the polysomnography, fasting blood samples were obtained. Waist circumference, weight, and height were measured and body mass index (BMI) was calculated. Complete data were available for 384 women. Informed consent was obtained from all participants and the study was approved by the ethics committee at the medical faculty at Uppsala University (Dnr 01-238).

Definitions

Polysomnography was performed and scored and the apnea-hypopnea index (AHI) was defined as previously described in detail.¹⁸ The oxygen desaturation index (ODI) was defined as the mean number of desaturations of $\geq 4\%$ per hour of sleep. The percentage of total sleep time spent with oxyhemoglobin saturation below 90% (TST90) was calculated. OSA was considered relevant at an AHI of ≥ 15 events/h.²⁰

Asthma was defined as a positive answer to either the question “Have you had an attack of asthma in the last 12 months?” and/or the question “Are you currently taking any medicine, including inhalers, aerosols or tablets, for asthma?”²¹

Depending on the presence of asthma and/or OSA, the population was divided into four groups; (1) the control group that had no asthma or OSA ($n = 224$), (2) subjects with asthma but no OSA ($n = 36$), (3) subjects with OSA but not asthma ($n = 109$), and (4) subjects with both asthma and OSA ($n = 15$) (Figure 1).

Allergic rhinitis was defined as a positive answer to the question “Do you suffer from hay fever or any other nasal allergy?”²¹

Daytime sleepiness was evaluated with the Epworth Sleepiness Scale and a score of ≥ 10 was considered significant.²¹

Subjective insomnia problems (difficulty initiating sleep [DIS], difficulty maintaining sleep [DMS] and early morning awakenings [EMA]) were evaluated with questions asking “How severe are your problems with...” The answers were given using a five-point scale and were considered positive if they were score 4 “severe” or 5 “very severe.”²²

Comorbidity in hypertension or diabetes was defined as ongoing pharmacological treatment or regular check-ups due to either condition.¹

Smoking habits were assessed using six questions.²² Based on the responses, the women were categorized into current smokers or ex-smokers and pack-years were calculated.

Chemical Analysis

Plasma C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α) were assayed at the Department of Clinical Chemistry, Uppsala University.²⁰ The minimum detectable levels were < 0.2 mg/L for CRP and < 0.5 ng/L for IL-6. In the statistical analyses, a value of 0.1 mg/L was used for all CRP results of < 0.2 mg/L and a value of 0.25 ng/L was used for all IL-6 results of < 0.5 ng/L.²⁰

Statistics

Univariate analyses of categorical variables were performed using the χ^2 test. Arithmetic mean values were calculated for normally distributed variables and geometric mean values were calculated for non-normally distributed variables (AHI, ODI, and TST90, CRP, IL-6, and TNF- α). χ^2 test and analysis of variance with Bonferroni correction were calculated for P values. Bonferroni correction was made for all pairwise comparisons. Separate multiple linear regression analyses with objective sleep data and inflammatory markers as dependent variables were used to analyze the associations with asthma and/or OSA in models adjusted for age, BMI, and smoking status. For the regression analyses, non-normally distributed variables were log-transformed using the base-10 log.^{19,20} All statistical analyses were performed using STATA IC 12 (Stata Corp, College Station, Texas, United States).

RESULTS

The characteristics of the participants are presented in **Table 1**. In both groups with asthma, the prevalence of rhinitis and chronic bronchitis was significantly higher than in the control group. Subjects belonging to either of the groups with OSA were older and had a higher prevalence of hypertension than subjects without OSA. Participants with both asthma and OSA

Table 1—Characteristics and self-reported sleep complaints of the subgroups.

	Controls (n = 224)	Asthma (n = 36)	P*	OSA (n = 109)	P*	Asthma + OSA (n = 15)	P*
Age, years	47.7 ± 11.3	46.1 ± 11.6	> .99	55.6 ± 8.8	< .01	55.5 ± 9.8	.04
BMI, kg/m ²	25.4 ± 4.1	27.0 ± 5.7	.33	28.2 ± 4.8	< .01	33.3 ± 8.7	< .01
Ex-smoker (%)	32.4	30.6	.85	34.9	.62	26.7	.66
Smoker (%)	19.6	22.2	.72	22.0	.61	33.3	.20
> 10 pack-years (%)	27.2	30.6	.68	37.6	.05	46.7	.11
Rhinitis (%)	18.0	57.1	< .01	19.2	.80	40.0	.04
Chronic bronchitis (%)	6.3	27.8	< .01	6.4	.95	40.0	< .01
Hypertension (%)	12.1	14.7	.67	21.3	.03	26.7	.11
DIS (%)	10.3	13.9	.52	12.8	.48	0.0	.19
DMS (%)	19.6	33.3	.06	26.6	.15	20.0	.97
EMA (%)	17.4	30.6	.06	19.3	.68	13.3	.69
ESS > 10 (%)	36.6	38.9	.79	44.4	.14	53.3	.20

* = versus control group. All *P* values for continuous values were calculated with analysis of variance with Bonferroni correction. *P* values for categorical variables were calculated with χ^2 test. BMI = body mass index, DIS = difficulty initiating sleep, DMS = difficulty maintaining sleep, EMA = early morning awakenings, ESS = Epworth Sleepiness Scale, OSA = obstructive sleep apnea.

Table 2—Polysomnography data and inflammatory markers.

	Controls (n = 224)	Asthma (n = 36)		OSA (n = 109)		Asthma + OSA (n = 15)	
	Mean (95%CI)	Mean (95%CI)	P**	Mean (95%CI)	P**	Mean (95%CI)	P**
AHI*	3.7 (3.1, 4.2)	3.6 (2.4, 5.4)	> .99	25.4 (23.3, 27.6)	< .01	29.9 (22.7, 39.3)	< .01
ODI*	1.3 (1.2, 1.5)	1.7 (1.2, 2.3)	.99	10.5 (8.8, 12.5)	< .01	12.4 (6.6, 23.1)	< .01
Mean satO ₂ (%)	95.8 (95.6, 96.0)	94.8 (94.1, 95.5)	< .01	94.7 (94.4, 95.0)	< .01	93.4 (92.2, 94.5)	< .01
TST90 (%)*	0.3 (0.2, 0.4)	0.6 (0.3, 1.1)	.25	2.4 (1.6, 3.5)	< .01	3.8 (1.0, 15.0)	< .01
Awakenings	8.4 (7.9, 9.0)	7.7 (6.5, 8.9)	> .99	10.3 (9.3, 11.3)	< .01	12.3 (9.0, 15.7)	.01
Stage N1 sleep/ stage N2 sleep (%)	71.1 (70.0, 72.2)	71.9 (68.5, 75.2)	> .99	74.3 (72.6, 76.0)	.01	79.2 (73.9, 84.4)	< .01
Stage N3 sleep (%)	10.1 (9.3, 10.8)	10.1 (8.3, 11.9)	> .99	8.9 (7.8, 10.0)	.49	7.3 (4.1, 10.5)	.42
Stage R sleep (%)	18.81 (8.1, 19.6)	18.0 (15.4, 20.7)	> .99	16.8 (15.6, 18.0)	.04	13.6 (9.6, 17.7)	.01
CRP*	1.3 (1.1, 1.5)	1.9 (1.3, 2.8)	.30	1.7 (1.4, 2.1)	.12	3.2 (1.4, 7.3)	.01
IL-6*	0.8 (0.7, 0.9)	1.1 (0.8, 1.7)	.38	1.0 (0.8, 1.2)	.52	2.1 (1.3, 3.5)	< .01
TNF- α *	2.0 (1.8, 2.2)	2.0 (1.6, 2.6)	> .99	2.1 (1.8, 2.4)	> .99	2.0 (1.5, 2.6)	> .99

* = geometric means for non-normally distributed variables ** = versus control group. All *P* values were calculated with ANOVA with Bonferroni correction. AHI = apnea-hypopnea index, CI = confidence interval, CRP = C-reactive protein, IL-6 = Interleukin 6, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, TNF- α = tumor necrosis factor α , TST90 = percentage of total sleep time spent with oxyhemoglobin saturation below 90%.

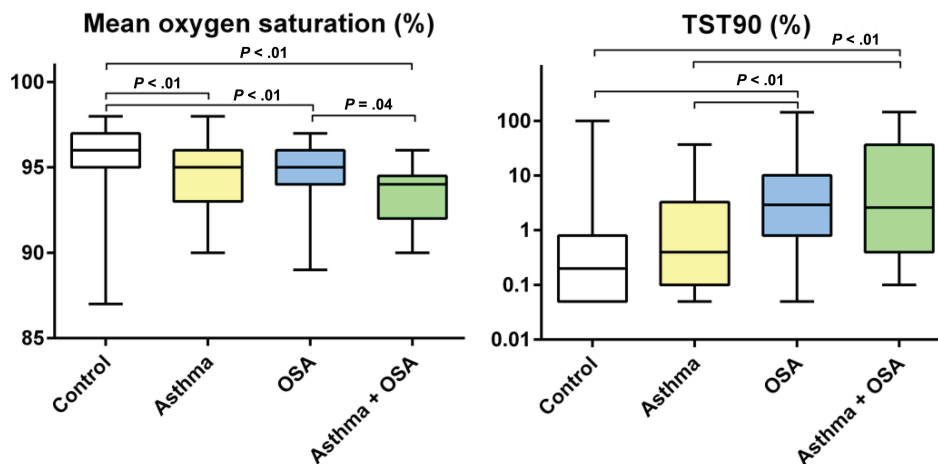
had a higher BMI than those with asthma ($P < .001$) or OSA alone ($P = .001$). Women with asthma alone had the highest prevalence of DMS and EMA, but there were no significant differences in self-reported sleep impairment or daytime sleepiness between any of the groups.

Of the women with asthma without OSA, 56% ($n = 20$) had ongoing medication with inhaled corticosteroids and 33% ($n = 12$) were regularly using long-acting beta-adrenoceptor agonists. In the group with both asthma and OSA, 73% ($n = 11$) used inhaled corticosteroids and 53% ($n = 8$) used long-acting beta-adrenoceptor agonists. One subject in each group used anticholinergic bronchodilators and one subject with only asthma used montelukast.

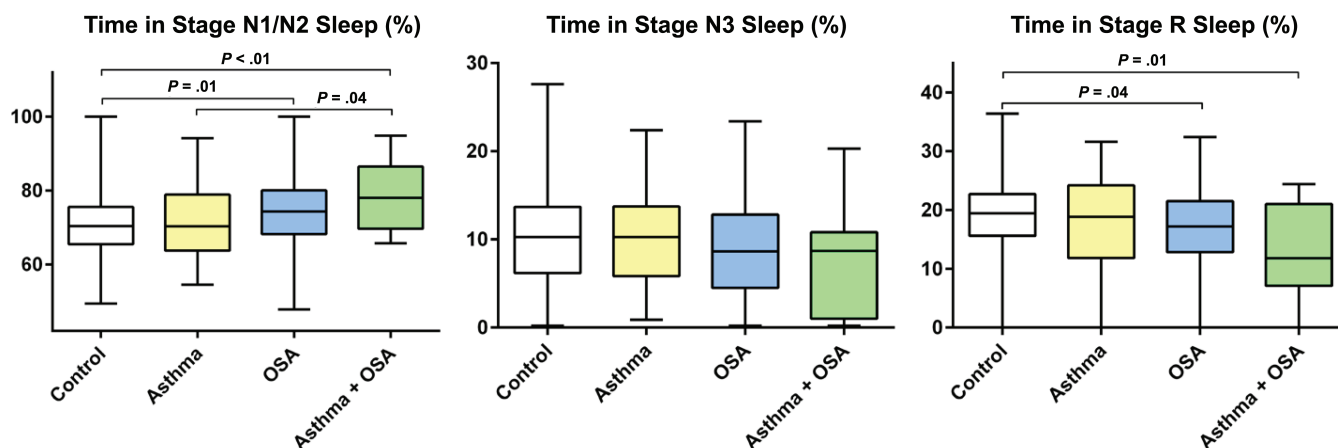
As expected, the AHI and ODI were higher in the groups with OSA (**Table 2**). There was no difference in the AHI or ODI between subjects with only OSA and those with asthma and OSA ($P > .9$). The mean oxygen saturation during sleep

was highest in the control group and belonging to any other group was associated with a lower mean saturation (**Figure 2**). The group with both asthma and OSA had a lower mean saturation than the group with only OSA ($P = .04$), whereas the difference compared with the group with only asthma did not reach significance ($P = .054$). Both groups with OSA had longer sleeping times with oxygen saturation below 90% than the control group and the group with only asthma ($P < .01$), but the difference between the group with the combination of asthma and OSA and the group with only OSA did not reach statistical significance ($P = .2$).

Women with both asthma and OSA had more awakenings ($P = .01$), a longer sleeping time in stage N1 sleep and stage N2 sleep ($P = .004$) and less time in stage R sleep ($P = .01$) than the control group (**Table 2, Figure 3**). The larger number of awakenings was also significant compared with the groups with only asthma or OSA ($P = .03$ and $P = .008$

Figure 2—Mean oxygen saturation and TST90.

Analysis of variance with Bonferroni correction was calculated for *P* values and all significant *P* values are presented in the figure. OSA = obstructive sleep apnea, TST90 = percentage of total sleep time spent with oxyhemoglobin saturation below 90%.

Figure 3—Sleep architecture.

Analysis of variance with Bonferroni correction was calculated for *P* values and all significant *P* values are presented in the figure. OSA = obstructive sleep apnea.

respectively) and the sleeping time in stage N1 sleep and stage N2 sleep was significantly longer than in the group with only asthma ($P = .04$).

CRP and IL-6 were higher in the group with asthma and OSA than in the control group (CRP: $P = .01$, IL-6: $P = .006$) (Table 2, Figure 4).

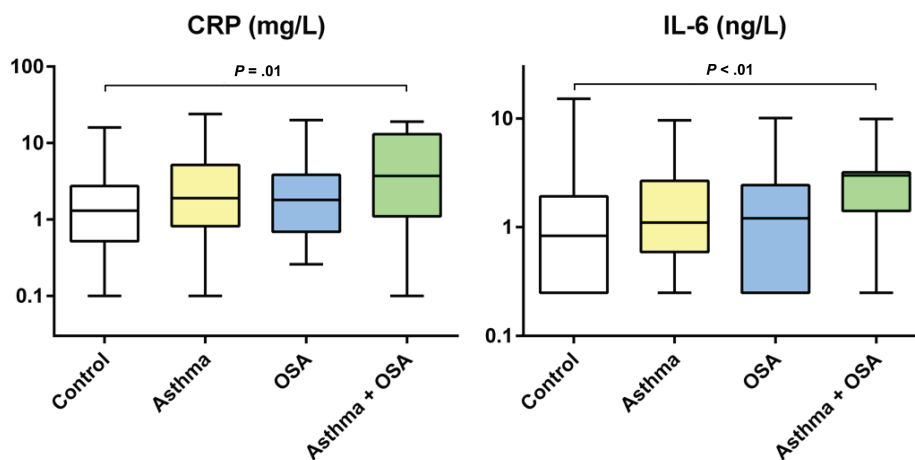
Prior to adjustments for multiple comparisons, there were also significant associations between asthma and longer sleeping time with oxygen saturation below 90% ($P = .03$), asthma and higher CRP ($P = .046$), and OSA and higher CRP ($P = .02$), in comparison to the control group.

The effect of asthma, OSA, and the combination of asthma and OSA on sleep architecture and systemic inflammation was further analyzed in a multiple linear regression model (Table 3). The combination of asthma and OSA was associated with lower mean oxygen saturation during sleep ($P = .02$). Moreover, asthma without OSA was associated with lower mean oxygen saturation ($P = .001$), whereas OSA without

asthma was not ($P = .09$). Both OSA with and without asthma were associated with higher ODI, longer total sleeping time with saturation below 90%, and more frequent awakenings. The combination of asthma and OSA was also associated with longer sleep time in stage N1 sleep and stage N2 sleep and a tendency toward less sleep time in stage N3 sleep and less stage R sleep. The higher IL-6 levels in the group with both asthma and OSA were consistent in the adjusted model ($P = .02$), whereas the higher CRP did not reach statistical significance ($P = .19$).

Because CRP and IL-6 are associated both with the severity of OSA and with central obesity,¹¹ the multiple linear regression analysis was recalculated using waist circumference instead of BMI. In this analysis, the combination of asthma and OSA was significantly associated with both higher CRP ($P = .008$) and higher IL-6 ($P = .001$), and there was also an independent association between asthma and higher CRP ($P = .04$).

Figure 4—Inflammation markers.



Analysis of variance with Bonferroni correction was calculated for *P* values and all significant *P* values are presented in the figure. CRP = C-reactive protein, IL-6 = interleukin 6, OSA = obstructive sleep apnea.

Table 3—Associations between polysomnography data, inflammation markers, and the different asthma and OSA groups.

	Asthma (n = 36)		OSA (n = 109)		Asthma + OSA (n = 15)	
	Beta	95% CI	Beta	95% CI	Coeff	95% CI
AHI**	-0.02	-0.16, 0.11	0.70	0.60, 0.79	0.76	0.55, 0.98
ODI**	0.07	-0.06, 0.20	0.75	0.66, 0.84	0.74	0.54, 0.94
Mean saturation (%)	-0.91	-1.42, -0.40	-0.30	-0.65, 0.05	-0.97	-1.80, -1.47
TST90**	0.27	-0.01, 0.54	0.62	0.43, 0.82	0.60	0.16, 1.02
Awakenings	-0.71	-2.37, 0.94	1.44	0.28, 2.61	4.06	1.46, 6.66
Stage N1 sleep/stage N2 sleep (%)	0.64	-2.41, 3.69	1.35	-0.79, 3.50	5.68	0.89, 10.5
Stage N3 sleep (%)	-0.02	-2.05, 2.02	-0.66	-2.09, 0.78	-2.31	-5.51, 0.89
Stage R sleep (%)	-0.59	-2.75, 1.57	-0.72	-2.24, 0.80	-3.37	-6.76, 0.03
CRP**	0.13	-0.03, 0.29	0.02	-0.09, 0.14	0.17	-0.08, 0.42
IL-6**	0.12	-0.05, 0.29	0.02	-0.10, 0.14	0.30	0.04, 0.57
TNF α **	0.01	-0.10, 0.12	-0.01	-0.09, 0.07	-0.06	-0.23, 0.12

Results presented as beta regression coefficients (95% CI) from separate multiple linear regression adjusted for age, BMI and smoking status, compared with the control group (n = 224). Statistically significant associations are presented in bold. ** = non-normally distributed variables are log-transformed and regression coefficients are presented for log-transformed variables. AHI = apnea-hypopnea index, CI = confidence interval, CRP = C-reactive protein, IL-6 = interleukin 6, ODI = oxygen desaturation index, TNF- α = tumor necrosis factor α , TST90 = percentage of total sleep time spent with oxyhemoglobin saturation below 90%.

DISCUSSION

Asthma and OSA had a significant effect on nocturnal oxygen saturation and several objectively measured sleep variables, respectively. However, the effect on sleep quality was most pronounced when both asthma and OSA were present. Furthermore, the combination of asthma and OSA was associated with lower mean oxygen saturation, a longer period of sleep with oxygen saturation below 90%, higher IL-6, and impaired sleep architecture. It was thus demonstrated that asthma and OSA have additive adverse effects, in agreement with the previously described COPD-OSA overlap syndrome.^{15,23}

The finding of a lower mean oxygen saturation, longer periods of time in stage N1 sleep and stage N2 sleep, and less stage R sleep in the group with both asthma and OSA than in the group with asthma alone is in accordance with previous data

on OSA and difficult-to-treat asthma.⁵ Lower oxygen saturation in patients with asthma was described in a small study in 1982,²⁴ but polysomnography studies of asthma using modern equipment and definitions are sparse and impaired oxygen saturation during sleep has previously only been described for severe asthma.⁴ The finding of lower mean oxygen saturation with asthma was also consistent when only never-smokers were included (data not shown). In contrast to OSA, isolated asthma did not have any effect on the period of sleep with oxygen saturation below 90%. This implies that asthma in itself is independently associated with mild nocturnal hypoxemia, which is aggravated in the presence of concomitant OSA. Subjects with OSA were older than those without OSA. However, there was no difference in age between the group with only OSA and the group with both asthma and OSA. The results were also consistent after adjusting for age. Hence, the changes

in sleep pattern seen with increasing age cannot explain the polysomnography results.

The self-reported sleep complaints did not correspond to the objectively measured sleep variables. This is in accordance with previous studies, showing a higher prevalence of self-reported insomnia with asthma but no significant differences in sleep efficiency or sleep architecture in polysomnography.²⁵ Nor did self-reported sleep complaints correspond to the level of hypoxemia, which is consistent with previous findings on COPD.²⁶

The underlying mechanisms of the effects seen with coexisting asthma and OSA are complex and both physiological and inflammatory pathways are likely to be involved. Busk et al. showed that airway reactivity, assessed with bronchial challenge, could be reduced by applying chronic mechanical strain with CPAP treatment in individuals with asthma without OSA.¹⁶ CPAP treatment has also been shown to improve asthma control among individuals with asthma and OSA and nocturnal asthma symptoms despite optimal medical treatment.²⁷ It has previously been reported that deep breathing has a bronchoprotective effect, which is reduced in asthma,²⁸ and that lung volumes during sleep are reduced by obesity. Accordingly, obese individuals with asthma have increased upper and lower airway resistance and it has been demonstrated that upper airway resistance can be reduced by increasing lung volumes via bilevel positive airway pressure.²⁹ Taken together, these findings may explain the impaired ventilation and hypoxemia seen with asthma and also illustrate some of the physiological connections between asthma and OSA. The overlap syndrome of asthma and OSA is probably common and a questionnaire-based study by Teodorescu et al. showed a significant association between high OSA risk and poor asthma control despite optimal therapy.³⁰

The levels of CRP and IL-6 were highest in the group with both asthma and OSA and the association remained significant for IL-6 after adjusting for age, BMI, and smoking status. In addition, the prevalence of allergic rhinitis was lower among individuals with asthma and OSA than among those with asthma without OSA. This indicates that the asthma phenotype seen with OSA is nonallergic and neutrophilic rather than allergic. Another explanation could be the overrepresentation of the “obese asthma phenotype,” which is characterized by neutrophilic inflammation and is more common in women than in men.^{31,32} However, defining asthma is always complicated in epidemiology, because asthma is a heterogeneous condition. This is also the main limitation of the study. Without spirometry data and bronchial challenges, it is difficult to distinguish asthma from COPD or obesity-related wheeze and distinguishing between asthma phenotypes is accordingly even more complicated. The asthma definition used here is common and it is based on having an asthma diagnosis and current medication.^{1,2} The results were also consistent after adjusting for smoking and the use of anticholinergic bronchodilators was low, indicating a low prevalence of misclassified patients with COPD. However, it is still possible that patients who are obese with nonasthmatic wheezing, for example, may be classified as having asthma. The misclassification of wheezing subjects as having asthma would not, however, change the outcome of the

study but only reduce its statistical power. For this reason, the results can be considered reliable.

The study benefits from a large community-based sample, standardized polysomnography procedures, blood samples, and well-validated questionnaires. However, the fact that the study exclusively comprised females may be regarded as a limitation, because the results cannot be directly generalized to apply to men. In the selection of participants for polysomnography there was an oversampling of habitual snorers to yield a sample with adequate variance of the AHI. The prevalence of asthma, OSA, and the combination of asthma and OSA thereby does not reflect the prevalence in the population but would not interfere with the results on differences between groups or associations.

Our findings on asthma, OSA, and objectively measured sleep are new and could potentially have high clinical relevance. First, it was demonstrated that asthma is associated with lower nocturnal oxygen saturation and this association was also consistent in adjusted multiple regression analyses. Second, the severe additive adverse effects of asthma and OSA were highlighted. This indicates that it may be important to pay attention to asthma symptoms in clinical evaluations of patients with OSA and, conversely, pay attention to OSA symptoms in patients with asthma.

ABBREVIATIONS

AHI, apnea-hypopnea index
 BMI, body mass index
 COPD, chronic obstructive pulmonary disease
 CPAP, continuous positive airway pressure
 CRP, C-reactive protein
 DIS, difficulty initiating sleep
 DMS, difficulty maintaining sleep
 EMA, early morning awakenings
 ESS, Epworth Sleepiness Scale
 IL-6, interleukin 6
 ODI, oxygen desaturation index
 OSA, obstructive sleep apnea
 TNF- α , tumor necrosis factor α
 TST90, percentage of total sleep time spent with oxyhemoglobin saturation below 90%

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