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Association between Asthma and Risk of Developing Obstructive Sleep Apnea

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Abstract

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Conception: MT, MP, TY, PEP
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Importance—Obstructive sleep apnea (OSA) is more common among patients with asthma; whether asthma is associated with the development of OSA is unknown.

Objective—To examine the prospective relationship of asthma with incident OSA.

Design—Population-based prospective epidemiology study (the Wisconsin Sleep Cohort).

Setting—Beginning in 1988, adult participants were recruited from a random sample of Wisconsin state employees to attend overnight polysomnography studies at 4-year intervals. Asthma and covariate information were assessed during polysomnography studies through March 2013.

Participants—Participants identified as free of OSA (apnea-hypopnea index<5 events/hr and not treated) by two baseline polysomnography studies and that had at least one additional polysomnography study were included. 547 participants (52% women; mean [SD] baseline age = 50 [8] years) provided 1105 4-year follow-up intervals.

Exposure—Questionnaire-assessed presence and duration of self-reported physician-diagnosed asthma.

Main Outcome—The associations of presence and duration of asthma with 4-year incidences of both OSA (apnea-hypopnea index ≥ 5 or positive airway pressure treatment) and OSA concomitant with habitual daytime sleepiness were estimated using repeated-measures Poisson regression, adjusting for confounders.

Results—Twenty-two out of 81 (27% [95% CI=17%–37%]) participants with asthma experienced incident OSA over their first observed 4-year follow-up interval compared to 75 incident cases of OSA among 466 participants without asthma (16% [95% CI, 13%–19%]). Using all 4-year intervals, participants with asthma experienced 45 incident OSA cases during 167 4-year intervals (27% [95% CI, 20%–34%]) and participants without asthma experienced 160 incident OSA cases during 938 4-year intervals (17% [95% CI, 15%–19%]); the corresponding adjusted relative risk was 1.39 (95% CI, 1.06–1.82), controlling for sex, age, baseline and change in body mass index, and other factors. Asthma was also associated with new-onset OSA with habitual sleepiness (relative risk: 2.72 [95% CI, 1.26–5.89], p=0.04). Asthma duration was related to both incident OSA (relative risk: 1.07 per 5-year increment in asthma duration [95% CI, 1.02–1.13], p=0.01) and incident OSA with habitual sleepiness (relative risk: 1.18 [95% CI, 1.07–1.31], p=0.02).

Conclusions and Relevance—Asthma was associated with increased risk of new-onset OSA. Studies investigating the value of periodic OSA evaluation in patients with asthma are warranted.

Keywords

asthma; lung; sleep apnea; obstructive

INTRODUCTION

In adults, obstructive sleep apnea (OSA) is highly and increasingly prevalent.[1] OSA is associated with cardiovascular morbidities, insulin resistance, neural injury, and accelerated mortality.[2]

Accumulating evidence suggests bidirectional relationships between asthma and OSA, whereby each disorder deleteriously influences the other.[3] In cross-sectional epidemiologic studies, the prevalence of sleepiness, snoring and apnea were significantly higher in participants with asthma.[4] Likewise, in clinic-based studies, OSA symptoms were more frequently reported by patients with asthma[5] than by Internal Medicine patients[6] and the general population.[5] Moreover, studies with polysomnographically-assessed OSA reported strikingly high OSA prevalences (~90%) in patients with difficult-to-control asthma.[7,8] Additionally, in a study of women with atopy, symptomatic asthma almost doubled the risk of snoring, a cardinal symptom of OSA.[9] One 14-year prospective study provided evidence supporting a pathogenic role for asthma in sleep-disordered breathing. Independent of confounders, incident asthma emerged as a significant risk factor for development of habitual snoring.[10] While these few studies suggest an asthma-OSA association, it remains unknown whether asthma is a causal risk factor for OSA.

Once OSA is established in patients with asthma, OSA may adversely impact asthma-related outcomes by negatively affecting asthma control. OSA risk relates to poor overall asthma control[11] during daytime and nighttime.[12] Additionally, OSA treatment leads to improved asthma symptoms, morning peak expiratory flow rates and quality of life, [13] prompting inclusion of OSA as a potential contributor to poor asthma control in the current asthma clinical guidelines.[14]

Therefore, understanding initiating processes of a potentially self-reinforcing asthma-OSA cycle is important to reduce the burden of both OSA and asthma. No studies, to our knowledge, have evaluated the prospective relationship of asthma with incident polysomnographically-evaluated OSA. We examined this relationship in the Wisconsin Sleep Cohort Study, a population-based longitudinal epidemiologic investigation of the natural history, risk factors and outcomes of OSA in adults. We hypothesized that preexistent asthma is a risk factor for later development of OSA.

METHODS

Study Participants and Design

Study protocols and informed consent documents were approved by the Health Sciences Institutional Review Board of the University of Wisconsin-Madison. Sampling and data collection protocols of the Wisconsin Sleep Cohort Study have been described previously.[1] The Cohort comprises 1,521 randomly-selected adult employees of state agencies, 30–60 years old in 1988. Since study inception, participants have attended in-laboratory overnight polysomnography and provided health-related questionnaires approximately every 4 years. Data presented here were collected through March, 2013.

Measurements

Overnight studies included polysomnography, and measurements of height and weight (used to calculate body mass index [BMI, in kg/m^2]) and waist, hip and neck girth (all in cm). Data on medical history, excessive daytime sleepiness (hereafter referred to as ‘sleepiness’), alcohol, smoking, nasal problems (congestion or stuffiness), menopausal status (pre-

menopausal, transitioning and post-menopausal) for women were obtained by questionnaires. Sleepiness was evaluated with the question: “Do you have feelings of excessive daytime sleepiness?”, with the following response categories: “never,” “rarely (once a month),” “sometimes (2–4 times a month),” “often (5–15 times a month)” and “almost always (>15 times a month).” Participants were classified as having habitual sleepiness if they responded “often” or “almost always.” Regular use of the sleepiness question in the exact form described above began in 1997; baseline sleepiness data were not available for 157 participants.

A polysomnography system (Grass Instruments, Quincy, MA) assessed sleep, and respiratory parameters by pulse oximetry (Ohmeda 3740, Englewood, CO), airflow by thermocouples (ProTec, Hendersonville, TN), nasal pressure by a transducer (Validyne Engineering Corp., Northridge, CA), and thoracic and abdominal excursions by inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY). Sleep scoring used conventional criteria.[15] An apnea was defined as cessation of airflow lasting ≥10 seconds. A discernible reduction in the sum of thoracic plus abdominal effort amplitude associated with a ≥4% reduction in oxyhemoglobin saturation defined a hypopnea. Between 1988 and 2000, sleep studies were scored using a paper-based system; since 2000 studies have been scored on a computer-screen system. All statistical modeling adjusts for the scoring changes; this removes instrumentation-related influences on OSA assessments after 2000.

Asthma status was self-reported on a questionnaire, asking about physician-diagnosis, year of diagnosis, and whether any treatments were received. All participants who indicated that they were ever diagnosed with asthma were adjudicated. To be defined as having asthma, participants had to have indicated that they were ever diagnosed with asthma on at least two interviews and provided year of diagnosis. If participants only indicated diagnosis on one interview but were never treated and never again mentioned diagnosis on later interviews, they were not considered to have had asthma. For calculating duration of asthma, the self-reported year of diagnosis was used; if a participant reported more than one year of diagnosis, the median year reported was used. Spirometry was performed from 1989–2000, and lung physiologic parameters were compared between participants with asthma (defined as above) to those without. Asthma medications were categorized as controllers (inhaled corticosteroids, long-acting beta-adrenergics or anti-cholinergics, leukotriene modifiers, and agents that block the release of hypersensitivity mediators) or not.

Statistical Analysis

To be included in this analysis, participants had to be free of OSA (AHI [apnea hypopnea index] < 5/h, and no use of continuous or bilevel positive airway pressure (hereafter referred to as positive airway pressure [PAP]) on their first two polysomnography studies, to establish OSA-free status at baseline (hereafter “baseline” sleep study refers to the second OSA-free confirmatory sleep study unless otherwise noted). Participants with OSA-free status so-established were observed for incident OSA from baseline for one or more 4-year follow-up periods. That is, participants could contribute multiple 4-year periods of follow-up (range: one to five 4-year follow-up intervals). For example, a participant with an AHI=0 in 1990, AHI=2 in 1994, AHI=0 in 1998, AHI=4 in 2002, and AHI=10 in 2006 would

contribute three 4-year follow-up periods: one initiated in 1994 and followed to 1998 (outcome = no incident OSA), one initiated in 1998 and followed to 2002 (outcome = no incident OSA), and one initiated in 2002 and followed to 2006 (outcome = incident OSA "event"). In addition to the analyses of 4-year intervals for OSA risk, in ancillary models we also examined incidence of OSA over 8-year intervals. As with the analyses of 4-year OSA risk, participants were required to be OSA-free for two consecutive baseline sleep studies to be eligible for 8-year OSA incidence analyses. For the 8-year analyses, only one 8-year interval was used per participant—the most recent interval available.

All analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC). Repeated measures analyses were performed to calculate standard errors and p-values for primary modeling outcomes. Poisson regression models with a logarithmic link function, accommodating repeated measures (i.e., multiple 4-year intervals from 61% of participants) by robust error variance estimates, were used to measure the association of asthma with subsequent development of OSA.[16,17] Relative risks with 95% confidence intervals are presented. Parameter estimates were considered statistically significantly different from null values (e.g., relative risk=1) if 2-sided tests yielded p-values < 0.05.

The outcome, incident OSA, was defined in two ways: 1) as developing an AHI $\geq$ 5/h or initiating PAP for OSA treatment; and 2) as developing an AHI $\geq$ 5/h or initiating PAP use with concomitant habitual sleepiness ("often" or "almost always").

The asthma variables included: 1) asthma diagnosed at any age up to the baseline polysomnography visit; 2) duration of asthma stratified by 5-year intervals; 3) duration of asthma stratified as short (≤10 years) or long (>10 years); and, 4) asthma controller medication use at baseline polysomnography study.

All models include covariates measured at baseline visit (age, sex, BMI, nasal problems [congestion or stuffiness, or other problems that cause congestion at night], current smoking status, and number of alcoholic drinks/week), in addition to baseline AHI (defined as the average across the two OSA-free confirmatory polysomnography studies) and change in BMI over the 4-year follow-up intervals. Results from additional ancillary analyses examined models that accounted for: asthma controller medications; menopausal status; and, additional measures of body habitus (neck girth, waist girth, and waist to hip ratio).

RESULTS

The final sample consisted of 547 participants who contributed a total of 1,105 sets of 4-year intervals: 211 (39%) participants with 1 set, 173 (32%) with 2 sets, 105 (19%) with 3 sets, 57 (10%) with 4 sets, and one with 5 sets.

Baseline characteristics

Table 1 presents the baseline characteristics summarized at the participant level for the first 4-year interval (if the participant contributed more than one 4-year interval) and stratified by asthma status and asthma duration group.

Incident OSA

In unadjusted analyses, 22 out of 81 (27% [95% CI=17%–37%]) participants with asthma experienced incident OSA over their first observed 4-year follow-up intervals vs. 75 incident cases of OSA among 466 asthma-free participants without asthma (16% [95% CI, 13%–19%], p-difference in proportions=0.02) (Table 2). Using all available 4-year intervals—i.e., including multiple 4-year interval observations per participant—participants with asthma experienced 45 incident OSA cases during 167 4-year intervals (27% [95% CI, 20%–34%]) and participants without asthma experienced 160 incident OSA cases during 938 4-year intervals (17% [95% CI, 15%–19%], p-difference in proportions=0.007). These differences in OSA risk were observed even though there were similar average BMI changes among those with and without asthma during 4-year follow-up intervals.

Regression modeling estimated that participants with pre-existing asthma, compared to those without, had relative risks of 1.39 (95% CI, 1.06–1.82) for incident OSA and 2.72 (95% CI, 1.26–5.89) for incident OSA with habitual sleepiness, independent of baseline covariates, baseline AHI, and BMI change over time (Table 3, Model 1). When the “any asthma” variable was substituted with continuous asthma duration, 5-year increments in duration were associated with higher risk for incident OSA and OSA with habitual sleepiness (5-year asthma duration relative risks = 1.07 [95% CI, 1.02–1.13] and 1.18 [1.07–1.31], respectively) (Table 3, Model 2). Reiteration of these models using asthma duration categories (no asthma, ≤10 years duration, >10 years duration) showed the highest risk for long asthma duration compared to no asthma, such that having had asthma of long duration was associated with higher risk of incident OSA, and of OSA with habitual sleepiness; the long-duration relative risks were, respectively, 1.65 (95% CI, 1.21–2.25) and 3.36 (95% CI, 1.49–7.56) (Table 3, Model 3). For both OSA and OSA with habitual sleepiness, there were significant trends in relative risks with longer duration asthma category (p-values for linear trend in the natural log of the relative risks=0.008 and 0.03, respectively).

Additional analyses

We performed a series of additional analyses to examine the robustness of our findings. First, in a smaller group of N=468 participants eligible to be followed for 8-year OSA incidence, participants with pre-existing asthma had higher absolute 8-year risk of incident OSA (risk=49% [95% CI: 38–61%]) compared to participants without asthma (risk=28% [95% CI: 23–32%], p<0.001) and OSA with habitual sleepiness (8-year risk=12% [95% CI: 5–19%] vs. 4% [95% CI: 2–6%], respectively, p=0.007) (Table 4). Regression modeling, adjusting for covariates, estimated that participants with pre-existing asthma, compared to those without, had relative risks of 1.58 (95% CI, 1.20–2.09) for incident OSA and 2.58 (95% CI, 1.20–5.55) for incident OSA with habitual sleepiness (Table 5, Model 1). As with the analysis of 4-year OSA incidence, 5-year increments in continuous asthma duration (Table 5, Model 2) and longer duration asthma category (>10 years) (Table 5, Model 3) were significantly associated with higher risk of incident OSA and OSA with habitual sleepiness.

Second, while we relied on self-report of physician-diagnosed asthma, we did have spirometry available on a limited subset (n=220) of participants. In these participants, even

though in the normal range, the adjusted mean FEV_1/FVC was lower for participants with (n=33) than those without (n=187) asthma (0.77 [95% CI, 0.74–0.79] vs. 0.82 [95% CI, 0.81–0.83], $p < 0.001$). Likewise, even though in the normal range, the adjusted mean FEV_1%-predicted was also lower for participants with asthma than those without asthma (0.92 [95% CI, 0.88–0.97] vs. 1.00 [95% CI, 0.98–1.02], p=0.003). Thus, in our sample, self-reported asthma was associated with worse objective measures of lung function.

Third, we examined whether the association of asthma and incident OSA depended on use of asthma controller medications. The association between asthma and OSA did not vary significantly by asthma controller-use status (eTables 1 and 2 in the Supplement).

Fourth, we investigated whether there was a selection bias related to asthma status—specifically, if availability of 4-year follow-up polysomnography studies was related to baseline asthma status. There was no association between asthma and availability of follow-up polysomnography: 64% of baseline participants with asthma and 65% of those without asthma had follow-up data available as of March 2013.

Fifth, we tested whether bias could have been introduced by the contribution of multiple 4-year follow-up intervals from 61% of the participants. A reiteration of the analyses presented in Table 3, but restricted solely to the *first* 4-year intervals from all n=547 individual participants, showed only small changes to the relative risks (e.g., using all intervals, the asthma–incident OSA relative risk was 1.39 and using only the first intervals, the relative risk was 1.34 [95% CI: 0.90–1.97]; similarly, the asthma–OSA with habitual EDS relative risk was 2.72 when all 4-year intervals were included, and 2.74 [95% CI: 1.00–7.50] when only the first 4-year interval was used).

Sixth, in addition to BMI, we examined models that adjusted for other anthropometric parameters including baseline and 4-year changes in neck girth, waist girth, and waist to hip ratio. The addition of these variables to presented models had no substantive impact (beyond the adjustment for BMI and change in BMI) on coefficients relating asthma to risk of new-onset OSA (eTable 3 in the Supplement).

Seventh, the analyses were repeated to include menopausal status as a covariate in the models (using the subset of 1071 4-year intervals for which this information was available). No evidence of confounding by menopause of the asthma-OSA association was observed (eTables 4 and 5 in the Supplement).

DISCUSSION

This study prospectively examined the relationship of asthma with OSA assessed with laboratory-based polysomnography and found that preexistent asthma was a risk factor for the development of clinically-relevant OSA in adulthood over a 4-year period. Furthermore, the asthma-OSA association was significantly dose-dependent on duration of asthma.

While a focus of our investigation was on incident OSA per se, we also examined OSA with concomitant sleepiness because OSA in the presence of sleepiness is of particular clinical interest (excessive daytime sleepiness is often used as a diagnostic criterion of “clinically

significant" OSA warranting treatment). We found significantly higher risks of OSA (with or without sleepiness) related to asthma, especially when examining asthma in relation to risk of developing OSA with sleepiness. However, our findings do not distinguish a direct association between asthma and sleepiness vs. an association between asthma and sleepiness mediated by OSA. That is, a stronger association of asthma with OSA and concomitant habitual sleepiness (vs. OSA without regard to the presence of sleepiness) might plausibly reflect one or more of: 1) an association of asthma with greater severity of OSA; 2) an interaction of asthma and OSA whereby the presence of both conditions synergistically enhance sleepiness; and, 3) an additional OSA-independent effect of asthma on sleepiness. Future studies aimed at measuring the longitudinal association of asthma with the development of sleepiness per se, while accounting for OSA, are warranted.

A few cross-sectional community[4,9] and clinic-based studies[5,6] have shown an association of asthma with OSA symptoms or polysomnography-based OSA diagnosis.[7,8] One study examined the longitudinal association of self-reported asthma and habitual snoring.[10] In this large (n=967) sample, followed for 14 years, 6% of the participants developed asthma during follow-up. Incident asthma was a strong predictor for development of habitual snoring (relative risk=2.8), independent of baseline BMI and BMI change during the interval, whereas pre-existent asthma was not. Furthermore, one cross-sectional study found that in asthma patients, asthma control, use of inhaled corticosteroids—in a dose-dependent fashion, and gastro-esophageal reflux disease were each associated with habitual snoring or high OSA risk, independent of traditional risk factors including excess weight and nasal congestion.[18] A role of asthma in OSA pathogenesis is also supported by the study by Julien et al.[7] in which age, sex and BMI-matched patients with severe and moderate asthma (n=26/group) underwent overnight polysomnography. In this study, OSA (AHI≥5/h) was significantly more prevalent among those with severe asthma (50%) vs. moderate disease (23%) or controls (12%).[7] These findings are consistent with ours and lend further support to a causal role of asthma in OSA development.

Asthma per se, its treatment, or comorbidities may alter pharyngeal airway patency, setting the stage for development of OSA. Asthma may change the fine balance between the forces that promote collapse and those maintaining the patency of the pharyngeal airway—a region lacking any bone or cartilaginous support and thus, vulnerable to collapse.[19] Although the underlying mechanistic links between asthma per se and OSA remain to be tested, several pathways seem plausible: 1) augmented inspiratory negative intraluminal pressure in the deformable pharyngeal airway could occur during asthma attacks, along with active contraction of the respiratory muscles during forced expiration, yielding increased pressure in the surrounding pharyngeal airway tissues,[20] with both phenomena promoting upper airway collapse; 2) alterations in pharyngeal airway stiffness during sleep resulting from reduction in its tracheal tug[21] due to the more abrupt decline in lung volumes observed in sleeping patients with asthma;[22] 3) sleep loss and fragmentation—caused by asthma—could affect upper airway collapsibility;[23] and 4) finally, the "spill-over" systemic inflammation resulting from the asthmatic process[24] may weaken the respiratory muscles,[25] and furthermore, trigger central nervous system inflammatory responses that could impair protective mechanisms of pharyngeal upper airway patency and destabilize the central breathing controller, as has been shown in response to other inflammatory insults.[26] An

additional pathway from asthma to OSA may be the effect of systemic[8] and inhaled corticosteroid therapy on the pharyngeal airway, as suggested by a recent study.[27] Corticosteroids, which are prescribed for the treatment of asthma, may affect the deformable pharyngeal airway by raising the surrounding tissue pressure from centripetal fat accumulation/redistribution, and by diminishing the contractile properties of its protective, dilator muscles (myopathy),[27] similar to the postulated mechanism underlying dysphonia.[28] Additionally, in *in vivo* studies, 2h incubation of canine tracheal muscle strips with dexamethasone significantly augmented forced fluctuations–induced relengthening of contracted muscle.[29] While such effect would favor bronchodilation, in the pharyngeal airway they would render its dilators more "floppy," hampering their ability to protect upper airway patency during sleep. Our small sample of asthma participants using controller medications (n=16) likely precluded finding significant associations with incident OSA, and thus our study does not negate such effects of corticosteroid medications on the upper airway. In addition, pharyngeal upper airway dysfunction resulting from commonly comorbid gastro-esophageal reflux disease may compound the above effects,[18,30] since proximal migration of gastric acid in the upper airway combined with extended acid clearance during sleep[311] could trigger pharyngeal spasm and cause mucosal exudative neurogenic inflammation.[32] How these effects arising from multiple insults interact on the upper airway in individual patients remains to be further examined in future studies.

The strengths of our study rely on its prospective design with a minimum of 4 years of follow-up per participant (most participants—61%—had a minimum of 8 years' follow-up, i.e., contributed two or more 4-year intervals), and use of the gold-standard laboratory-based polysomnography with and without symptoms to diagnose OSA. Our study has some important limitations. First, we used participant-recalled physician-diagnosed asthma (including dates of diagnosis) and do not have details (doses, frequency) on medications used over time for asthma treatment. However, as we found with the pulmonary testing in our study, Senthilselvan[33] also reported a significant relationship of self-reported asthma with measures of airways obstruction concurrently obtained on spirometry. Furthermore, Oksanen et al.[34] found that self-reported physician diagnosis of asthma had 91% sensitivity and 97% specificity for presence of asthma diagnoses in medical records. If these sensitivity and specificity parameters are applicable to our asthma assessment, then we would expect slight underestimates of asthma-OSA associations due to asthma misclassification in our study. While self-report of physician-made asthma diagnosis has been typical in related epidemiologic studies,[9,30,35] future studies should incorporate objective assessments to confirm and characterize control of asthma, along with its treatment over time. Second, we lack detailed characterization of asthma comorbidity with rhinitis (and treatment of rhinitis with nasal steroids) and gastro-esophageal reflux disease, commonly found co-occurring with asthma. Likewise, in future studies, these conditions need to be characterized in detail by incorporating objective confirmatory and control methods. Finally, we had insufficient numbers of participants transitioning from OSA-free status to more severe OSA disease (e.g., AHI>30/h) over 4-year intervals to include analyses of incident moderate-severe OSA.

CONCLUSION

The presence and duration of asthma among adults was associated with an increased 4-year risk of new-onset obstructive sleep apnea. These data emphasize a need to investigate the value of periodic OSA evaluation in individuals with asthma, as well as the mechanistic underpinnings of this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant-level Baseline[a] Descriptive Statistics by Asthma Duration Status

Participant Characteristics:	All	Asthma	Asthma Duration Group		No Asthma
			Short (≤10 years)	Long (>10 years)	
No. (%)	547 (100)	81 (15)	39 (7)	42 (8)	466 (85)
Age (years), mean (SD)	50.4 (7.7)	49.0 (6.8)	48.8 (6.2)	49.1 (7.4)	50.6 (7.8)
Gender (Female), No. (%)	284 (52)	50 (62)	29 (74)	21 (50)	234 (50)
BMI (kg/m^2), mean (SD)	28.9 (5.5)	30.6 (6.4)	31.0 (6.6)	30.3 (6.2)	28.6 (5.3)
Apnea-hypopnea Index (events/hour)[b], median (IQR)	0.7 (0.3–1.7)	1.1 (0.3–2.0)	1.1 (0.3–2.1)	0.9 (0.4–1.6)	0.7 (0.2–1.6)
Incidence of OSA[c], No. (%)	97 (18)	22 (27)	9 (23)	13 (31)	75 (16)
Incidence of OSA + Habitual Sleepiness[d], No. (%)	19 (3)	7 (9)	3 (8)	4 (10)	12 (3)
Duration of Asthma (years), mean (SD)	3 (9)	18 (16)	5 (3)	30 (13)	NA
Duration of Asthma (years), median (IQR)	0 (0–0)	12 (5–28)	5 (3–7)	28 (17–40)	NA
Asthma Controller Medication Use, No. (%)	16 (3)	16 (20)	9 (23)	7 (17)	NA
Nasal Problems[e], No. (%)	224 (41)	45 (56)	22 (56)	23 (55)	179 (38)
Alcohol (#drinks/ week), median (IQR)	2.0 (0.0–4.0)	1.0 (0.3–2.0)	0.0 (0.0–3.0)	1.0 (0.0–2.0)	0.7 (0.2–1.6)
Current Smoker, No. (%)	69 (13)	9 (11)	6 (15)	3 (7)	60 (13)
Menopause Status	n=272				
Pre/Peri Menopause[f], No. (%)	92 (34)	19 (38)	12 (41)	7 (33)	73 (33)
Transitioning from Pre/Peri[g] to Post, No. (%)	53 (19)	10 (20)	6 (21)	4 (19)	43 (19)
Post Menopause[h], No. (%)	127 (47)	21 (42)	11 (38)	10 (48)	106 (48)
Excessive Daytime Sleepiness[i]	n=390				
Not Habitually Sleepy[j], No. (%)	322 (83)	41 (75)	18 (78)	23 (72)	281 (84)
Habitual Sleepiness[k], No. (%)	68 (17)	14 (25)	5 (22)	9 (28)	54 (16)

Abbreviations: BMI=body mass index (kg/m^2); IQR = interquartile range; OSA=obstructive sleep apnea; SD=standard deviation.

[a] Collected at the second OSA-free confirmatory sleep study visit (from the first 4-year follow-up interval for participants with multiple follow-up intervals).

[b] Expressed as the average apnea-hypopnea index across the two OSA-free confirmatory sleep study visits (both of which were, by design, <5 events/hr).

[c] Incident OSA from first 4-year study interval for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 4-year interval).

[d] Incident OSA + Habitual Sleepiness from first 4-year study interval for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 4-year interval) and follow-up excessive daytime sleepiness was reported as occurring “often” or “almost always.”

[e] Nasal congestion or stuffiness or other nasal problems that cause nasal stuffiness at night.

[f] Women who were pre- or peri-menopausal at both baseline and follow-up sleep studies.

[g] Women who transitioned from pre- or peri-menopausal at baseline sleep study to postmenopausal at follow-up sleep study.

[h] Women who were postmenopausal at both baseline and follow-up sleep studies.

[i] Administration during sleep study visits of the specific excessive daytime sleepiness question used for the present analyses began in 1997; baseline sleepiness data were missing for 157 participants.

[j] Not Habitually Sleepy defined as excessive daytime sleepiness occurring “never”, “rarely” or “sometimes”.

[k] Habitual Sleepiness defined as excessive daytime sleepiness occurring “often” or “almost always”.

Table 2

OSA Incidence, Polysomnography Indices and Changes in Relevant Characteristics Across All Examined 4-Year Study Intervals.

			Asthma Duration Group			
Study Characteristics	**All**	**Asthma**	**Short (≤10 yrs)**	**Long (>10 yrs)**	**No Asthma**	**Asthma vs. No Asthma P-value**
N=1,105 4-year Interval Sleep Studies from 547 participants	1105	167	73	94	938	-
Incident OSA[a], No. (%)	205 (19)	45 (27)	15 (21)	30 (32)	160 (17)	0.007
Incident OSA + Habitual Sleepiness[b], No. (%)	33 (3)	12 (7)	3 (4)	9 (10)	21 (2)	0.02
PAP user at end of 4-year interval, No. (%)	7 (1)	1 (1)	1 (1)	0 (0)	6 (1)	0.95
AHI[c] at end of 4-year interval (events/hr), mean (95% CI)	2.9 (2.6 – 3.1)	3.5 (2.9 – 4.1)	3.5 (2.5 – 4.5)	3.5 (2.7 – 4.3)	2.7 (2.5 – 3.0)	0.03
Change in BMI over 4-year interval (kg/m^2), mean (95% CI)	0.4 (0.3 – 0.6)	0.4 (0.3 – 0.6)	0.6 (0.1–1.1)	0.3 (−0.1 – 0.8)	0.4 (0.1 – 0.8)	0.97

Abbreviations: BMI=body mass index (kg/m^2); OSA=obstructive sleep apnea; PAP= positive airway pressure; AHI=apnea-hypopnea index; CI=confidence interval.

[a] Incident OSA indicates 4-year study intervals for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 4-year interval).

[b] Incident OSA + Habitual Sleepiness indicates 4-year study intervals for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 4-year interval) and follow-up excessive daytime sleepiness was reported as occurring “often” or “almost always.”

[c] PAP users were not included in this calculation.

Table 3

Adjusted Relative Risks for Asthma and Asthma Duration Predicting 4-year Incidence of OSA (Apnea-Hypopnea Index ≥ 5 or PAP Use) (without and with Sleepiness)

	Incident OSA[a]		Incident OSA + Habitual Sleepiness[b]	
	Relative Risk (95% CI)	**P-value**	**Relative Risk (95% CI)**	**P-value**
Model 1[c]: Any Asthma vs. No Asthma				
No Asthma	1.00 (reference)	-	1.00 (reference)	-
Any Asthma	1.39 (1.06, 1.82)	0.03	2.72 (1.26, 5.89)	0.045
Model 2[c]: Continuous Duration of Asthma				
Duration of Asthma (5 year increments)	1.07 (1.02, 1.13)	0.01	1.18 (1.07, 1.31)	0.02
Model 3[c]: Duration of Asthma Categories				
No Asthma	1.00 (reference)	-	1.00 (reference)	-
Short Duration of Asthma (≤10 years)	1.06 (0.67, 1.67)	0.82	1.75 (0.49, 6.26)	0.39
Long Duration of Asthma (>10 years)	1.65 (1.21, 2.25)	0.002	3.36 (1.49, 7.56)	0.003
p-trend in relative risks	0.008		0.03	

Abbreviations: OSA=obstructive sleep apnea; PAP= positive airway pressure; CI=confidence interval

[a] Incident OSA indicates 4-year study intervals for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 4-year interval).

[b] Incident OSA + Habitual Sleepiness indicates 4-year study intervals for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 4-year interval) and follow-up excessive daytime sleepiness was reported as occurring “often” or “almost always.”

[c] Models adjusted for: baseline apnea-hypopnea index (average of the two confirmatory OSA-free sleep study visits), sex, baseline age, body mass index, percent change in body mass index, nasal congestion or stuffiness, current smoking and number of alcoholic drinks per week.

Table 4

OSA Incidence, Polysomnography Indices and Changes in Relevant Characteristics Across Participants' Most Recent Available 8-Year Study Intervals.

			Asthma Duration Group			
Study Characteristics	**All**	**Asthma**	**Short (≤10 yrs)**	**Long (>10 yrs)**	**No Asthma**	**Asthma vs. No Asthma P-value**
N=468 8-year Interval Sleep Studies from 468 participants	468	77	34	43	391	-
Incident OSA[a], No. (%)	146 (31)	38 (49)	14 (41)	24 (56)	108 (28)	<0.001
Incident OSA + Habitual Sleepiness[b], No. (%)	25 (5)	9 (12)	3 (9)	6 (14)	16 (14)	0.007
PAP user at end of 8-year interval, No. (%)	15 (3)	4 (5)	3 (9)	1 (2)	11 (3)	0.28
AHI[c] at end of 8-year interval (events/hr), mean (95% CI)	4.3 (6.3)	5.6 (5.5)	5.0 (5.9)	6.0 (5.2)	4.0 (6.4)	0.05
Change in BMI over 8-year interval (kg/m^2), mean (95% CI)	0.6 (2.8)	0.5 (3.3)	−0.0 (3.5)	0.9 (3.0)	0.6 (2.8)	0.69

Abbreviations: BMI=body mass index (kg/m^2); OSA=obstructive sleep apnea; PAP=positive airway pressure; AHI=apnea-hypopnea index; CI=confidence interval.

[a] Incident OSA indicates 8-year study interval for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 8-year interval).

[b] Incident OSA + Habitual Sleepiness indicates 8-year study interval for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 8-year interval) and follow-up excessive daytime sleepiness was reported as occurring "often" or "almost always."

[c] PAP users were not included in this calculation.

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Table 5

Adjusted Relative Risks for Asthma and Asthma Duration Predicting 8-year Incidence of OSA (Apnea-Hypopnea Index ≥ 5 or PAP Use) (without and with Sleepiness)

	Incident OSA[a]		Incident OSA + Habitual Sleepiness[b]	
	Relative Risk[c] (95% CI)	**P-value**	**Relative Risk[c] (95% CI)**	**P-value**
Model 1[c] Any Asthma vs. No Asthma:				
No Asthma	1.00 (reference)	-	1.00 (reference)	-
Any Asthma	1.58 (1.20, 2.09)	0.004	2.58 (1.20, 5.55)	0.06
Model 2[c]: Continuous Duration of Asthma				
Duration of Asthma (5 year increments)	1.07 (1.02, 1.12)	0.02	1.17 (1.06, 1.28)	0.05
Model 3[c]: Duration of Asthma Categories				
No Asthma	1.00 (reference)	-	1.00 (reference)	-
Short Duration of Asthma (≤10 years)	1.40 (0.93, 2.12)	0.11	2.06 (0.59, 7.20)	0.26
Long Duration of Asthma (>10 years)	1.71 (1.22, 2.39)	0.002	2.94 (1.24, 6.97)	0.01
p-trend in relative risks	0.003		0.06	

Abbreviations: OSA=obstructive sleep apnea; PAP=positive airway pressure; CI=confidence interval

[a] Incident OSA indicates 8-year study intervals for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 8-year interval).

[b] Incident OSA + Habitual Sleepiness indicates 8-year study intervals for which: i) the initial AHI was <5 events/hr (and no PAP use); and, ii) the follow-up AHI was ≥5 events/hr (or initiation of PAP use over the 8-year interval) and follow-up excessive daytime sleepiness was reported as occurring “often” or “almost always.”

[c] Models adjusted for: baseline apnea-hypopnea index (average of the two confirmatory OSA-free sleep study visits);,sex, baseline age, body mass index, percent change in body mass index, nasal congestion or stuffiness, current smoking and number of alcoholic drinks per week.