Associations between obstructive lung disease and symptoms of obstructive sleep apnoea in a general population

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Abstract

Objectives: To examine the prevalence of self-reported symptoms of obstructive sleep apnoea (OSA) in relation to asthma, respiratory symptoms and pulmonary function. A secondary objective was to determine how sex impacted these relationships.

Methods: A random sample of all adults aged 47–48 and 71–73 years living in Bergen, Norway, were invited. Participants (3506, 69%) underwent spirometry testing and completed a questionnaire on sleep, respiratory symptoms and past medical history. OSA was defined by positive answers to questions on snoring, breathing cessations and daytime sleepiness. Current asthma was defined by ever having received a physician's diagnosis of asthma and current use of anti-asthma medication. Logistic regression analyses, including interaction analyses between sex and the different explanatory variables, were used to examine associations between OSA and current asthma, pre- and post-bronchodilator pulmonary function tests, smoking habits and respiratory symptoms. All models were adjusted for age, sex, waist-hip ratio and smoking.

Results: OSA was more prevalent in the middle-aged compared to the elderly (6.2% vs 3.6%), and in subjects reporting respiratory symptoms. 4.8% had OSA and 6.1% had current asthma. Current asthma and the lowest quartile of post-bronchodilator FVC were significantly associated with OSA with ORs of 2.5 (1.5, 4.2) and 1.7 (1.1, 2.7), respectively. In interaction analyses, women with post-bronchodilator $FEV_1/FVC < 0.7$ had an increased risk of OSA [OR of 4.1 (1.7, 9.7)] compared to women with a $FEV_1/FVC \geq 0.7$.

Conclusions: Current asthma was associated with increased risk of OSA. Women with chronic airflow limitation, but not men, had increased risk of OSA.

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Key words
asthma – COPD – epidemiology – gender differences – obstructive sleep apnoea

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Trygve Müller Jonassen analyzed the data and wrote the paper. Tomas M. Eagan helped with analysis and writing of the paper. Bjørn Bjorvatn designed the study. Sverre Lehmann designed the study, analyzed the data and helped in writing the paper.

Ethics
Written informed consent was provided by all participants and the study was approved by the Regional Committee for Medical and Health Research Ethics, region West (REC-West), approval number 2010/2560.

Conflict of interest
We hereby confirm that there are no conflicts of interest associated with the enclosed manuscript and there has been no significant financial support for this work that could have influenced its outcome. All authors have read and approved the manuscript.

Introduction

Obstructive lung diseases (OLD), represented by the main entities asthma and chronic obstructive pulmonary disease (COPD), are common with prevalence estimates ranging from 5% to 10% in adults (1, 2). Obstructive sleep apnoea (OSA) is also a common disease affecting at least 9% of middle-aged women and 24% of middle-aged men (3).

Obesity is the main risk factor for OSA and there is accumulating evidence linking obesity to asthma, making obesity a possible common pathway for the development of these disorders.

OSA has been related to poorly controlled asthma (4), but epidemiological data is lacking regarding how often these morbidities co-exist. There have, however, been a few studies reporting associations between asthma and various symptoms of OSA such as snoring, witnessed apnoea and daytime sleepiness (5–7). A more recent prospective epidemiologic study found that asthma was associated with increased risk of developing OSA (8). Several studies have examined associations between asthma and obesity, providing robust evidence for obesity being a major risk factor for the development of asthma (9, 10). Some studies have found obese women to be more at risk for asthma than obese men (11, 12), a finding disputed by others (9). OSA is underdiagnosed in women (13) and there is mounting evidence of important sex differences in both aetiology and presentation. There are at least two studies suggesting that OLD might be related to OSA in women only (14, 15).

Early studies indicated a relationship between OSA and COPD (16, 17). More recent epidemiological studies have, however, disputed these findings by demonstrating that the co-existence of COPD and OSA is not higher than one would expect to occur by chance alone (18, 19).

Thus, there is a paucity of data on the co-existence of OLD and OSA. The main objective of our study was to examine the prevalence of self-reported symptoms of OSA in relation to physician-diagnosed asthma, respiratory symptoms and pulmonary function. A secondary objective was to determine how sex impacted these relationships.

Materials and methods

Population

This investigation used data from the 1998–1999 survey of the Hordaland Health Study (HUSK). The target population for this study included all persons born in 1925–1927 and 1950–1951 living in Bergen, Norway, and who had participated in a prior phase of the HUSK study; in 1992–1993 ($n = 7949$, attendance 67%) (20). A total of 7456 were eligible for inclusion in the study, the remaining 493 were deceased or had moved out of the municipality. Among those 7456, random samples of 510 women and 510 men from each birth year ($n = 5100$) were sent a postal invitation to attend. A total of 3506 subjects (1780 women and 1726 men) responded to the invitation and were examined at the HUSK study centre. The study was approved by the Regional Ethics Committee in Western Norway (REK-Vest).

Measurements

Symptoms of OSA were evaluated using three items from the Karolinska Sleep Questionnaire (21). These self-report items were questions about snoring, breathing cessation during sleep and daytime sleepiness. Participants who responded either 'sometimes (several times a month)', 'often (several times a week)' or 'always' on all three items were classified as OSA cases. A similar definition based on the Hawaii Sleep Questionnaire (the apnoea score) has previously been validated against polysomnography (PSG), identifying 100% of cases with severe sleep apnoea [apnoea-hypopnoea index (AHI) ≥ 40]. For an AHI of ≥ 10 the questionnaire had a sensitivity of 78% and specificity of 67% (22).

Questionnaire information was also collected on respiratory symptoms, whether the patient had a physician's diagnosis of asthma, use of anti-asthma medication and smoking habits. Respiratory symptoms covered by the questions were chronic cough (S1), dyspnoea on climbing two flights of stairs (S2), wheeze (S3), waking with chest tightness (S4) and being woken by attack of breathlessness (S5). The questions on symptoms were taken from the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire (S1–S3) (23, 24) and from the Norwegian Respiratory Questionnaire (S4–S5) (25). The wording of the questions on both the sleep symptoms and respiratory symptoms are given in the appendix.

Current asthma was defined by ever having received a physician's diagnosis of asthma and current use of anti-asthma medication. Airflow limitation was examined both by the fixed ratio and the lower limit of normal (LLN), i.e. either having a fixed FEV_1/FVC ratio below 0.7 or a FEV_1/FVC ratio below LLN. LLN values were calculated with prediction equations derived from the Hordaland County Cohort Study (26), which collected data from the same source population as the current study.

Spirometry including bronchodilator test inhaling 400 μg Salbutamol was performed by all subjects. All tests were guided by a well-trained technician. Bronchodilator response (BDR) was measured as the difference in percent predicted between post- and pre-bronchodilator forced expiratory volume in one second (FEV_1). 201 subjects were excluded because of failure to perform adequate spirometry (ATS 1994 criteria), leaving 3305 cases eligible for all further analyses. The characteristics of subjects that were excluded ($n = 201$) have been described previously (27). In all analyses, post-

bronchodilator results for FEV_1, forced vital capacity (FVC) and FEV_1/FVC were used. Predicted values of FEV_1 and FVC were estimated using regression equations from a Norwegian reference population (28).

Statistical analyses

Univariate analyses from categorical explanatory variables were quantified with the presence or absence of OSA symptoms using two-sided Chi square test. Explanatory variables with a P value of <0.05 in univariate analyses were included in multiple logistic regression models to further explore possible associations to OSA symptoms. First, a model including age, sex, body mass index (BMI), waist-hip ratio (WHR) and smoking habits was built. BMI was removed after backward stepwise regression, possibly because WHR having more explanatory power. To this core model, current asthma, BDR in quartiles, lung function variables in quartiles and respiratory symptoms were added. Because of collinearity between these variables, they were all added one at a time to the core model.

To test a potential sex interaction, for each explanatory variable, a new model was built where an interaction term between sex and the explanatory variable was added to the core model.

All analyses were performed using SPSS version 20.0, except for the sex interactions, which were performed using Stata version 12.0.

Results

Population characteristics

The attendance rate was 69% and did not differ by gender (70% women and 68% men), but it was higher in the middle-aged cohort compared to the elderly (76% vs 64%, $P<0.01$). 53% of the middle-aged cohort and 48% of the elderly cohort were women. The distribution of BMI, WHR, smoking habits, current asthma, BDR, levels of lung function and respiratory symptoms are listed in Table 1. There was no difference between the sexes regarding the occurrence of current asthma. Being overweight, defined by a BMI ≥ 25 was more common among the male participants. Airflow limitation, as defined by both FEV_1/FVC < 0.7 and $<$ LLN, and current smoking were also more prevalent in the male group, whereas two of the respiratory symptoms (S1, S4) were more common among the female participants.

Univariate analyses

The overall prevalences of OSA symptoms and current asthma were 4.8% and 6.1%, respectively. Symptoms of OSA were more prevalent in the middle-aged cohort compared to the elderly (6.2% vs 3.6%, $P<0.01$), and in subjects reporting current smoking, current asthma and each of the respiratory symptoms (Table 2). Obesity, measured by both BMI and WHR, increased the risk of OSA symptoms.

A low FVC increased the risk of having OSA symptoms, but no such relationship was found for FEV_1 and FEV_1/FVC (Table 3).

Multivariate analyses

Middle age, male sex, a high WHR and current smoking were all significantly associated with OSA symptoms (Table 4).

Further, current asthma, lower FVC and three of the five respiratory symptoms (S1, S2, S5) were associated with symptoms of OSA, after adjustment (Table 5). There was no relationship between OSA symptoms and BDR, FEV_1 or FEV_1/FVC.

Interaction analyses performed for sex are summarized in Fig. 1. Current asthma, current smoking and airflow limitation (FEV_1/FVC < 0.7 and $<$ LLN) all had significant ORs in women only and there was a trend for this pattern also with two of the respiratory symptoms (S3, S4).

Discussion

In this study of middle-aged and elderly community dwelling subjects, current asthma was associated with symptoms of OSA. We found a low FEV_1/FVC to be associated with OSA symptoms in women only. Also the associations between asthma, smoking, respiratory symptoms and symptoms of OSA were stronger in the female group.

The strengths of this study were a large sample and high response rate, allowing for precision in estimates. All spirometry testing was guided by one well-trained technician, eliminating between-operator measurement variation.

The major limitation of this study was the use of a questionnaire as a surrogate marker for OSA. A diagnosis of OSA relies on the objective measurement of an elevated AHI by either PSG or polygraphy, whereas in the present study a self-report questionnaire was used to identify participants likely to suffer from this disorder. This poses some problems as participants may be unaware of snoring or breathing cessations during sleep, and this method leaves us unable to assess the severity of OSA. In addition, it is well documented that in the elderly population there is a discrepancy between OSA symptoms and findings on PSG/polygraphy (29). Thus it is likely that the

Table 1. Characteristics of the study population within age and gender strata

	Middle-aged					Elderly				
	Women		Men			Women		Men		
	n	%	*n*	%	*P**	*n*	%	*n*	%	*P**
Body Mass Index										
<25	491	62.4	270	38.8	<0.01	358	41.6	369	40.6	<0.01
25–30	215	27.3	355	51.1		360	41.9	453	49.8	
>30	81	10.3	70	10.1		142	16.5	87	9.6	
Waist-hip ratio, quartiles[†]										
Q1	276	34.5	260	36.9	0.06	147	16.9	153	16.5	0.49
Q2	199	24.9	201	28.5		214	24.6	211	22.7	
Q3	182	22.8	150	21.3		251	28.9	259	27.9	
Q4	142	17.8	94	13.3		258	29.7	306	32.9	
Smoking habits										
Never	288	36.8	242	34.7	0.32	488	57.5	190	20.7	<0.01
Ex	217	27.7	218	31.3		232	27.4	581	63.4	
Current	278	35.5	237	34.0		128	15.1	145	15.8	
Current asthma										
No	757	94.7	678	96.0	0.24	807	92.7	861	92.7	0.98
Yes	42	5.3	28	4.0		64	7.3	68	7.3	
Bronchodilator response, quartiles[‡]										
Q1	284	35.5	224	31.7	<0.01	306	35.2	325	35.0	<0.01
Q2	174	21.8	146	20.7		31	3.6	160	17.2	
Q3	155	19.4	226	32.0		251	28.9	200	21.5	
Q4	186	23.3	110	15.6		282	32.4	244	26.3	
Spirometry[§]										
FEV1/FVC $\geq$ 0.7	783	98.0	682	96.6	0.09	798	91.6	739	79.6	<0.01
FEV1 $\geq$ 80%	689	88.0	563	82.6		693	86.8	568	76.9	
50% $\leq$ FEV1 < 80%	94	12.0	117	17.2		105	13.2	169	22.9	
FEV1 < 50%	0	0	2	0.3		0	0	2	0.3	
FEV1/FVC < 0.7	16	2.0	24	3.4		73	8.4	190	20.5	
FEV1 $\geq$ 80%	6	37.5	4	16.7		19	26.0	48	25.3	
50% $\leq$ FEV1 < 80%	9	56.2	19	79.2		41	56.2	109	57.4	
FEV1 < 50%	1	6.2	1	4.2		13	17.8	33	17.4	
FEV1/FVC $\geq$ LLN	755	94.5	682	96.6	0.05	791	90.8	739	79.6	<0.01
FEV1/FVC < LLN	44	5.5	24	3.4		80	9.2	190	20.5	
Respiratory symptoms (yes)										
Chronic cough	96	12.0	56	7.9	0.01	96	11.0	105	11.3	0.85
Dyspnoea stairs	110	13.8	70	9.9	0.02	284	32.6	214	23.0	<0.01
Wheeze	192	24.0	140	19.8	0.05	183	21.0	223	24.0	0.13
Waking with chest tightness	81	10.1	56	7.9	0.14	68	7.8	51	5.5	0.05
Woken by attack of breathlessness	55	6.9	33	4.7	0.07	56	6.4	51	5.5	0.40

*Chi-square test, difference between sexes.
[†]Quartiles stratified by sex.
[‡]Quartiles stratified by percentage difference between post- and pre-bronchodilator FEV1% predicted in the total sample.
[§]Post-bronchodilator.

prevalence of OSA is underestimated in the elderly cohort of our study population.

There have been few epidemiological studies examining a possible relationship between asthma and OSA, and most of the studies that have been published, have used surrogates for OSA, and not PSG. The population study by Fitzpatrick *et al.* (5) reported a higher prevalence of snoring among asthmatics compared to non-asthmatic adults and Larsson *et al.* (7) found snoring and relatives' concerns of witnessed apnoea to be positively related to asthma. In agreement with these studies, using a composite surrogate for OSA, we found more than a twofold risk of having OSA symptoms among subjects with asthma compared to the non-

Table 2. The prevalence of OSA symptoms by body mass index, waist-hip ratio, smoking habits, presence of asthma, bronchodilator reactivity or respiratory symptoms by age group and sex

		Middle-aged					Elderly				
		Women		Men			Women		Men		
		%	*P**	%	*P**	*P*†	%	*P**	%	*P**	*P*†
Body Mass Index			0.09		0.10			0.30		0.53	
	<25	2.6		7.4		<0.01	2.0		4.1		0.10
	25–29.9	4.2		9.3		0.02	1.4		4.9		<0.01
	≥30	7.4		15.7		0.11	3.5		6.9		0.25
Waist-hip ratio, quartiles			<0.01		0.34			0.58		0.02	
	Q1	1.8		8.1		<0.01	1.4		3.3		0.27
	Q2	1.5		7.5		<0.01	2.3		4.3		0.27
	Q3	4.4		11.3		<0.01	1.2		3.1		0.14
	Q4	8.5		12.8		0.29	2.7		8.2		<0.01
Smoking habits			<0.01		0.86			0.20		0.82	
	Never	0.7		8.7		<0.01	1.4		4.2		0.03
	Ex	2.8		9.2		<0.01	2.2		5.3		0.05
	Current	6.8		10.1		0.18	3.9		4.8		0.71
Current asthma			<0.01		0.17			<0.01		0.77	
	No	2.8		8.8		<0.01	1.5		5.0		<0.01
	Yes	16.7		17.9		0.90	7.8		5.9		0.66
Bronchodilator response, quartiles			0.52		0.73			0.93		0.54	
	Q1	3.9		10.7		<0.01	1.6		4.3		0.05
	Q2	1.7		8.2		<0.01	3.2		3.8		0.89
	Q3	4.5		8.0		0.18	2.0		5.5		0.05
	Q4	3.8		10.0		0.03	2.1		6.6		0.01
Respiratory symptoms											
Chronic cough			<0.01		0.01			0.11		0.10	
	No	2.3		8.3		<0.01	1.7		4.6		<0.01
	Yes	12.5		19.6		0.24	4.2		8.6		0.21
Dyspnoea stairs			<0.01		<0.01			<0.01		0.08	
	No	2.5		7.9		<0.01	1.0		4.3		<0.01
	Yes	10.0		21.4		0.03	3.9		7.5		0.08
Wheeze			<0.01		0.05			0.01		0.11	
	No	2.1		8.1		<0.01	1.3		4.4		<0.01
	Yes	7.8		13.6		0.09	4.4		7.2		0.23
Waking with chest tightness			<0.01		0.01			<0.01		1.00	
	No	2.6		8.3		<0.01	1.5		5.1		<0.01
	Yes	11.1		19.6		0.16	7.4		3.9		0.43
Woken by attack of breathlessness			<0.01		<0.01			<0.01		0.17	
	No	3.0		8.5		<0.01	1.5		4.8		<0.01
	Yes	10.9		24.2		0.10	8.9		9.8		0.88

*Chi-square test, difference within age and sex stratum.
†Chi-square test, difference between sexes.

asthma group. A recently published prospective study, utilizing PSG as the diagnostic tool for OSA, found asthma to be associated with increased risk of incident OSA (8), thus lending support to a causal relationship between these conditions.

Given the association found between OSA symptoms and current asthma, one would expect us to also find a relationship between OSA symptoms and BDR, which we did not. We offer the following two points as an explanation to this. First, study participants were not asked to abstain from taking their anti-asthma medication due to concern of increased risk of exacerbations. Thus it is likely that current use of anti-asthma medication diminished the bronchodilator effect of Salbutamol in the group reporting current asthma. Second, the association between BDR and

Table 3. The prevalence of OSA symptoms by post-bronchodilator lung function

	Middle-aged					Elderly				
	Women		Men			Women		Men		
	%	*P**	%	*P**	*P*†	%	*P**	%	*P**	*P*†
FEV1, quartiles‡		0.68		0.30			0.04		0.88	
Q1	4.5		12.6		<0.01	4.1		4.8		0.74
Q2	4.0		8.4		0.07	1.4		6.1		<0.01
Q3	3.0		9.0		0.01	0.5		4.7		<0.01
Q4	2.5		6.9		0.04	1.9		4.7		0.09
FVC, quartiles‡		0.12		0.03			0.06		0.79	
Q1	6.1		14.3		<0.01	4.2		5.7		0.46
Q2	2.0		7.8		<0.01	1.4		5.2		0.03
Q3	3.5		9.7		0.02	0.9		3.8		0.04
Q4	2.5		5.1		0.19	1.4		5.6		0.02
FEV1/FVC		0.44		1.00			<0.01		0.85	
≥ 0.7	3.4		9.2		<0.01	1.4		5.0		<0.01
< 0.7	6.2		8.3		0.81	8.2		5.3		0.37
		0.55		1.00			<0.01		0.85	
≥ LLN	3.4		9.2		<0.01	1.4		5.0		<0.01
< LLN	4.6		8.3		0.53	7.5		5.3		0.48

*Chi-square test, difference within age and sex stratum.
†Chi-square test, difference between sexes.
‡Stratified by age and gender.

asthma is poor, exemplified by a number of studies indicating that reversibility testing differentiates poorly between asthma and COPD (30–32).

Several studies have examined possible associations between COPD, defined by a $FEV_1/FVC < 0.7$, and sleep apnoea, most notably the Sleep Heart Health Study (18) and the study by Bednarek *et al.* (19). These utilized PSG as the diagnostic test for OSA, and both studies concluded that there is no independent association between OSA and COPD. In general, our findings are in line with these results as we did not find any increased prevalence of self-reported OSA symptoms among subjects with chronic airflow limitation. Our analysis did, however, demonstrate a striking difference between the sexes in this regard. Based on our data, women with airflow limitation were more likely than women without to report symptoms suggestive of OSA. Sex interaction analyses have not been reported for the two previous studies (18, 19), and, to the best of our knowledge, there have not been epidemiological studies examining if such relationships exist. There have, however, been retrospective chart review studies finding OLD associated with OSA in women only. Smith *et al.* (15) found female OSA patients more than twice as likely as matched control subjects to have OLD. When compared to male patients with OSA, female patients had more than a twofold risk of suffering from OLD. This result was supported by Shepertycky *et al.* (14) who reported that female OSA patients were more likely than male OSA patients to be suffering from asthma or allergies and were found to be taking significantly more asthma medications. In our study, we found current asthma, current smoking and chronic airflow limitation to be strongly associated with symptoms of OSA in the female population.

Table 4. Adjusted odds ratios for having OSA in a general Norwegian population

		OR	95% CI
Age			
	47–48	2.1	1.5–3.0
	71–73	1	
Sex			
	Women	1	
	Men	2.7	1.9–3.9
Waist-hip ratio, quartiles			
	Q1	1	
	Q2	1.1	0.6–1.8
	Q3	1.3	0.8–2.1
	Q4	2.3	1.4–3.6
Smoking habits			
	Never	1	
	Ex	1.3	0.8–2.0
	Current	1.8	1.2–2.8

Table 5. Adjusted* odds ratios for having OSA

	OR	95% CI
Current asthma	2.5	1.5 - 4.2
Bronchodilator response, quartiles		
Q1	1	
Q2	0.8	0.5–1.4
Q3	1.0	0.7–1.6
Q4	1.2	0.8–1.8
FVC, quartiles†		
Q1	1.7	1.1–2.7
Q2	1.0	0.6–1.7
Q3	1.1	0.7–1.9
Q4	1	
FEV1, quartiles†		
Q1	1.3	0.8–2.1
Q2	1.1	0.7–1.8
Q3	1.0	0.6–1.6
Q4	1	
FEV1/FVC†		
$\geq$ 0.7	1	
$<$ 0.7	1.3	0.8–2.2
$\geq$ LLN	1	
$<$ LLN	1.3	0.7–2.2
Respiratory symptoms		
Chronic cough	1.9	1.3–3.0
Dyspnoea stairs	2.0	1.4–3.0
Wheeze	1.4	0.9–2.0
Waking with chest tightness	1.5	0.9–2.5
Woken by attack of breathlessness	1.9	1.1–3.2

*Adjusted for sex, age, WHR and smoking.
†Post-bronchodilator.

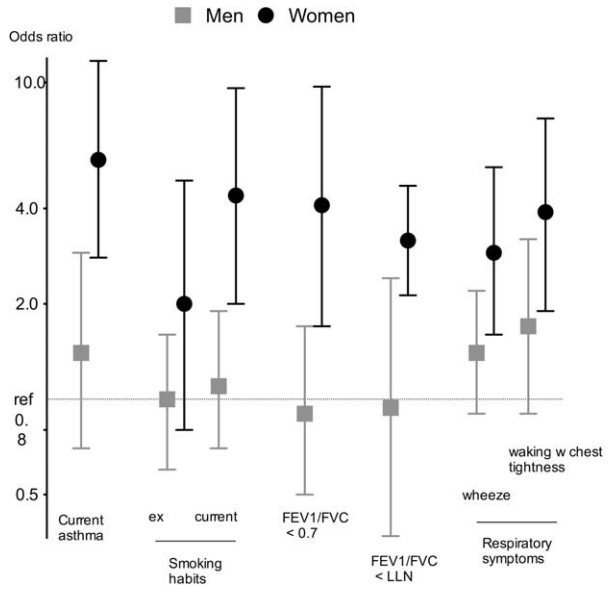

Figure 1. The adjusted* OR (95% confidence interval) for having symptoms of OSA in a general population. *Adjusted for sex, age, waist-hip ratio and smoking habits.

These relationships might be explained by hormonal factors. Smoking has anti-oestrogen effects and is known to induce early menopause (33), and low levels of oestrogen can cause worsening of asthma (34). A large population based study reported an increased prevalence of sleep disordered breathing (SDB) in postmenopausal women who were not taking hormone replacement therapy (HRT), compared to premenopausal women and to postmenopausal women on HRT, indicating that low levels of oestrogen also play a central role in the development of SDB (35).

We found three of the respiratory symptoms (chronic cough, dyspnoea on walking two flights of stairs, being woken by attack of breathlessness) to be independently associated with OSA symptoms. As far as we know, this is the first study to examine a possible relationship between cough and symptoms of OSA in a general population, but our findings are in agreement with results from patient studies. Chan *et al.* (36) found chronic cough in 33% of patients with SDB. Another study reported that 93% of OSA patients with chronic cough experienced a significant improvement in cough with continuous positive airway pressure treatment (37), lending credence to the notion that cough and OSA might be related. Previous studies have also found associations between OSA and dyspnoea. Aihara *et al.* (38) found that OSA patients had worse dyspnoea scores [Medical Research Council (MRC) scale] than non-OSA patients, and in a population based study from Turkey snoring and observed apnoea were associated with an increasing MRC score (39). Finally, it was not surprising that the nocturnal symptom was positively associated with symptoms of sleep apnoea, as a similar symptom (awakening because of gasping or choking) is common in OSA (40), and is included in the American Academy of Sleep Medicine's clinical definition of the condition (41).

The main result of our study was the demonstration of an independent association between asthma and symptoms of OSA. Also of importance was the finding of sex differences regarding pulmonary function and the presence of sleep apnoea symptoms. This study suggests that women with chronic airflow limitation also are at particular risk for OSA. Studies using PSG or polygraphy as the diagnostic test for OSA are needed to confirm these results.

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