Self-Reported Insufficient Sleep Is Associated With Clinical and Inflammatory Features of Asthma: A Prospective Cohort Study

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INTRODUCTION

Asthma is a common, chronic inflammatory airway disease affecting 1% to 18% of the population in different countries and is characterized by variable symptoms such as wheezing, shortness of breath, and chest tightness with or without coughing and with variable expiratory airflow limitation.1 These symptoms frequently disrupt sleep in adult patients with asthma, who are more likely to experience a variety of sleep disorders such as difficulty falling asleep, nocturnal awakening, early morning awakening, decreased subjective sleep quality, and increased daytime sleepiness.1,2 Sleep has an important role in promoting health.3 Short sleep duration is prevalent worldwide and is associated with a significant increase in important adverse health outcomes.4,5 Previous epidemiologic investigations indicated that short sleep duration is associated with a high risk for all-cause mortality and morbidity, including type 2 diabetes mellitus, obesity, hypertension, and coronary heart disease in the general population.5-8 Moreover, short sleep duration is potentially associated with certain allergic diseases, such as asthma and eczema.9,10

In recent years, a few studies found that patients with short sleep duration may have worse patient-reported asthma outcomes, including a high risk for asthma prevalence, more previous asthma-related attacks, poorer health-related quality of life, and increased general health care use.11-14 However, those findings were based on a cross-sectional design. In addition, asthma was defined by patient self-reports. Despite a large sample of self-reported asthma cases from public databases, some may be misdiagnosed. Aaron et al15 indicated that 33% of diagnoses in adults with physician-diagnosed asthma could no longer be confirmed as asthma after reassessment. To data, no prospective cohort study has elucidated the relationship between sleep duration and asthma exacerbations (AEs).

Therefore, we designed this prospective cohort study to investigate the association between sleep duration and asthmarelated clinical and inflammatory characteristics. We then explored whether sleep duration was associated with poorly controlled asthma at baseline or AEs over a 12-month follow-up.

METHODS Study design and participants

This was a 1-year prospective cohort study in a real-world setting based on the Australasian Severe Asthma Network.16 We consecutively assessed a total of 546 Chinese participants aged more than 18 years with stable asthma from the Asthma Clinic of the West China Hospital at Sichuan University, between January 2015 and September 2019 (Figure 1).

Asthma was diagnosed in accordance with American Thoracic Society17 and Global Initiative for Asthma (GINA)1 guidelines, which define asthma as a history of variable respiratory symptoms (such as wheezing, shortness of breath, and chest tightness with or without coughing) and variable expiratory airflow limitation. The variable expiratory airflow limitation was confirmed by either a positive bronchial challenge test or bronchodilator responsiveness with more than a 12% and 200-mL increase in FEV1

after a shortacting b2-agonist treatment.1 Stable asthma was defined as no respiratory tract infection and exacerbation or no change in maintenance therapy in the previous 4 weeks.18 Inability to understand the questionnaires or perform spirometry or sputum induction, as well as pregnancy and breastfeeding were listed as exclusions.
Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of West China Hospital at Sichuan University, Chengdu, China (No. 2014e30) and registered in the Chinese Clinical Trial Registry (ChiCTR-OOC-16009529; http://www.chictr.org.cn).

Sleep duration assessment

We assessed sleep duration through the patient self-reported question "How many hours of sleep do you usually get per night on average?" Patients were divided into three groups based on selfreported habitual sleep duration at study entry: short sleep duration group (<6 h/night), normal sleep duration group (6-8 h/night), and long sleep duration group (>8 h/night).11,19-21

Data collection and clinical multidimensional assessments

Multidimensional assessments were performed in patients with stable asthma, as described in our previously published studies.22,23 Further detailed assessments, including demographics, anthropometrics, atopy, health status, FeNO, and spirometry are provided in the Supplemental Methods (in this article's Online Repository at www.jaci-inpractice.org).

Blood collection and processing

We collected fasting intravenous blood samples to analyze complete blood cell counts and serum total IgE. Details regarding blood processing are provided in the Supplemental Methods.

Sputum induction, processing, and analysis

We performed sputum induction using routine standard methods, as described in our previous study.24 Total and differential sputum cell counts and sputum inflammatory biomarkers, including IL-1b, IL-4, IL-5, IL-6, IL-8, IL-13, IL-17A, TNF-a, and IFNgamma, were measured. Detailed information is provided in the Supplemental Methods.

Definitions of asthma phenotypes

Eosinophilic asthma was defined as 3% or greater sputum eosinophils or 0.3109 cells/L or greater blood eosinophils if sputum was unavailable.25,26 Late-onset asthma was defined as age of asthma onset of 12 years or greater.27 Type 2 asthma was defined when two or more of these factors were present: (1) 150 cells/mL or greater blood eosinophil count, (2) 2% or greater sputum eosinophils, (3) 30 parts per billion (ppb) or greater FeNO, or (4) atopy.1,28 Otherwise, it was classified as nonetype 2 asthma.
Asthma severity was classified as mild, moderate, or severe based on the GINA guidelines.29 Severe asthma was defined as asthma that requires GINA step 4 to 5 treatment regimens, requiring moderate to high doses of inhaled corticosteroids (ICS) to prevent it from becoming uncontrolled, or asthma that remains uncontrolled for at least 6 months despite this treatment.29 Moderate asthma is wellcontrolled with step 3 treatment, such as low-dose ICS/long-acting b-agonist (ICS/LABA).29 Mild asthma is well-controlled with step 1 or 2 treatment, such as as-needed reliever medication alone or lowintensity controller treatment, including low-dose ICS, leukotriene receptor antagonists, or chromones.29

Primary outcomes

Asthma control at baseline. We assessed asthma control at baseline using the Asthma Control Questionnaire (ACQ), with an ACQ of 0.75 or less indicating well-controlled asthma, 0.75 to 1.5 partly controlled asthma, and 1.5 or greater poorly controlled asthma.30

Asthma exacerbations within 1-year follow-up. All patients underwent face-to-face or telephone interviews (if unavailable to attend) during the 12-month follow-up on a regular basis to collect data on moderate to severe AEs. Patients with asthma were invited to visit the Asthma Clinic of West China Hospital at Sichuan University at baseline (visit 1) and at 1 month (visit 2), 3 months (visit 3) after baseline; they underwent face-toface or telephone interviews (if unavailable to attend) at 6 months (visit 4) and 12 months (visit 5) after baseline (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Asthma exacerbations were defined based on the American Thoracic Society/European Respiratory Society statement.31 Moderate AE was defined as a deterioration in symptoms and lung function and increased rescue bronchodilator use, with a duration of 2 days or more, but not severe enough to warrant systemic corticosteroid use.31 Severe AE was defined as worsening of asthma symptoms leading to at least one of the following: temporary use of systemic corticosteroids or an increase from a stable maintenance dose for at least 3 days; or hospitalization or an emergency department or intensive care unit visit for asthma requiring systemic corticosteroids.31

Secondary outcomes

Secondary outcomes included asthma-related clinical and inflammatory characteristics, including systemic inflammatory markers, airway inflammatory markers, and asthma phenotypes.

Statistical analysis

Categorical variables are expressed as frequencies and proportions. Continuous variables are presented as means (SDs) or medians (quartiles 1 and 3) according to the data distribution. Differences between groups were analyzed with ANOVA or Kruskal-Wallis test for continuous variables and c2 or Fisher exact test for categorical variables, as appropriate. In addition, we analyzed multiple comparisons between groups using Bonferroni or Dunn's test, according to their distribution.

We used logistic regression to assess the association between sleep duration and poorly controlled asthma at baseline. Adjusted odds ratios with 95% CIs were calculated by adjusting for sex, age, body mass index (BMI), smoking status, atopic status, medication (ICS/ LABA) use, severe AE (SAE) in previous years, FEV1 % predicted, and severe asthma. Furthermore, we used a negative binomial regression model to evaluate relationships between sleep duration and AEs during the follow-up year by adjusting for confounders including sex, age, BMI, smoking status, atopic status, medication (ICS/LABA) use, SAE in previous years, FEV1 % predicted, and severe asthma. Detailed information about the multicollinearity issue tests in the multivariable regression is provided in the Supplemental Methods.

Data were analyzed using the Statistical Package for Social Sciences (version 26.0, IBM Corp, Armonk, NY). Two-sided P less than .05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics

In total, 522 patients were assessed for eligibility. Of them, 58, 380, and 84 patients were classified into the short (<6 h/ night), normal (6-8 h/night), and long (>8 h/night) sleep duration groups, respectively (Figure 1).

Table I lists the demographic and clinical characteristics of the patients, grouped according to sleep duration. Compared with patients in the normal sleep duration group, those in the short sleep duration group had more older patients (53.0 [43.0, 63.3] vs 44.0 [34.0, 53.0] years; P < .001). However, no statistically significant difference was observed in FEV1 % predicted among the three groups. Intriguingly, the long sleep duration group had a greater proportion of atopy and a lower proportion of ICS/ LABA use than the normal sleep duration group (51.9% vs 36.2%; P < .05; and 44.0% vs 60.3%; P < .05, respectively). No statistically significant differences were found in BMI, health status (Asthma Quality of Life Questionnaire scores), and comorbidities among the three groups.

Systemic and airway inflammation

No significant differences in counts or percentages of peripheral blood granulocytes (including total cells, eosinophils, neutrophils, lymphocytes, monocytes, and basophils) were observed among the three groups (all P > .05) (Table II). Patients in the short sleep duration group had lower serum total IgE levels than those in the normal sleep duration group (76.63 [36.89, 166.34] vs 146.00 [53.00, 333.00] IU/mL; P ¼ .019) (Table II).

Interestingly, patients in the normal sleep duration group had higher FeNO levels than those in the short and long sleep duration groups (41.00 [22.00, 76.00] vs 25.00 [12.75, 58.75] ppb; P ¼ .006; and 41.00 [22.00, 76.00] vs 32.00 [16.00, 49.00] ppb; P ¼ .048, respectively) (Table II). However, no significant differences in counts or percentages of sputum granulocytes (including total cells, eosinophils, neutrophils, lymphocytes, and macrophages) (all P > .05) were observed among the three groups (Table II). Patients in the short sleep duration group had significant airway inflammation, characterized by higher sputum levels of IL-6 and TNF-a, compared with patients in the normal sleep duration group (53.52 [23.71, 91.69] vs 16.41 [4.94, 43.75] pg/mL; P ¼ .006; and 24.75 [6.09, 59.05] vs 8.90 [3.76, 26.46] pg/mL; P ¼ .020, respectively) (Figure 2).

Asthma phenotype and sleep duration

A lower proportion of patients with type 2 asthma was found in the short sleep duration group compared with in the normal and long sleep duration groups (44.8% vs 69.7% vs 64.3%; P ¼ .001) (Table I). No differences in proportions were observed for eosinophilic asthma, late-onset asthma or severerity of asthma among the three groups (Table I).

Primary outcomes

Association of sleep duration with asthma control at baseline. Although we observed no difference in ACQ score among the three groups, the short sleep duration group had a greater proportion of poorly controlled asthma compared with the normal sleep duration group (41.4% vs 23.7%; P < .017) (Table I). We further explored the association between poorly controlled asthma (ACQ 1.5) and sleep duration using a logistic regression model with or without adjusting for confounders including sex, age, BMI, smoking status, atopic status, medication (ICS/LABA) use, SAE in previous years, FEV1 % predicted, and severe asthma. Short sleep duration was significantly associated with poorly controlled asthma (odds ratio [95% CI] ¼ 2.275 [1.282, 4.036], P ¼ .005; adjusted odds ratio [95% CI] ¼ 2.741 [1.379, 5.447], P ¼ .004) (Figure 3).

Sleep duration and risk for moderate to severe AEs within 1-year follow-up. We analyzed 491 patients (94.1%) who completed the 1-year follow-up in a real-world setting. There were 363, 53, and 75 patients in the normal, short, and long sleep duration groups, respectively. Of them, 132 patients (26.9%) experienced moderate to severe AEs at the 1year follow-up. No significant difference in the incidence and frequency of moderate to severe AEs was observed among the three groups (Table III). However, the adjusted incidence rate ratio of moderate to severe AEs in the following 12 months was 1.798 (95% CI, 1.098-2.942) in patients with short sleep duration compared with those in the normal sleep duration group after controlling for sex, age, BMI, smoking status, atopic status, medication (ICS/LABA) use, SAE in previous years, FEV1 % predicted, and severe asthma (Figure 4). Moreover, we found no multicollinearity issues in the multivariable regression models (see Figure E1 and Table E2 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

To the best of our knowledge, this is the first prospective cohort study to assess the association between sleep duration and asthma. We found that patients with short sleep duration were older, had lower serum total IgE and FeNO levels, and had elevated IL-6 and TNF-a levels in the induced sputum, which exhibited nonetype 2 inflammation compared with patients with normal sleep duration. Patients with short sleep duration had a significantly increased risk for poorly controlled asthma and moderate to severe AEs. Therefore, sleep duration may be a potentially treatable trait in the clinical relevance of asthma management.

Our study confirmed a U-shaped relationship between sleep duration and FeNO levels in patients with stable asthma. Two previous studies reported consistent results regarding the association between sleep duration and FeNO levels in adults. Yang et al11 showed that both short and long sleep durations were associated with lower FeNO levels in US adults. Moreover, Hu et al12 demonstrated that patients with self-reported asthma and healthy sleep duration had higher FeNO levels than those with short and long sleep durations. A possible mechanism is that short sleep duration changes the autonomic nervous system balance toward sympathetic predominance, which further leads to endothelial-dependent vasodilator dysfunction and a reduction in NO bioavailability.4,32,33 Since previous studies indicated a clear association between high FeNO levels and a greater likelihood of responding to ICS,34,35 patients with asthma and short sleep duration may have a greater insensitivity to ICS.34,35 Moreover, in our study, we found increased airway inflammatory biomarkers, including IL-6 and TNF-a, in patients with asthma and short sleep duration compared with those with asthma and normal sleep duration. This is consistent with the findings of previously published experimental studies. Irwin et al36 showed that night sleep loss induced more than a threefold increase in IL-6 and a twofold increase in TNF-a gene transcription. In addition, Sauvet et al37 demonstrated a persistently evaluated concentration of whole blood TNF microRNA during 6 days of sleep restriction and 12 days of recovery compared with baseline. However, those studies were based on healthy participants to explore the association between circulating inflammatory markers and sleep duration. To our knowledge, no studies have elucidated the relationship between airway inflammation and sleep duration in patients with asthma. In general, sleep affects two major effector systems: the sympathetic nervous system and the hypothalamicepituitaryeadrenal axis.38 Therefore, sleep loss may alter the

molecular signaling pathways that drive cellular immune activation and induce inflammatory cytokines,36 which may lead to increased airway inflammatory biomarkers in patients with asthma and short sleep duration.

Furthermore, we demonstrated that short sleep duration was associated with poorly controlled asthma after adjusting for confounders. A previous study showed that poorly controlled asthma had a significant impact on sleep in children.39 Notably, short sleep duration had a negative impact of on asthma control. Our study demonstrated that patients with short sleep duration had more poorly controlled asthma, and short sleep duration is associated with an increased risk for poor asthma control. These observations may have resulted for the following reasons. Patients with short sleep duration had higher levels of inflammatory factors, such as IL-6 and TNF-a, and lower FeNO levels compared with patients with normal sleep duration, which may reduce responsiveness to corticosteroids in patients with asthma.34,35,40-42 The association between sleep duration and poorly controlled asthma may be bidirectional. Poorly controlled asthma is associated with somatic symptoms, respiratory physiology abnormalities, and inflammation, which may be associated with short sleep duration in these patients.1,43-46 On the other hand, patients with short sleep duration may have a high nonetype 2 inflammatory burden (ie, IL-6 and TNF-a), driving an insensitive response to corticosteroids, which may contribute to the detrimental effects of short sleep duration on poor asthma control.36,40-42 The detailed mechanisms of the bidirectional association between short sleep duration and poorly controlled asthma need to be studied further.

Our study found that patients with short sleep duration had an increased risk for future moderate to severe AEs. Previous cross-sectional studies found that patients with self-reported asthma and short sleep duration had more asthma-related episodes or attacks and emergency department visits in the previous year.13,14 Our study further strengthens the evidence linking short sleep duration and future moderate to severe AEs in a 1-year prospective cohort study. Patients with short sleep duration had a higher proportion of poorly controlled asthma at baseline compared with those with normal sleep duration, who were more likely to have more AEs in the following year, as described in our previous study.47 Moreover, the short sleep duration group had lower FeNO levels, which may lead to a lower response to corticosteroids.34,35 Furthermore, increased airway inflammation, such as IL-6 and TNF-a, in patients reporting short sleep duration correlated with an increased risk for future AEs.48,49

Short sleep duration is a global health problem.3,38 Several biological mechanisms have been proposed as possible links between short sleep duration and asthma, as mentioned earlier. Physicians should consider sleep duration as a potentially behavioral treatable trait in patients with asthma and short sleep duration, and future research should focus on therapeutic interventions to improve sleep in these patients. If supported by future evidence, interventions to help sleep duration and quality can be an important and simple preventive strategy with potentially beneficial effects on the overall health of patients with asthma and short sleep duration. Sleep duration may be a modifiable behavioral trait or risk factor,50 which would benefit from tailored behavioral interventions to improve asthma control and reduce future AEs.

Our study has several strengths. First, the assessment methods included blood processing and sputum induction and had standard procedures according to the

Australasian Severe Asthma Network program.16 In addition, it exhibited higher comparability between patients with asthma among the three sleep duration groups because all of the patients included in our study underwent face-to-face or telephone interviews (if unavailable to attend) to collect data on AEs during the 12-month follow-up on a regular basis and were provided with standardized asthma management according to the general principles of GINA.

This study has some limitations that need to be addressed. First, sleep duration was measured based on patient self-report rather than polysomnography. Although polysomnography is considered the reference standard for quantifying sleep, it has several obvious disadvantages, including resource-intensive consumption, a high cost, discomfort, limited availability, and limited accuracy of interrater interpretation.51,52 According to the National Sleep Foundation's updated sleep duration recommendations,19 sleep data from large cohort studies characteristically involve self-report, which is easily accessible and applicable.5 A previous prospective cohort study published by the Sleep Research Society53 demonstrated that total sleep duration had moderate long-term stability in 2 nights with a gap of 2.6 years between visits (interclass correlation coefficient ¼ 0.50; P < .001). Second, we did not collect data on other potential confounders, including insomnia, sleep quality, and sleep hygiene, which may disturb the relationships between sleep duration and asthma-related clinical and inflammatory characteristics. Third, the sample size was relatively small, and only Chinese people were included in our study. Further large-sample studies are warranted to validate our findings, which would be of great relevance to clinical practice. Fourth, although our prospective cohort study demonstrated that short sleep duration at baseline was associated with poorly controlled asthma and AEs, short sleep duration could also be a consequence of poorly controlled asthma leading to insufficient sleep, forming a vicious circle.2,36,37

CONCLUSION

This study found that patients with short sleep duration were older and had decreased serum total IgE and FeNO levels and elevated IL-6 and TNF-a levels in the induced sputum, characterized as nonetype 2 inflammation. Moreover, short sleep duration was associated with poor asthma control and was an independent risk factor for future moderate to severe AEs. This study suggests that sleep duration may be a potentially treatable trait for asthma management, which may benefit from tailored behavioral interventions to improve asthma control and reduce future AEs.

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