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Excessive daytime sleepiness in asthma: What are the risk factors?

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ABSTRACT

Objective: Previous studies have found that excessive daytime sleepiness (EDS) is a more common problem in asthmatic subjects than in the general population. The aim of this study was to investigate whether the prevalence of EDS is increased in asthmatic subjects and, if so, to analyse the occurrence of potential risk factors for EDS in asthmatics. **Methods:** Cross-sectional epidemiological study. In 2008, a postal questionnaire was sent out to a random sample of 45,000 individuals aged 16–75 years in four Swedish cities. **Results:** Of the 25,160 persons who participated, 7.3% were defined as having asthma. The prevalence of EDS was significantly higher in asthmatic subjects (42.1% vs. 28.5%, $p < 0.001$) compared with non-asthmatic subjects. Asthma was an independent risk factor for EDS (adjusted OR 1.29) and the risk of having EDS increased with asthma severity. Risk factors for EDS in subjects with asthma included insomnia (OR, 3.87; 95% CI, 3.10–4.84); chronic rhinosinusitis (OR, 2.00; 95% CI, 1.53–2.62); current smoking (OR, 1.60; 95% CI, 1.15–2.22) and obesity (OR, 1.53; 95% CI, 1.09–2.13). **Conclusions:** EDS is a common problem among subjects with asthma. Asthma is an independent risk factor for having EDS. Furthermore, subjects with asthma often have other risk factors for EDS, many of them potentially modifiable.

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Introduction

Excessive daytime sleepiness (EDS) is an increasing problem [1] affecting 6–23% of the general population [2,3]. EDS has been implied to impair both cognitive performance [4,5] and work performance [5,6], as well as being associated with reduced quality of life [7,8] and an increased risk of both motor vehicle [9] and work-related accidents [6]. EDS thus has a negative impact on daily functioning and consequently affects both the personal and professional aspect of an individual's life.

In the 1990s, the prevalence of EDS was reported to be 50% higher in adult subjects with asthma compared with non-asthmatic subjects [10]. More recent studies have found a strong association between asthma and daytime sleepiness in children [11], and an association between poor asthma control and daytime sleepiness have been found in several studies in children, adolescents and adults [12–15]. It has been suggested that sleep disturbances might contribute to the high prevalence of daytime sleepiness [16], as it has been observed that

asthmatic subjects have a reduced quality of sleep [12,17,18]. Furthermore, asthma often co-exists with other respiratory diseases of the upper airways, such as allergic rhinitis and obstructive sleep apnoea (OSA), conditions which has in turn been associated with an increased risk of having EDS [19,20].

Apart from asthma, insomnia [21,22] has a well-established association with EDS. Studies have also implied that EDS is more common in the younger population [21,23], as well as in the very old [23], and a higher risk of daytime sleepiness has been seen in women [8,24,25]. Being overweight has also been associated with an increased risk of having EDS [8,23,26] and in subjects with EDS, a low physical activity is more commonly seen [21].

The aim of this study was to investigate the association between EDS and asthma. Our hypothesis was that the prevalence of EDS is increased in asthmatic subjects and that this increase is associated both to asthma control and to risk factors not directly related to asthma.

Method

Population

The Global Allergy and Asthma European Network (GA²LEN) is a network of the leading European clinical and research facilities in the field of asthma and allergology. It is the largest multidisciplinary network of researchers in the field and consists of 27 research institutes in more than 20 European countries [27]. In this study, the Swedish version of the 2008 GA²LEN survey was used. The questionnaire consisted of 40 questions about asthma, allergic diseases, sinusitis, chronic obstructive lung disease (COPD), eczema, air pollution, damp and mould in the home environment, educational and occupational status, and lifestyle factors including BMI, exercise and sleeping habits, and tobacco use.

In 2008, the survey was sent out to a total of 45,000 randomly selected individuals aged 16–75 years in four Swedish cities—10,000 randomly selected individuals in each of the cities of Uppsala, Stockholm and Umeå and 15,000 in Gothenburg. Up to three reminders were mailed out.

The study was approved by the local ethics committee in 2008 (Dnr: 2008/014).

Definitions of disorders and conditions derived from the questionnaire

Excessive daytime sleepiness (EDS) was defined as having trouble with sleepiness during the daytime at least three times a week in the last few months [10,24,25].

Asthma was defined as a positive answer to either of the questions “Have you ever had an asthma attack in the last 12 months?” or “Are you currently taking any medicine for asthma, including inhalers, aerosols or tablets?” [28].

Asthma-related symptoms were defined as, in the last 12 months, having had one or more of the following symptoms: (A) wheezing or whistling in the chest, (B) waking up with chest tightness and (C) being woken up by shortness of breath. The number of asthma-related symptoms was used as a marker of asthma severity [28].

Allergic rhinitis was defined as a positive answer to the question: “Do you have any nasal allergies including hay fever?”

Insomnia included (A) difficulty maintaining sleep (DMS) “waking up several times during the night”, (B) difficulty inducing sleep (DIS) “having trouble falling asleep at night” and (C) early morning awakening (EMA) “waking up too early and then having trouble falling asleep again”, of which any of these symptoms had to have a

Table 1. Characteristics of participants with and without asthma (mean $\pm$ SD or %).

	No asthma (n = 23,780)	Asthma (n = 1830)	p-Value
Women	53.9	61.1	<0.001
Age (years)	43.8 $\pm$ 16.1	41.8 $\pm$ 15.9	<0.001
Age group (years)			0.001
16–<35	35.9	40.2	
35–<65	52.7	49.6	
$\geq$ 65	11.4	10.3	
BMI (kg/m ²)	24.7 $\pm$ 4.1	25.5 $\pm$ 4.8	<0.001
BMI group			<0.001
<20	8.4	7.5	
20–<25	51.2	46.5	
25–<30	31.0	30.4	
$\geq$ 30	9.4	15.6	
Physical activity			<0.001
$\geq$ 4 times/week	17.8	22.3	
1–3 times/week	55.2	53.2	
$\leq$ 1 time/month	27.1	24.5	
Current smoking	14.0	12.5	0.077
Insomnia	36.9	47.3	<0.001
Snoring	15.9	19.9	<0.001
Allergic rhinitis	20.7	63.0	<0.001
Chronic rhinosinusitis	7.2	21.6	<0.001

frequency of at least three times a week in the past few months [28].

Habitual snoring was defined as, in the past few months, having “loud and disturbing snoring” at least three nights a week [10,24].

Current smoking was defined as a positive answer to both of the questions “Have you ever smoked one or more cigarettes a day for more than a year?” and “Have you smoked at all during the last month?”

Low physical activity was defined as “Exercising so hard that you get sweaty or out of breath” once a month or less.

Chronic rhinosinusitis (CRS) was defined according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) criteria as a positive answer to at least two of the questions (A)–(D) of which one had to be (A) or (C); (A) “Have you suffered from a blocked nose for more than 12 weeks during the last 12 months?”, (B) “Have you suffered from pain or pressure around the forehead, nose or eyes for more than 12 weeks during the last 12 months?”, (C) “Have you had discoloured snot or phlegm for more than 12 weeks during the last 12 months?” and (D) “Have you suffered from a reduced or total loss of sense of smell for more than 12 weeks during the last 12 months?” [29].

To be included in this study, the participants had to have answered all the questions in the survey used to define “Asthma” and “Excessive daytime sleepiness” and, as a result, the total study population consisted of 25,160 subjects. Of these, 1,830 (7.3%) subjects were defined as having asthma. The characteristics of the subjects are presented in Table 1.

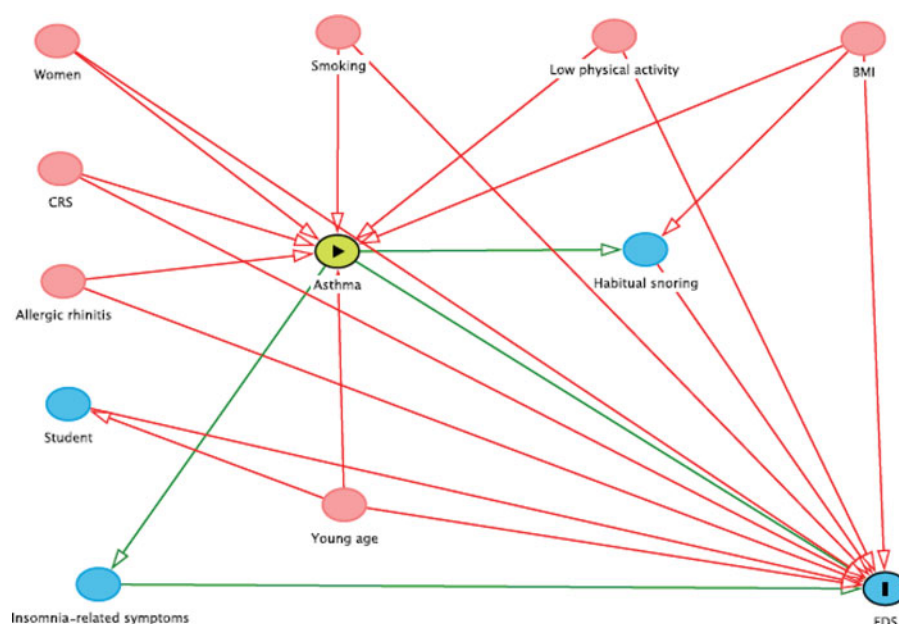


Figure 1. Causal diagram between asthma and excessive daytime sleepiness (EDS). Green arrows indicate causal paths, while red arrows show biasing paths. Blue circles show ancestors of outcome. Red circles show ancestors of exposure and outcome. The green circle indicates the exposure and the blue circle with the black line inside it indicates the outcome. From this diagram, the model used in the logistic regression analysis was extracted by DAGitty.net.

Statistical analyses

The statistical analyses were performed using StatView version 5.0.1 (SAS Institute Inc., North Carolina, USA) and STATA version 12 (Stata Corporation, College Station, Texas, USA). Bivariate analyses were performed using the chi-square test and unpaired *t*-test to compare the data between subjects with and without asthma. Logistic regression was then used to calculate crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CI) in the multivariate analysis. Analyses of interaction were done in order to see if the association between EDS and independent variables was significantly different in women than in men. A *p*-value of <0.05 was regarded as statistically significant.

To decide which variables to adjust for in the multiple logistic regression models, a directed acyclic graph (DAG) was used. It was created by using DAGitty (<http://www.dagitty.net>) [30], a browser-based environment for creating and analysing causal models. From this diagram (Figure 1), the smallest set of co-variables necessary to control for bias, the minimal sufficient adjustment set, was extracted by DAGitty. This model was then used in the multiple logistic regression analysis.

Results

The subjects with asthma were significantly younger, were more often women and had a higher mean BMI than the subjects without asthma (Table 1). There was

a higher prevalence of obesity (BMI ≥ 30) and subjects <35 years old in the asthma group. However, asthmatic subjects were significantly more physically active than non-asthmatics.

The subjects with asthma had a significantly higher prevalence of allergic rhinitis and CRS compared with subjects without asthma. Snoring and insomnia were also significantly more common in the asthma group (Table 1).

The prevalence of EDS was significantly higher in the asthma group than in the group of subjects without asthma (42.1% vs. 28.5%). The prevalence of EDS was higher in both men and women in the asthma group compared with non-asthmatic subjects (46.2% vs. 31.1% and 35.7% vs. 25.5% for women and men, respectively) (Figure 2).

The association between asthma and EDS remained significant after adjusting for possible confounders (Table 2). Other independent risk factors for having EDS included female sex, age <35 years, insomnia, snoring, CRS, allergic rhinitis, obesity, current smoking and having a low physical activity level (Table 2).

Allergic rhinitis, low physical activity and obesity were statistically significant risk factors for EDS in both men and women. The strongest risk factors for EDS for both sexes were CRS, insomnia, snoring and age <35 years (Table 3).

There was a significant sex-related interaction for age and current smoking. The association between age <35 years and EDS was significantly stronger for women than men and a similar gender difference was found for current

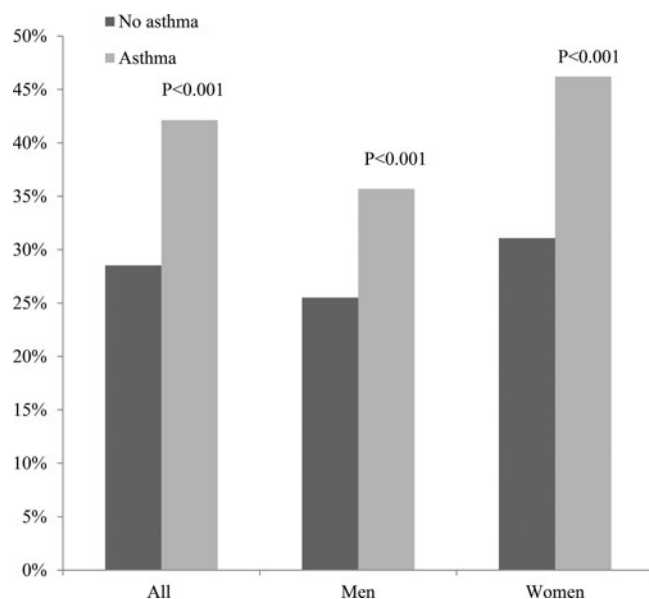


Figure 2. Prevalence of EDS in subjects with and without asthma, divided by sex.

smoking (Table 3). There was also an almost significant gender interaction for asthma, with an independent significant association between EDS and asthma in women but not in men.

EDS in participants with asthma

Of the asthmatic subjects, 15.8% reported three asthma-related symptoms, 25.4% reported two symptoms, and 40.3% and 18.5% of the subjects reported one and no asthma-related symptoms, respectively (data not shown). The number of asthma-related symptoms correlated positively with having EDS. In the group with three reported

Table 2. Unadjusted and adjusted odds ratios (95% CI) for the association between excessive daytime sleepiness and asthma, sex, age, BMI, physical activity, current smoking, insomnia, snoring, allergic rhinitis and chronic rhinosinusitis among the entire study population.

	Unadjusted OR (n = 25,160)	Adjusted OR* (n = 23,106)
Women	1.34 (1.27–1.41)	1.28 (1.20–1.37)
Age <35 years	1.75 (1.66–1.85)	2.52 (2.35–2.70)
BMI <20	1.28 (1.16–1.41)	1.02 (0.91–1.14)
BMI 20–25	1	1
BMI 25–30	0.97 (0.91–1.03)	1.06 (0.98–1.14)
BMI ≥30	1.40 (1.28–1.53)	1.23 (1.11–1.38)
Low physical activity	1.27 (1.19–1.34)	1.26 (1.17–1.35)
Current smoking	1.35 (1.25–1.45)	1.19 (1.09–1.30)
Insomnia	3.98 (3.76–4.21)	4.06 (3.81–4.33)
Snoring	1.66 (1.55–1.78)	1.67 (1.53–1.82)
Allergic rhinitis	1.56 (1.47–1.66)	1.29 (1.20–1.39)
Chronic rhinosinusitis	2.99 (2.74–3.26)	2.14 (1.93–2.38)
Asthma	1.83 (1.66–2.01)	1.29 (1.15–1.45)

Note. *The odds ratios are adjusted for asthma, sex, age, BMI, physical activity, current smoking, insomnia, snoring, allergic rhinitis and chronic rhinosinusitis.

Table 3. The entire study population divided into two groups: men and women. Adjusted odds ratios (95% CI)* for the association between excessive daytime sleepiness and asthma, age, BMI, physical activity, current smoking, insomnia, snoring, allergic rhinitis and chronic rhinosinusitis in men and women, respectively.

	Men (n = 10,642)	Women (n = 12,464)	p-value
Age <35 years	2.17 (1.96–2.41)	2.83 (2.58–3.10)	0.001
BMI <20	1.05 (0.82–1.34)	1.00 (0.88–1.13)	0.97
BMI 20–<25	1	1	
BMI 25–<30	1.00 (0.90–1.11)	1.11 (1.00–1.23)	0.81
BMI ≥30	1.25 (1.06–1.46)	1.20 (1.04–1.40)	0.82
Low physical activity	1.23 (1.11–1.37)	1.27 (1.16–1.40)	0.73
Current smoking	1.02 (0.89–1.17)	1.33 (1.18–1.49)	0.007
Insomnia	3.92 (3.56–4.31)	4.20 (3.85–4.57)	0.74
Snoring	1.63 (1.46–1.82)	1.70 (1.49–1.94)	0.96
Allergic rhinitis	1.25 (1.12–1.40)	1.33 (1.21–1.47)	0.20
Chronic rhinosinusitis	2.24 (1.91–2.61)	2.08 (1.80–2.40)	0.89
Asthma	1.13 (0.94–1.36)	1.40 (1.20–1.62)	0.058

Note. *Odds ratios are adjusted for asthma, age, BMI, physical activity, current smoking, insomnia, snoring, allergic rhinitis and chronic rhinosinusitis.

symptoms, 57.3% suffered from EDS, while only 31.9% had EDS in the group with no reported symptoms (Figure 3). The association between EDS and the number of asthma-related symptoms remained significant after adjusting for sex, age, BMI, physical activity, current smoking, insomnia, snoring, allergic rhinitis and chronic rhinosinusitis (Table 4).

Insomnia was the strongest risk factor for EDS in the group of subjects with asthma (Table 4). Apart from the number of asthma symptoms EDS was also independently associated with CRS, young age, current smoking and

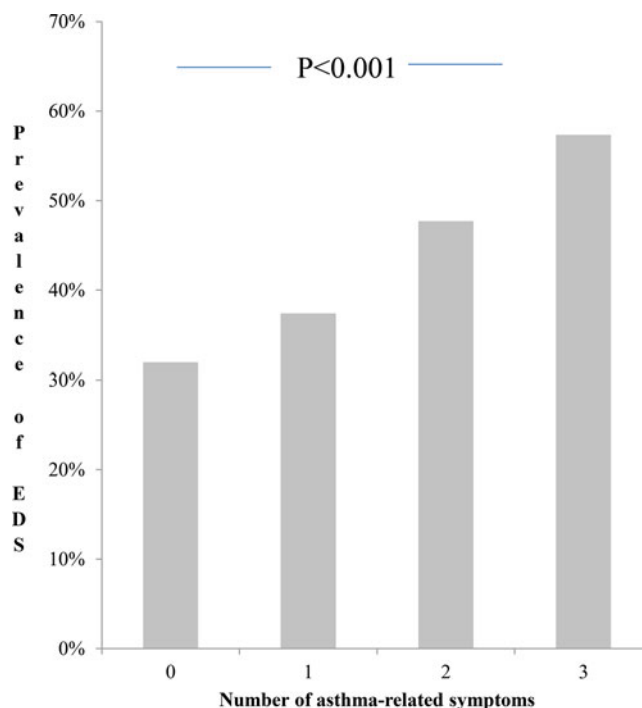


Figure 3. Number of asthma-related symptoms and their association with excessive daytime sleepiness (EDS) in subjects with asthma.

Table 4. Adjusted odds ratios (95% CI)* for the association between excessive daytime sleepiness and sex, age, BMI, physical activity, current smoking, insomnia, snoring, allergic rhinitis, chronic rhinosinusitis and number of asthma-related symptoms among subjects with asthma.

All subjects with asthma (n = 1667)	
Women	1.50 (1.19–1.88)
Age <35 years	2.03 (1.60–2.58)
BMI <20	0.95 (0.62–1.44)
BMI 20–<25	1
BMI 25–<30	1.07 (0.83–1.40)
BMI ≥30	1.53 (1.09–2.13)
Low physical activity	1.25 (0.96–1.61)
Current smoking	1.60 (1.15–2.22)
Insomnia	3.87 (3.10–4.84)
Snoring	1.25 (0.94–1.67)
Allergic rhinitis	1.22 (0.98–1.53)
Chronic rhinosinusitis	2.00 (1.53–2.62)
Number of asthma-related symptoms	
1	1.17 (0.86–1.60)
2	1.47 (1.05–2.06)
3	1.72 (1.17–2.53)

Note. *Odds ratios are adjusted for sex, age, BMI, physical activity, current smoking, insomnia, snoring, allergic rhinitis, chronic rhinosinusitis and number of asthma-related symptoms.

obesity. No significant sex interaction was found for the association between EDS and the various independent variables.

Discussion

The present study shows that asthmatic subjects have a prevalence of excessive daytime sleepiness (EDS) that is considerably higher than that in non-asthmatics. Furthermore, in asthmatic subjects, EDS was related to asthma severity and several potentially modifiable risk factors, including obesity, current smoking, insomnia and CRS. Somewhat surprisingly, we found that the association between asthma and EDS was stronger in women.

The finding of a higher prevalence of EDS in asthmatic subjects is in line with previously published results [1,10,12,19]. In the present study the number of asthma symptoms was used as a marker of asthma control and the prevalence of EDS increased with the number of symptoms in the group of participants with asthma. Thus our results are in accordance with previous studies showing an association between asthma control and EDS [12–15]. Mastronarde et al. [12] found that improved asthma control was associated with an improvement in both sleep quality and Epworth Sleepiness Scale (ESS) scores [31]. However, as these improvements were small, poorly controlled asthma is unable solely to explain the high prevalence of EDS in asthmatic subjects. In fact in the present study insomnia was a stronger risk factor than asthma control. Our results are therefore in line with what was reported by Melzer et al. [16] who found that asthma severity accounted for only 2% of the variance of daytime

sleepiness, compared to 28% of the variance accounted for by insomnia severity in a study on adolescents with asthma.

It is unclear why insomnia is so common in asthmatic subjects. It has been suggested that nocturnal asthma symptoms due to a circadian variation in airway resistance and hormone secretion might account for the sleep disturbances [32]. However, Mastronarde et al. [12] reported a much higher frequency of nocturnal awakenings than nocturnal asthma symptoms, suggesting that factors other than just asthma control might cause the sleep disturbances in asthmatic subjects.

Apart from insomnia and asthma control we have found several other risk factors for EDS in the asthmatic population, including obesity and current smoking. In the general population, obesity has been found to increase the risk of developing EDS [33,34] and weight loss has in turn been associated with its remission [34]. Furthermore, a recent study by Theorell-Haglöw et al. [33] found that insomnia and smoking were two of the strongest risk factors for developing EDS. In addition, our results showed that CRS was an independent risk factor for EDS in asthmatic subjects. Patients with CRS have a high prevalence of sleep pathology [35], and in a recent study by Jiang et al. [36] 38% of the patients with CRS were found to suffer from EDS. Furthermore, studies have indicated that subjects with CRS have experienced a significant reduction in excessive daytime sleepiness following endoscopic sinus surgery [37,38].

Interestingly, there were indications that asthma was a stronger risk factor for EDS in women than in men. Sex-related differences have been shown in both asthma epidemiology and disease expression [39] but not specifically for the association between asthma and EDS. However, McCallister et al. [40] demonstrated that women with poor asthma control reported more asthma symptoms than men, despite having better pulmonary function. Women were more likely to report nocturnal awakenings and difficulty sleeping due to their asthma. This indicates that women's sleep might be more affected by their asthma and this could in turn explain why we found that asthma was a stronger risk factor for EDS in women.

The current study is based on a questionnaire answered by more than 25,000 randomly selected individuals in the general population. The study areas (Gothenburg, Uppsala, Stockholm and Umeå) are a fairly good representation of both the geographic and demographic features of Sweden. The sample can therefore be assumed to represent the general population of Sweden—in contrast to similar studies with enriched populations [10]. However, some limitations need to be addressed. First, all the data are self-reported. Second, EDS was assessed by the participants' own estimation of the frequency of

daytime sleepiness instead of a more common measurement, such as the ESS, an eight-item questionnaire for measuring the level of daytime sleepiness [31]. However, this way of assessing EDS has been used in other similar studies [10,41]. Third, because of the cross-sectional study design, no conclusions can be drawn about the causality between asthma, other co-morbidities and EDS.

Conclusions

This study confirms that asthmatic subjects have a higher prevalence of EDS than non-asthmatics. Furthermore the asthmatic population was found to have several potentially modifiable risk factors for EDS, including obesity, current smoking, insomnia and CRS, all of which could contribute to the high prevalence of EDS in this population.

Since EDS has a negative impact on the daily life of the people suffering from it, it is important that this problem is recognised and addressed by physicians. We therefore suggest that physicians treating asthmatic patients specifically should try to identify both the occurrence of daytime sleepiness and treatable risk factors for EDS. Special consideration should be paid to women, since asthma had a stronger association with EDS in women. Future interventional studies are warranted to determine whether specific therapy for multiple risk factors has an additive effect on improving daytime sleepiness in subjects with asthma.

Declaration of interest

None of the authors has declared any conflict of interest.

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