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Permalink

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Journal

CHEST Journal, 150(6)

ISSN

0012-3692

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Publication Date

2016-12-01

DOI

10.1016/j.chest.2016.09.020

Peer reviewed

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Association Between Insomnia and Asthma Burden in the Severe Asthma Research Program (SARP) III

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BACKGROUND: Sleep difficulties are commonly reported by patients with asthma; however, the prevalence of insomnia and its association with disease burden and well-being is unknown. We aimed to determine the prevalence of insomnia, defined as combined sleep-specific complaints with associated daytime symptoms, among a large sample of adults with asthma, and to compare well-being, asthma control, and asthma-related health care utilization in individuals with asthma and insomnia and those without insomnia.

METHODS: Baseline data from adults with physician-confirmed asthma enrolled in the Severe Asthma Research Program III was used for analyses (N = 714). Participants completed the Insomnia Severity Index (ISI), Asthma Control Test, Asthma Quality of Life Questionnaire, and Hospital Anxiety and Depression Scale.

RESULTS: Insomnia (ISI ≥ 10) was identified in 263 participants (37%). Presence of insomnia was associated with higher levels of depression and anxiety symptoms and poorer quality of life. Those with insomnia had a 2.4-fold increased risk for having not well-controlled asthma and a 1.5-fold increased risk for asthma-related health care utilization in the past year compared with those without insomnia.

CONCLUSIONS: Insomnia is highly prevalent in asthma and is associated with adverse outcomes. Further studies are needed to gain a better understanding of the interaction between insomnia and asthma control.   CHEST 2016; 150(6):1242-1250

KEY WORDS: asthma; depression; health care utilization; insomnia; quality of life

Asthma exacerbations are exceedingly common and result in nearly one-half million hospitalizations and roughly 2 million ED visits yearly.[1,2] Health care utilization and reductions in quality of life are greatest among those with poorly controlled asthma.[3-5] With > 50% of patients failing to achieve disease control,[6] identifying additional approaches for optimizing asthma control is critical for the prevention of serious asthma exacerbations and the consequent reduction in hospitalizations and ED visits.

Sleep difficulties are commonly reported among persons with asthma, with 22% to 47% reporting difficulties initiating and maintaining sleep and > 75% reporting poor sleep quality.[7-12] Sleep difficulties are often considered a consequence of nocturnal awakenings resulting from nighttime asthma symptoms and/or the need for rescue inhaler medication, which will resolve with adequate control of asthma symptoms. Previous studies suggest that sleep difficulties persist even in those without asthma-related nocturnal awakenings, with 20% to 46% reporting moderate to severe difficulty staying asleep.[7,10,12] These data suggest that poor sleep may not solely be due to nighttime

asthma awakenings, but may represent comorbid insomnia. Insomnia disorder is characterized by self-reported difficulty falling asleep, staying asleep, or poor quality sleep and accompanying daytime symptoms such as fatigue, irritability, and impaired concentration. The prevalence of insomnia in asthma is unknown, because previous studies have only examined sleep-specific complaints without assessment of associated daytime symptoms.[7-12]

The impact of insomnia on asthma control and asthma-related health care utilization has not been examined. Limited studies have shown associations between difficulty falling asleep and frequent awakenings at night and nighttime asthma symptoms and rescue inhaler use, both of which are indications of poor asthma control.[7-9,12,13] The aims of the present study were to determine the prevalence of insomnia, defined as combined sleep-specific complaints with associated daytime symptoms, among a large sample of adults with physician-diagnosed asthma, and to compare asthma control, well-being, and asthma-related health care utilization in those with asthma and insomnia and those without insomnia.

Methods

Study Participants

Participants were part of the longitudinal phase (III) of the ongoing multicenter Severe Asthma Research Program (SARP). Details of SARP I-II have been previously described.[14] Participants were current nonsmokers or had less than 5 pack years of smoking and were classified according to the European Respiratory Society/American Thoracic Society's definition of severe asthma.[15] Each institutional review board approved the study and informed consent was obtained from all participants (e-Table 1).

Of the 957 participants who met eligibility criteria and were enrolled in SARP III, 228 were excluded because they were < 18 years of age. An additional 15 were excluded because of missing data on the Insomnia Severity Index (ISI); thus, our final sample included a total of 714 participants.

Measures

All questionnaires and pulmonary function testing were conducted at the baseline visit. SARP-specific questionnaires were administered to gather data on demographics, smoking, medical history and comorbidities (gastroesophageal reflux disease [GERD] and sleep apnea), medication history, and asthma-related health care utilization, including unscheduled doctor visits, ED visits, hospital admissions, and ICU admissions. In addition to analyzing each health care use separately, an overall asthma-related health care utilization variable was created to represent any of the previously mentioned health care use in the prior year.

The ISI is a seven-item scale assessing current (past 2 weeks) perceived severity of symptoms (difficulty falling asleep, difficulty staying asleep,

and early morning awakenings), satisfaction with current sleep pattern, interference with daytime functioning, noticeability of impairment resulting from the sleep problem, and degree of concern caused by the sleep problem.[16] A 5-point Likert scale is used to rate each item (0 = not at all, 4 = extremely), with scores ranging from 0 to 28. A cutoff of ≥ 10 has been shown to optimize sensitivity (86.1%) and specificity (87.7%) in community samples.[17] The ISI has good psychometric properties.[16,17]

The Asthma Control Test (ACT) is a 5-item questionnaire that assesses interference with activity, shortness of breath, nocturnal symptoms, rescue medication use, and self-rating of asthma control.[18,19] Each item is scored using a scale of 1 to 5. Total scores range from 5 to 25, with higher scores indicating better asthma control. Cutoff scores for well-controlled asthma (ACT ≥ 20), not well-controlled asthma (ACT 16-19), and uncontrolled asthma (ACT ≤ 15) have been established.[18,19] Asthma control was categorized as not well-controlled defined as an ACT score ≤ 19.

The Asthma Quality of Life Questionnaire (AQLQ) is a 32-item measure assessing condition-specific health-related quality of life within four life domains: activity limitations, symptoms, emotional distress, and environmental stimuli.[20] Each item is rated from 1 (totally impaired) to 7 (not at all impaired). An overall AQLQ score is computed by averaging the four domains. The AQLQ has demonstrated excellent psychometric properties.[21]

The Hospital Depression and Anxiety Scale (HADS) is a 14-item self-report questionnaire designed to assess the occurrence of depression and anxiety symptoms in the past week.[22] Items on both subscales (HADS-D for depression and HADS-A for anxiety) are rated on a 4-point response scale (0-3). Scores for each subscale range from 0 to 21. The HADS-D and HADS-A have acceptable internal

consistency with Cronbach's alpha ranging from 0.67 to 0.93.[23] Probable depression and anxiety was defined as a HADS-D and HADS-A scores ≥ 8.[23]

Pulmonary function testing was performed according to American Thoracic Society guidelines.[24] FEV_1 percent predicted and FVC percent predicted were recorded.[25]

Statistical Analysis

Categorical variables were summarized as counts and percentages, and continuous variables as mean ± SD. Comparisons of variables between those with and those without insomnia were performed using Student t test or χ^2 test. African Americans were compared with Caucasians and all other races combined. Logistic regression was used to test the associations of insomnia with dichotomous dependent variables (asthma control, depression, anxiety, and asthma-related health care utilization) in both univariate and multivariate analyses. For continuous dependent variables, linear regression was performed. The following covariates were included in all regression analyses: age, sex, BMI, oral corticosteroid use in the past 3 months, GERD, and sleep apnea. Removal of the sleep items from the calculation of the ACT and AQLQ total scores did not yield differing results in analyses so these items were retained. A two-sided P value < .05 was set for statistical significance. SPSS 23 for Windows (SPSS Inc) was used to conduct the statistical analyses.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of participants. No differences in age, sex, race, smoking status, or asthma duration were found between the participants with and without insomnia. Those with insomnia had a higher BMI, worse lung functions, and lower annual household income than those without insomnia. Participants with insomnia had more frequent self-reported GERD and sleep apnea compared with those without insomnia. Among those without insomnia and self-reported sleep apnea (n = 71), 42 (59%) were being treated with CPAP or BiPAP. Among those with insomnia and self-reported sleep apnea (n = 76), 50 (66%) were being treated with CPAP or BiPAP.

Insomnia Symptoms

The mean ISI score in the overall sample was 8.3 (6.3). Using a cutoff of ≥ 10 on the ISI, clinically significant insomnia was present in 37% (283 of 714) of participants with asthma, with 34% reporting severe to very severe difficulty falling asleep, 36% reporting severe to very severe difficulty staying asleep, 31% reporting severe to very severe problems with waking up too early, and 33% reporting much to very much interference with daily functioning. Greater insomnia severity was associated with more frequent nighttime asthma symptoms that disturbed sleep (ie, ACT item, "During the past 4 weeks, how often did your asthma symptoms [wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?"] (r = -0.42, P < .001). To distinguish insomnia from nocturnal awakenings resulting from nighttime asthma symptoms, the previously mentioned item from the ACT was used to identify participants who did not have nighttime asthma symptoms that disturbed their sleep (n = 267 within the total sample).

Of these individuals, 23% (n = 62) had clinically significant insomnia.

Insomnia and Asthma Control and Well-being

As shown in Table 2, participants with insomnia had worse asthma control and asthma-specific quality of life and higher levels of depression and anxiety symptoms. More than 75% of participants with insomnia had asthma that was not well-controlled defined by an ACT score of ≤ 19, whereas roughly one-half of those without insomnia had not well-controlled asthma (χ^2 = 41.19, P < .001). Of the participants with not well-controlled asthma (n = 204), those with insomnia had worse asthma control than those without insomnia (mean ACT score = 15.12 ± 3.18 and 12.77 ± 4.01, respectively) (t = 6.82, P < .001). Using a cutoff score of ≥ 8 on the HADS to indicate probable depression and anxiety, those with insomnia had higher proportions with probable depression and anxiety compared with participants without insomnia (23% vs 6% and 51% vs 19%, respectively) (χ = 42.39, p <0.001; χ = 81.84, p <0.001).

Insomnia and Asthma-Related Health Care Utilization

Compared to those without insomnia, analyses of asthma-related health care utilization showed participants with insomnia reported more frequent health care use in the past 12 months, including unscheduled doctor visit (53% vs 39%), emergency room visit (37% vs 19%), and hospital admission (15% vs 9%) (all P < .01) (Fig 1). ICU admissions in the past 12 months were similar between the two groups. Overall, 60% of participants with insomnia reported having any asthma-related health care utilization (including unscheduled doctor visit, emergency room visit, hospital admission, and/or ICU admission) in the past year compared with 45% of those without insomnia (χ^2 = 15.21, P < .001). Among

TABLE 1] Characteristics of Participants With Asthma by Presence of Insomnia

Variable	Total Sample[a] (N = 714)	No Insomnia[a] (n = 451)	Insomnia[a] (n = 263)	P Value[b]
Age (y)	47.4 (14.0)	47.5 (14.4)	47.3 (13.4)	.87
Female, No. (%)	482 (67.5)	298 (65.5)	79 (69.5)	.29
Race, No. (%)				
Caucasian	466 (65.3)	306 (67.9)	160 (60.8)	.16
African-American	159 (22.3)	94 (20.8)	65 (24.7)	
Other	89 (12.5)	51 (11.3)	38 (14.5)	
Annual household income, No. (%) (n = 713/450/263)				
< $25,000	115 (16.1)	58 (12.9)	57 (21.7)	.005
$25,000-$49,999	150 (21.0)	97 (21.6)	53 (20.2)	
$50,000-$99,999	201 (28.2)	122 (27.1)	79 (30.0)	
> $100,000	148 (20.8)	109 (24.2)	39 (14.8)	
Declined to answer/don't know	99 (13.9)	64 (14.2)	35 (13.3)	
BMI	32.3 (8.2)	31.4 (7.9)	34.0 (8.7)	< .001
Ever smoked, No. (%) (n = 449/279/170)	101 (22.5)	62 (22.2)	39 (22.9)	.86
Asthma duration (y) (n = 330/197)	20.6 (16.7)	30.8 (15.8)	30.3 (16.1)	.70
Medications				
SABA use in past mo, No. (%) (n = 712/449/263)	640 (89.9)	398 (88.6)	242 (92.0)	.15
LABA use in past 3 mo, No. (%) (n = 712/449/263)	554 (77.8)	341 (75.9)	213 (81.0)	.12
Inhaled corticosteroid use in past 3 mo, No. (%) (n = 712/449/263)	636 (89.3)	396 (88.2)	240 (91.3)	.20
Oral corticosteroid use in past 3 mo, No. (%) (n = 712/449/263)	90 (12.6)	39 (8.7)	51 (19.4)	< .001
Prebronchodilator FEV_1% predicted (n = 684/430/254)	74.6 (21.1)	76.7 (20.8)	71.1 (21.2)	< .001
Prebronchodilator FVC% predicted (n = 684/430/254)	84.8 (18.2)	86.5 (17.3)	81.8 (19.2)	< .001
Prebronchodilator FEV_1/FVC% predicted (n = 685/430/255)	87.8 (18.2)	88.0 (13.5)	86.0 (13.6)	.07
Supplemental oxygen, No. (%)	22 (3.1)	6 (1.3)	16 (6.1)	< .001
GERD, No. (%)	327 (45.8)	172 (38.1)	155 (58.9)	< .001
Sleep apnea, No. (%)	147 (20.6)	71 (15.7)	76 (28.9)	< .001
CPAP or BiPAP treatment, No. (%)	92 (12.9)	42 (9.3)	50 (19.0)	< .001
Total ISI score	8.3 (6.3)	4.3 (2.9)	15.2 (4.3)	< .001

Values presented as mean (SD) or No. (%). eNO = fraction of exhaled nitric oxide; GERD = gastroesophageal reflux disease; ISI = Insomnia Severity Index; LABA = long-acting beta-agonist; SABA = short-acting beta-agonist.
[a]No. of participants unless otherwise noted (where numbers are shown for total sample/no insomnia/insomnia).
[b]Denotes P values from χ^2 tests (for categorical variables) or t tests (for continuous variables).

participants with controlled asthma (ACT score > 19) (n = 269), those with insomnia more frequently reported having an unscheduled doctor visit (44% vs 28%) and any asthma-related health care use (48% vs 31%) in the past 12 months than those without insomnia (P values = 0.02) (Fig 2). Emergency room visits, hospital admissions, and ICU admissions were similar between the two groups with controlled asthma. Among participants with not well-controlled asthma (ACT score ≤ 19), those with insomnia had a higher frequency of emergency room visits in the past year (42% vs 28%) than those without insomnia (P = .002). No differences were found in the other asthma-related health care utilization variables between the two groups with not well-controlled asthma.

TABLE 2] Asthma Control and Well-Being in Participants With Asthma With and Without Insomnia

Variable	No Insomnia (n = 451)	Insomnia (n = 263)	P Value[a]
ACT			
Total score	18.3 (4.2)	14.8 (5.3)	< .001
Not well-controlled,[b] No. (%)	241 (53.4)	204 (77.6)	< .001
AQQ			
Total score	5.2 (1.1)	4.2 (1.3)	< .001
Symptoms	5.3 (1.1)	4.3 (1.4)	< .001
Activities	5.6 (1.2)	4.5 (1.4)	< .001
Emotions	5.3 (1.5)	4.1 (1.7)	< .001
Environment	5.2 (1.4)	4.3 (1.6)	< .001
HADS			
Depression total score	2.3 (2.6)	5.2 (3.5)	< .001
Probable depression,[c] No. (%)	28 (6.2)	60 (22.8)	< .001
Anxiety total score	4.9 (3.3)	7.5 (3.9)	< .001
Probable anxiety,[d] No. (%)	84 (18.6)	134 (50.9)	< .001

Values presented as mean (SD) or No. (%). ACT = Asthma Control Test; AQLQ = Asthma Quality of Life Questionnaire; HADS = Hospital Depression and Anxiety Scale.
[a]Denotes P values from χ^2 tests (for categorical variables) or t tests (for continuous variables).
[b]Poor asthma control, ACT total score ≤ 19.
[c]Probable depression, HADS depression total score ≥ 8.
[d]Probable anxiety, HADS anxiety total score ≥ 8.

Univariate and Multivariable Analyses

Analyses were performed with presence of insomnia as the independent factor and asthma control, quality of life, depression, anxiety, and health care utilization as dependent variables. In univariate analyses, having insomnia was associated with increased odds for having not well-controlled asthma, probable depression and anxiety, and asthma-related health care utilization in the past year (Table 3). Having insomnia was associated with worse asthma-specific quality of life. With adjustment for age, sex, BMI, oral corticosteroid use,

GERD, and sleep apnea, all relationships remained statistically significant (Table 3), although the magnitude of the estimates was slightly reduced. More specifically, those with insomnia had a 2.4-fold greater odds of having not well-controlled asthma (95% CI, 1.7-3.4; P < .001), 3.5-fold greater odds of having probable depression (95% CI, 2.1-5.8; P < .001), 4.6-fold odds of having probable anxiety (95% CI, 3.2-6.6; P < .001), and 1.5-fold odds of having asthma-related health care utilization (95% CI, 1.0-2.0; P = .03) compared with those without insomnia.
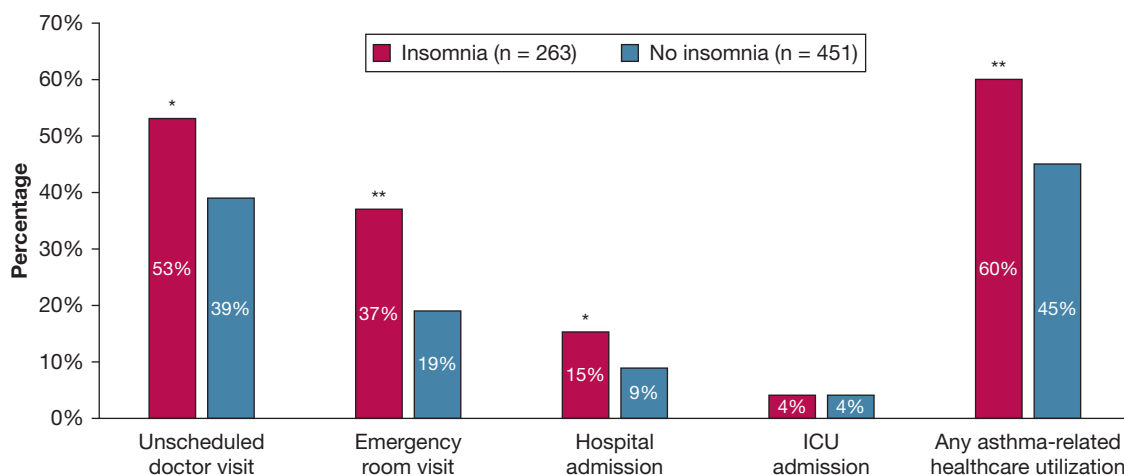

Figure 1 – Proportions of asthma-related health care utilization in the past 12 months in participants with asthmas and with or without insomnia (defined as score on the Insomnia Severity Index ≥ 10). *P < .01. **P < .001.
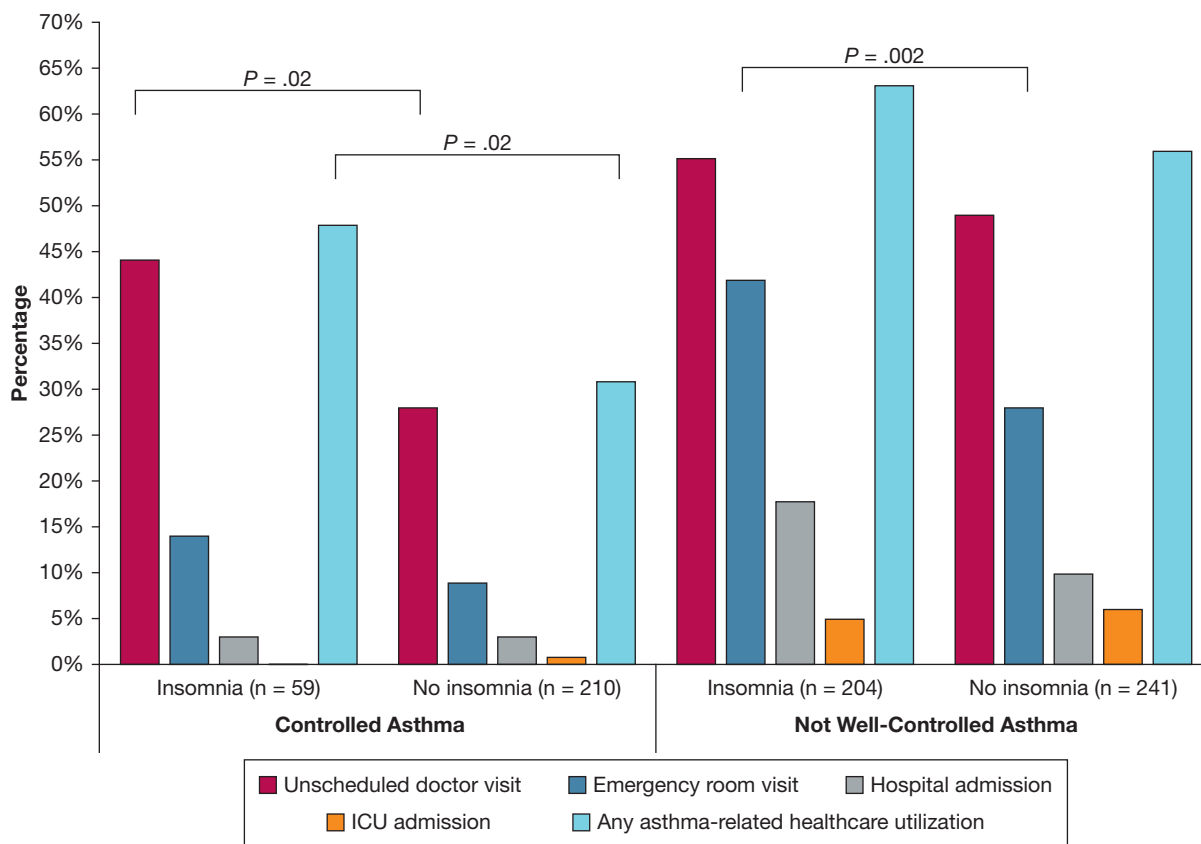
Figure 2 – *Proportions of asthma-related health care utilization in the past 12 months in participants with asthma and with or without comorbid insomnia (defined as score on the Insomnia Severity Index ≥ 10) by asthma control (defined by the Asthma Control Test: < 19 = controlled asthma; ≤ 19 = not well-controlled asthma).*

Discussion

In this study, we examined the prevalence of insomnia disorder in a large sample of adults with physician-diagnosed asthma and its associations with asthma control and disease-specific health care utilization. The prevalence of insomnia disorder was found to be approximately three times higher than rates reported in the general population.[26] Presence of insomnia was associated with higher levels of depression and anxiety symptoms, worse asthma control, poorer quality of life, and more frequent asthma-related health care utilization. These results suggest that adults with asthma who have insomnia disorder may be at increased risk for adverse outcomes.

TABLE 3] Associations of Insomnia[a] With Asthma Control, Well-Being, and Asthma-Related Health Care Utilization

Variable	Univariate Analyses[b]		Multivariate Analyses[b,c]	
	β or OR (95% CI)	P Value	β or OR (95% CI)	P Value
Not well-controlled asthma[d]	3.01 (2.14-4.25)	< .001	2.40 (1.67-3.44)	< .001
AQLQ total score	−0.38 (−1.18 to −0.82)	< .001	−0.28 (−0.92 to −0.57)	< .001
Probable depression[e]	4.47 (2.77-7.21)	< .001	3.52 (2.13-5.82)	< .001
Probable anxiety[f]	4.53 (3.23-6.37)	< .001	4.62 (3.21-6.63)	< .001
Asthma-related health care utilization in past year	1.84 (1.35-2.51)	< .001	1.45 (1.04-2.03)	.03

See Table 1 and 2 legends for expansion of abbreviations.
[a]ISI score ≥ 10.
[b]Analyses used linear regression (for continuous dependent variable: AQLQ total score) or logistic regression (for dichotomous dependent variables).
[c]Adjusted for age, sex, BMI, oral corticosteroid use in past 3 mo, GERD, and sleep apnea.
[d]Poor asthma control, ACT total score ≤ 19.
[e]Probable depression, HADS depression total score ≥ 8.
[f]Probable anxiety, HADS anxiety total score ≥ 8.

The high prevalence of insomnia in patients with asthma (37%) confirms prior reports of disturbed sleep in asthma.[7-12] A key strength of our study is that it assessed the prevalence of insomnia symptoms and associated daytime consequences that encapsulate the diagnostic criteria presented in the International Classification of Sleep Disorders-Third Edition.[27] Our findings indicate that poor sleep may not be entirely related to nocturnal awakenings resulting from asthma symptoms.[7,10,12] Despite reporting no nighttime asthma symptoms that disturbed their sleep, almost 25% of participants met criteria for clinically significant insomnia.

Our results strengthen previous findings in patients with asthma in which disturbed sleep was associated with greater depression and anxiety and lower disease-specific quality of life.[10,11,28,29] Studies in patients with asthma, including severe asthma, that used the HADS, found rates of depression and anxiety to be 9% to 14% and 11% to 37%, respectively,[29,30-32] which are lower than the prevalence rates found in participants with asthma and insomnia. The AQLQ score in participants with asthma and no insomnia were similar to the score found in a population-based study of 864 adults with asthma.[33] The presence of insomnia in patients with asthma may lead to more severe depression and anxiety symptoms and further reductions in quality of life.

The current study provides further evidence for an association between sleep difficulties and asthma control and builds upon this evidence by also examining asthma-related health care utilization. We found a 2.4-fold increased risk for having not well-controlled asthma and a 1.5-fold increased risk for asthma-related health care utilization in the past year in participants with insomnia relative to those without insomnia. Furthermore, participants with well-controlled asthma and insomnia had more frequent unscheduled doctor visits and overall disease-specific health care use than those with well-controlled asthma without insomnia. This suggests that comorbid insomnia may play an important role in asthma outcomes. Although the potential mechanisms whereby insomnia may aggravate asthma have not been explored, sleep loss and sleep

difficulties (similar to insomnia) have been shown to decrease lung function and increase systemic inflammation.[34-37] We found worse lung function (FEV_1 percent predicted and FVC percent predicted predicted) among those with insomnia compared with those without insomnia.

The study has several limitations. First, the cross-sectional nature of the data precludes causal inferences. The interaction between insomnia and asthma is likely to be bidirectional; however, intervention studies, such as implementing cognitive-behavioral treatment for insomnia, are needed to provide more insight into the likely complex relationship between insomnia and asthma control. Second, the assessment of GERD and sleep apnea were based on self-report rather than gold standards to diagnose GERD and sleep apnea; thus, we may not have captured all individuals with GERD or sleep apnea. Third, we did not have a matched control group free of respiratory disease, which would have allowed for comparison of insomnia prevalence between those with asthma and those without respiratory disease. Finally, other potential contributing factors to asthma control and asthma-related health care utilization, including recurrent respiratory infections, could have influenced the results.

Conclusions

We have demonstrated that insomnia is highly prevalent in adults with asthma and is associated with worse asthma control, higher prevalence of depression and anxiety symptoms and worse disease-specific quality of life, and more frequent asthma-related health care utilization independent of oral corticosteroid use and relevant comorbidities, including sleep apnea and GERD. Prospective and intervention studies are needed gain a deeper understanding of the interaction between insomnia and asthma control and the possible underlying mechanisms. Our study demonstrated a significant impact of comorbid insomnia on disease burden and well-being; therefore, evaluation and treatment of insomnia should be considered among patients with asthma.

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