Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Nocturnal symptoms perceived as asthma are associated with obstructive sleep apnoea risk, but not bronchial hyper-reactivity

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ABSTRACT

Background and objective: **Obstructive sleep apnoea (OSA) and asthma are associated, and nocturnal breathing difficulty that is usually identified as asthma-like symptoms can be present in both conditions. We investigated how nocturnal asthma-like symptoms (NAS) and bronchial hyper-reactivity (BHR) contribute to the association between OSA risk and current asthma, which is currently unknown but a clinically important question.**

Methods: **We used data from 794 middle-aged participants in a population-based cohort who provided information on OSA risk (defined by a STOP-Bang questionnaire score of at least 3), current asthma and NAS, and underwent methacholine bronchial challenge testing. Using regression models, we examined the association between OSA risk and current asthma-NAS subgroups and investigated any effect modification by BHR.**

Results: **The participants were aged 50 years (49.8% male). OSA risk was associated with NAS with or without current asthma (odds ratio (OR): 2.6; 95% CI = 1.3–5.0; OR: 4.2; 95% CI = 1.1–16.1, respectively), but not with current asthma in the absence of NAS. BHR was associated with current asthma with or without NAS (OR: 2.9; 95% CI = 1.4–5.9; OR: 3.4; 95% CI = 2.0–7.0, respectively) but not with NAS in the absence of current asthma. The associations between OSA risk and current asthma were neither modified nor mediated by BHR.**

Conclusion: **Our findings suggest that some of the nocturnal symptoms perceived as asthma may be OSA symptoms. Patients with nocturnal asthma symptoms should be considered for possible OSA.**

SUMMARY AT A GLANCE

We assessed the roles of nocturnal asthma-like symptoms (NAS) and bronchial hyper-reactivity (BHR) in obstructive sleep apnoea (OSA)–asthma association. OSA is associated with NAS with or without the presence of asthma, but BHR is not associated with NAS when asthma is absent. Some NAS perceived as nocturnal asthma could be symptoms of OSA.

Key words: airway resistance, asthma, bronchial hyper-reactivity, sleep apnoea syndromes, sleep apnoea, obstructive.

INTRODUCTION

Obstructive sleep apnoea (OSA) is common[1] and associated with asthma[2] that is better controlled when coexisting OSA is treated.[2] Nocturnal breathing difficulty is common to both, which may partly contribute to this link. Evidence on whether nocturnal breathing symptoms are shared by asthma and OSA, however, is limited. Clarifying this is important to facilitate clinical decision-making related to potential further investigation for one disease in the presence of the other.

Another area of uncertainty is the link between OSA and bronchial reactivity.[3] Asthma is characterized by reversible airflow obstruction due to inflammatory changes and smooth muscle contraction in bronchi.[4–6] Excessive reactivity of bronchi (bronchial hyper-

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Received 23 May 2018; invited to revise 15 July and 3 November 2018, 26 February 2019; revised 1 October 2018, 28 January and 9 April 2019; accepted 15 April 2019
Associate Editor: M. Safwan Badr; Senior Editor: Fanny Ko

responsiveness or bronchial hyper-reactivity (BHR))[7] can be elicited by a challenge test using inhaled methacholine (MCh)[8] and is associated with asthma.[9] A possible association between OSA and BHR has been suggested, which may be partly due to association of asthma with both BHR and OSA, and partly due to inflammatory changes in airways that are seen in both asthma and OSA which would likely facilitate BHR.[10,11] BHR has also been proposed as a possible mediator of the association between asthma and OSA,[10] but supportive evidence is scarce.

Given these gaps in knowledge, we investigated the association between OSA risk and asthma in the presence or absence of nocturnal asthma-like symptoms (NAS) in a middle-aged population-based sample. We also investigated whether these associations are mediated or modified by BHR.

METHODS

Details of the Tasmanian Longitudinal Cohort Study (TAHS) have previously been published.[12,13] Out of a subgroup of TAHS that is enriched for asthma and selected at 43 years of age (n = 2397), 57.7% (n = 794) completed a survey and a full laboratory assessment at 53 years of age.

Survey questions included STOP-Bang questionnaire (STOP-Bang)[14] to determine OSA risk and validated questions to detect asthma.[15] Eight-item STOP-Bang (each item scored 0 or 1; total 0–8) can also be used in an ordinal scale, where higher scores predict higher probability of severe OSA.[16] At laboratory visit, lung function was measured using EasyOne Ultrasonic Spirometer (Ndd Medizintechnik AG, Zürich, Switzerland) and a standard MCh inhalational challenge test[17] was administered. Pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured according to joint American Thoracic Society and European Respiratory Society guidelines.[18] MCh was delivered by a dosimeter until FEV_1 fell by 20% from the initial value or up to a cumulative dose of 2 mg.

This study was conducted in accordance with the Declaration of Helsinki and was approved by Human Research Ethics Committee of the University of Melbourne (approval number 040375). Participants provided written informed consent.

Definitions

OSA risk was defined as a STOP-Bang score ≥ 3[14,19]using validated scoring format.[16]

Likelihood of more severe OSA was defined by STOP-Bang score on an ordinal scale.

Current asthma was defined as affirmative responses to one or more of following questions: (i) Have you had an attack of asthma or wheezy breathing in the last 12 months?; (ii) Have you taken any medicines including inhalers or tablets for asthma or wheezy breathing in the last 12 months?; and (iii) Have you had wheezing or whistling in your chest in the last 12 months?.

NAS was defined as been woken due to one or more of the following in the past 12 months: (i) feeling of tightness in chest, (ii) an attack of shortness of breath or (iii) asthma.

Current asthma with NAS was defined as the presence of both current asthma and NAS.

Current asthma without NAS was defined as the presence of current asthma but not NAS.

NAS without current asthma was defined as the presence of NAS but not current asthma.

Neither current asthma nor NAS was defined as absence of current asthma as well as NAS.

Degree of bronchial reactivity was expressed as change in log dose–response slope (LogDRS) per % change of FEV_1 from baseline to when last dose of MCh was administered divided by cumulative dose of MCh (mg) administered.[20]

BHR was identified by a cumulative dose of MCh provoking a 20% fall in FEV_1 from post-saline FEV_1 (PD_{20} FEV_1) $\leq$ 2 mg.

FVC and FEV_1 were derived from the best values for FEV_1 and FVC out of three attempts made.

Statistical analysis

We used survey weights to account for the sampling method.[21] We examined associations between OSA risk (as exposure) and current asthma/current asthma-NAS subgroups (as outcomes) using multinomial logistic regression and presented as odds ratios (OR) with 95% CI. We investigated the role of BHR in these associations as a mediator (using percentage mediated) or an effect-modifier (considered significant if $P < 0.1$).[22–24] Logistic and linear regression models were used to determine association between OSA risk (exposure) and BHR (outcome), and between OSA risk and degree of bronchial reactivity, respectively, and reported for those with and without current asthma as an a priori decision. Possible effect modification and confounding of these associations by smoking was examined (considered significant if $P < 0.1$ and <0.05, respectively). Sensitivity analysis of models were done defining OSA risk using the OSA-50[25] questionnaire to minimize gender effect on OSA classification and excluding those who were on asthma/allergy medications (Appendix S1, Table S1, Supplementary Information) during the past 1 month.

As age, sex and body mass index (BMI) were already considered within STOP-Bang score, we compared our analytical models with and without these factors as confounders. Their inclusion in regression models did not change the results except for widening the CI.

RESULTS

Mean $\pm$ SD age of the sample was 49.6 $\pm$ 0.6 years and 49.8% were male. Other basic characteristics and the prevalence of OSA, current asthma-NAS subgroups and BHR are shown in Table 1. The distribution of current asthma-NAS subgroups among those with current asthma and those with OSA risk is shown in Table 2. FEV_1/FVC ratio was significantly lower in those who had current asthma without NAS but not in those with NAS regardless of presence/absence of current asthma, compared to those with neither condition (Table S2,

Table 1 Sociodemographic and clinical information of the sample

Characteristic		*n* (%†) or mean ± SD
Age		49.6 ± 0.6
	>50 years	223 (27.2)
Sex	Males	408 (49.8)
BMI (kg/m^2)		27.9 ± 5.1
	Normal (<25)	231 (29.5)
	Overweight (25 to < 30)	329 (41.9)
	Obese (≥30)	224 (28.6)
Waist–hip ratio		0.9 ± 0.09
OSA risk‡		241 (32.9)
Current asthma		266 (62.2)
Asthma-NAS subgroups	No current asthma or NAS	91 (28.8)
	Current asthma with NAS	81 (25.5)
	Current asthma without NAS	131 (41.3)
	NAS without current asthma	14 (4.4)
Degree of bronchial reactivity (change in LDRS)		2.4 ± 1.4
BHR		134 (19.6)
Current smoking		130 (15.9)
Doctor-diagnosed COPD		3 (0.4)
Marital status	Never married	80 (9.8)
	Widowed/divorced/separated	101 (12.4)
	De facto relationship/married	638 (77.8)

†Percent out of the valid responses.

‡95.3% (*n* = 28) of those who reported having doctor-diagnosed OSA (*n* = 29) were correctly identified by STOP-Bang questionnaire as having OSA risk.

BHR, bronchial hyper-reactivity (PD_{20} < 2 mg MCh; see text); BMI, body mass index; FEV_1, forced expiratory volume in 1 s; LDRS, log dose–response slope for MCh bronchial challenge test (per %change in FEV_1 per MCh(mg)); MCh, methacholine; NAS, nocturnal asthma-like symptom; OSA, obstructive sleep apnoea.

Supplementary Information). There was no difference in mean pre-bronchodilator FEV_1/FVC ratio between those with and without OSA risk. Similarly, FEV_1/FVC ratios in both these groups were similar to the ratios in those who had NAS without current asthma and those who did not have current asthma or NAS.

OSA risk and asthma-NAS subgroups

Current asthma was associated with OSA risk (OR: 1.6; 95% CI: 1.1–2.5; P = 0.027) and likelihood of more severe OSA (OR: 1.2 per unit increase in STOP-Bang score; 95% CI: 1.1–1.4; P = 0.005). Both OSA risk and likelihood of more severe OSA were associated with increased risk of NAS regardless of current asthma status (Table 3) but were not associated with current asthma without NAS. These findings were largely consistent when those who were on respiratory medication were excluded from analysis (Table S3, Supplementary Information) and when the OSA-50[25] questionnaire was used instead of STOP-Bang (Table S4, Supplementary Information). There was modest evidence that association observed between OSA risk and current asthma with NAS was significantly stronger (P < 0.06) than any association between OSA risk and current asthma without NAS.

Table 2 Distribution of current asthma-NAS subgroups by current asthma status and high risk for OSA

	No current asthma	Current asthma	No OSA risk	OSA risk
Current asthma-NAS subgroups	*n* (%)	*n* (%)	*n* (%)	*n* (%)
No current asthma or NAS	90 (86.8)	0 (0.0)	59 (33.2)	22 (21.2)
Current asthma with NAS†	0 (0.0)	81 (38.2)	38 (21.4)	35 (33.8)
Current asthma without NAS	0 (0.0)	130 (61.8)	77 (43.4)	38 (36.3)
NAS without current asthma‡	14 (13.2)	0 (0.0)	4 (2.0)	9 (8.7)
Total	104 (100.0)	211 (100.0)	178 (100.0)	104 (100.0)

†Contribution of individual NAS to this category was 32% tightness in the chest, 17% shortness of breath and 51% perceived asthma.

‡Contribution of individual NAS to this category was 47% tightness in the chest, 47% shortness of breath and 6% perceived asthma.

NAS, nocturnal asthma-like symptom; OSA, obstructive sleep apnoea.

Table 3 Association of OSA risk and likelihood of more severe OSA with current asthma-NAS subgroups

Current asthma-NAS subgroup	OSA risk[†]	Likelihood of more severe OSA[‡]
	OR (95% CI)	OR[§] (95% CI)
No current-asthma or NAS (base group)	1.0	1.0
Current-asthma without NAS	1.6 (0.9, 2.9)	1.2 (1.0, 1.4)
Current-asthma with NAS	2.6 (1.3, 5.0)**	1.5 (1.2, 1.8)**
NAS without current-asthma	4.2 (1.1, 16.1)*	1.8 (1.2, 2.6)**

*$P < 0.05$; **$P < 0.01$.

[†]Defined as STOP-Bang score ≥ 3.

[‡]Defined as ordinal increase in the STOP-Bang score from 0 to 8.

[§]Per one-unit increase in the STOP-Bang score.

NAS, nocturnal asthma-like symptom; OR, odds ratio; OSA, obstructive sleep apnoea; STOP-Bang, STOP-Bang questionnaire.

The strength of association (OR) between likelihood of more severe OSA and current asthma with NAS was also significantly higher than that between likelihood of more severe OSA and current asthma without NAS ($P = 0.017$). Association of OSA risk with individual nocturnal symptoms are shown in Table S5 (Supplementary Information), and those for males and females in Table S6 (Supplementary Information).

Dichotomized BHR or degree of bronchial reactivity did not modify the association between OSA risk and current asthma or current asthma-NAS subgroups; similarly, these also did not modify the association between likelihood of more severe OSA and current asthma or current asthma-NAS subgroups ($P > 0.7$ for all interaction effects).

We found no significant mediation of associations between OSA risk (considered as the exposure) and current asthma or OSA risk and asthma-NAS subgroups (considered as the outcomes) by BHR. Average mediation by BHR was −0.6% (95% CI: −5.4% to 4.8%) for those with current asthma with NAS, −0.9% (95% CI: −6.3% to 4.9%) for those with current asthma without NAS and −0.03% (95% CI: −2.6% to 2.1%) for those with NAS without current asthma. Similarly, there was no significant mediation by BHR in the association between likelihood of more severe OSA and current asthma and current asthma-NAS subgroups.

BHR and asthma-NAS subgroups

BHR was strongly associated with current asthma with NAS (OR: 2.9; 95% CI: 1.4–5.9) and current asthma without NAS (OR: 3.8; 95% CI: 2.0–7.0). However, in the absence of current asthma, there was no evidence of an association between BHR and NAS (OR: 0.9; 95% CI: 0.2–4.6). These findings were almost identical when those who were on medication were excluded from analysis (Supplementary Information).

OSA risk and BHR

OSA risk was associated with neither BHR nor the degree of bronchial reactivity in the overall sample, in those with current asthma or in those without (Table S7, Supplementary Information). None of the analyses was affected by adjusting the models for the effect of smoking.

DISCUSSION

Our study showed that both OSA risk and likelihood of more severe OSA were associated with increased risk of NAS (shortness of breath, chest tightness and awaking with asthma) regardless of whether those with NAS had current asthma. In contrast, these OSA risk markers were not associated with current asthma without NAS. BHR did not modify or mediate the association between OSA risk and current asthma-NAS subgroups. However, BHR was associated with current asthma regardless of the presence or absence of NAS. In contrast, BHR was not associated with OSA risk or NAS. Our findings suggest that NAS in some asthmatic patients may be symptoms of OSA.

Treatment for OSA helps to control asthma, both daytime and nocturnal.[26–29] There could be a subset of patients where OSA is worsening asthma control, including in daytime. In addition, some of 'nocturnal asthma' in those with OSA could be OSA symptoms that respond to OSA treatment.[30] While we did not look specifically at daytime asthma symptoms, our findings raise the possibility that OSA and nocturnal asthma symptoms may be confused in the general practice setting. Further investigation/evaluation may be useful for some individuals who have nocturnal symptoms unamenable to asthma treatment. It is noted that 14.7% of those who reported nocturnal symptoms did not report current asthma in our study; they had woken due to tightness in the chest, shortness of breath or 'asthma' but not had attacks of asthma, or wheezing or whistling in the chest, or taken medication for asthma. This indicates a greater likelihood of their nocturnal symptoms being unrelated to asthma. In addition, FEV_1/FVC ratio was not different between those with OSA risk and those without, and both these in turn were similar to FEV_1/FVC ratios in those with NAS without current asthma and those with neither current asthma nor NAS. These similarities and significantly lower FEV_1/FVC ratio in those with current asthma without NAS also suggest that nocturnal symptoms in those with NAS without current-asthma are less likely to be symptoms of asthma than OSA. Others have also found the prevalence of undiagnosed OSA to be high,[31–33] and those with NAS without current asthma likely constitute part of that group.

We also considered the opposite interpretation of our findings, that is, NAS represented undiagnosed nocturnal asthma rather than undiagnosed OSA. Nocturnal asthma is associated with increased BMI[34] and potentially increases tiredness, both of which are components of STOP-Bang. However, the strong association between BHR and current asthma with and without NAS and lack of any association between BHR and NAS in the absence of current asthma in our study

suggests that NAS are more likely to be undiagnosed OSA symptoms.

Chronic pan-airway inflammation and hypoxaemia resulting from OSA could worsen BHR and, in turn, asthma.[3,10,11] However, OSA risk was not associated with BHR in our study and did not mediate any association between OSA risk and current asthma-NAS subgroups. The specificity of STOP-Bang is low[35] and resulting false positives for OSA risk might have attenuated any observable association between OSA risk and BHR.

BHR is reduced by treatment for asthma[36,37] and such treatment of our study participants is also likely to have influenced mediation effect of BHR. Although we have included current treatment for asthma when we defined current asthma, how the duration of treatment and type of treatment affected BHR in this sample was not determined, as it was beyond our aims. We also did not know disease duration for those who had OSA (diagnosed or undiagnosed) nor the type or duration of treatment for those with diagnosed OSA. These factors are likely to influence BHR, although the evidence available for this is limited and inconclusive.[38–40] In summary, these clinical factors are likely to have affected any mediation of the association between OSA risk and asthma-NAS subgroups by BHR.

The main strength of our study is that the sample was population-based and was enriched for respiratory symptoms enabling the study of associations which were likely to exist in the general population. However, our findings also have some limitations. The cross-sectional nature of the analysis prevented establishing any causal effect of OSA risk on BHR or current asthma-NAS subgroups. Most importantly, OSA was determined using STOP-Bang rather than overnight polysomnography. The diagnostic utility of STOP-Bang in detecting any OSA (high sensitivity) increases false positives (low specificity) and this[19] may have attenuated associations towards the null. Use of STOP-Bang and OSA-50 questionnaires showed different risk estimates indicating the difficulty in questionnaire-based studies for OSA. In addition, all participants were aged close to 50 years and were more likely to have relatively higher OSA prevalence and increased OSA severity compared with those in younger ages, limiting the generalizability of our findings. Over 22% of participants were never married, widowed, separated or divorced. It is possible that the absence of a regular bed partner and/or sole-living may have led to under-reporting of some questions in STOP-Bang such as snoring and observed apnoea, leading to differential misclassification. Although sampling weights were used in analyses, the selection bias in this asthma-enriched sample might not have been eliminated and may explain the similar gender distribution of asthma. But, females are less likely to have OSA than males[1] that possibly explain the gender differences in risk estimates with similar magnitudes in females for current asthma with and without NAS. Additionally, the use of survey questions instead of clinical diagnosis to define asthma phenotypes and information biases associated with these questions could also have influenced the results, and incomplete responses to some questions are likely to have underpowered our statistical estimates. Use of medications could have influenced BHR but the findings were consistent when those who were on respiratory medication during the past 1 month were excluded.

Overall, our findings suggest that OSA risk as assessed by STOP-Bang score is associated with NAS, and some of the nocturnal symptoms perceived as asthma, are likely to be OSA symptoms. Ideally, patients with NAS who have other clinical features that predispose to OSA should be screened for potentially undiagnosed OSA, in addition to optimizing asthma management for those who have ongoing symptoms attributable to asthma. The association between OSA risk and asthma is unlikely to be modified or mediated by BHR. Our findings need confirmation by further research but may have significant therapeutic implications. Prospective studies in this or similar populations using polysomnography to determine the presence and severity of OSA are needed to determine these associations more accurately and to establish the causal role of OSA on BHR and asthma symptom subgroups.

Acknowledgements: We acknowledge the National Health and Medical Research Council for funding and the Australian government for graduate training and scholarships. We also thank Dr Frances Chung and the University Health Network of Canada for their permission to use STOP-Bang (www.stopbang.ca).

Disclosure statement: G.H. has received equipment from Resmed, Philips and Air Liquide Healthcare to support research unrelated to the current project. M.J.A. has received grants from Pfizer and Boehringer-Ingelheim, and assistance with conference attendance from Sanofi, outside the submitted work. A.J.L. has received grants from National Health and Medical Research Council, during the conduct of the study. None of the other authors declared any financial or non-financial competing interest. Some authors have received research equipment and grants from third parties for unrelated research.

Author contributions: Conceptualization: S.C.D., J.L.P., C.V.S., E.H.W., G.H., A.J.L., C.L., J.B., B.E., G.G.G., P.T., M.J.A., B.T. Data curation: S.C.D. C.V.S., E.H.W., G.H., A.J.L., J.L.P., C.L., J.B., B.E., G.G.G., P.T., M.J.A., B.T. Formal analysis: C.V.S., S.C.D., J.L.P., A.J.L., G.H. Funding acquisition: S.C.D., E.H.W., G.H., A.J.L., B.E., G.G.G., P.T., M.J.A., B.T. Investigation: S.C.D., E.H.W., B.E., G.G.G., P.T., M.J.A., B.T., G.H., A.J.L., J.L.P., C.L., J.B. Methodology: C.V.S., S.C.D., E.H.W., G.H., A.J.L., J.L.P., C.L., J.B., B.E., G.G.G., P.T., M.J.A., B.T. Project administration: S.C.D. Resources: S.C.D., E.H.W., B.E., G.G.G., P.T., M.J.A., B.T., G.H., A.J.L., J.L.P., C.L., J.B. Supervision: S.C.D. Visualization: C.V.S., S.C.D., A.J.L., J.L.P., G.H., M.J.A., B.E. Writing—original manuscript: C.V.S., S.C.D., E.H.W., G.H., A.J.L., J.L.P., C.L., J.B., B.E., G.G.G., P.T., M.J.A., B.T. Writing—review and editing: C.V.S., S.C.D., E.H.W., G.H., A.J.L., J.L.P., C.L., J.B., B.E., G.G.G., P.T., M.J.A., B.T.

Abbreviations: BHR, bronchial hyper-reactivity; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MCh, methacholine; NAS, nocturnal asthma-like symptom; OSA, obstructive sleep apnoea; STOP-Bang, STOP-Bang questionnaire.; TAHS, Tasmanian Longitudinal Cohort Study.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Methods.
Table S1 Use of medications prior to methacholine challenge test.
Table S2 Means and SD of FEV_1, FVC and FEV_1/FVC ratio among those with and without OSA risk and among current asthma-NAS subgroups.
Table S3 Association of OSA risk and likelihood of more severe OSA with current asthma-NAS subgroups (when those on inhalers and other respiratory medication during the past 1 month were excluded).
Table S4 Association of OSA risk with current asthma-NAS subgroups in males and females when OSA-50 questionnaire was used.
Table S5 Association of OSA risk and likelihood of more severe OSA with individual nocturnal respiratory symptoms.
Table S6 Association of OSA risk and likelihood of more severe OSA with current asthma-NAS subgroups in males and females.
Table S7 Association of OSA risk with BHR and degree of bronchial reactivity in those with and without asthma.