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Nocturnal symptoms perceived as asthma are associated with Obstructive Sleep Apnoea risk, but not bronchial hyper-reactivity

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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.

ABSTRACT

Background and objective: Obstructive sleep apnoea 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 (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; 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.

Keywords: Sleep Apnea Syndromes; Sleep Apnea, Obstructive; Asthma; Bronchial Hyperreactivity; Airway Resistance

Short title: Nocturnal asthma and BHR in sleep apnoea

List of abbreviations

BHR – bronchial hyper-reactivity

BMI – body-mass index

CI – confidence interval

FEV_1 - forced expiratory volume in one second

FVC - forced vital capacity

MCh – methacholine

NAS – nocturnal-asthma-like symptoms

OR – odds ratio

OSA - Obstructive sleep apnoea

STOP-Bang - STOP-Bang questionnaire

TAHS - Tasmanian Longitudinal Cohort Study

Author contribution roles using the CRediT Taxonomy

Please note that not all categories are relevant to each type of research. Only select those contribution roles that are relevant to your study.

Role	***Degree***	***Author initials*** *(reflecting the full author name on the manuscript)*
1 **-Conceptualization**	Lead	SCD
	Equal	JLP, CVS
	Supporting	EHW, GH, AJL, CL, JB, BE, GGG, PT, MJA, BT
2 **- Data curation**	Lead	**SCD**
	Equal	
	Supporting	CVS, EHW, GH, AJL, JLP, CL, JB, BE, GGG, PT, MJA, BT
3 **-Formal analysis**	Lead	**CVS**
	Equal	
	Supporting	**SCD, JLP, AJL, GH**
4 **- Funding acquisition**	Lead	**SCD**
	Equal	
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5 **- Investigation**	Lead	SCD
	Equal	EHW, BE, GGG, PT, MJA, BT
	Supporting	GH, AJL, JLP, CL, JB
6 **- Methodology**	Lead	**CVS**
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7 - **Project administration**	Lead	**SCD**
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	Supporting	
8 - **Resources**	Lead	SCD
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9 - **Software**	Lead	
	Equal	
	Supporting	
10 - **Supervision**	Lead	SCD
	Equal	
	Supporting	
11 - **Validation**	Lead	
	Equal	
	Supporting	
12 - **Visualization**	Lead	CVS
	Equal	
	Supporting	SCD, AJL, JLP, GH, MJA, BE
13 - **Writing – original draft**	Lead	**CVS**
	Equal	
	Supporting	SCD, EHW, GH, AJL, JLP, CL, JB, BE, GGG, PT, MJA, BT

14 - **Writing – review & editing**	Lead	**CVS**
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	Supporting	SCD, EHW, GH, AJL, JLP, CL, JB, BE, GGG, PT, MJA, BT

INTRODUCTION

Obstructive sleep apnoea (OSA) is common[1] and associated with asthma[2] that is better controlled when co-existing 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 characterised by reversible airflow-obstruction due to inflammatory changes and smooth-muscle contraction in bronchi.[4-6] Excessive reactivity of bronchi (bronchial hyper-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 age of 43-years (n=2,397), 57.7% (n=794) completed a survey and a full laboratory assessment at age of 53-years.

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, Switzerland] and a standard MCh inhalational challenge test[17] was administered. Pre-bronchodilator forced expiratory volume in one second (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: (1) *Have you had an attack of asthma or wheezy breathing in the last 12 months?*, (2) *Have you taken*

any medicines including inhalers or tablets for asthma or wheezy breathing in the last 12 months?, and (3) *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: (1) *feeling of tightness in chest*, (2) *an attack of shortness of breath*, or (3) *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) ≤ 2mg.

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 (ORs) with 95% confidence intervals (CIs). 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 minimise gender effect on OSA classification and excluding those who were on asthma/allergy medications (see Appendix S1 and Table S1 in Supplementary Information) during the past one-month.

As age, sex and 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 confidence intervals.

RESULTS

Mean±SD age of the sample was 49.6±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 in 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 in place 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. 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 in Supplementary Information, and those for males and females in Table S6 in Supplementary Information.

Dichotomised 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%, 4.8%) for those with current-asthma with NAS, -0.9% (95%CI -6.3%, 4.9%) for those with current-asthma without NAS, and -0.03% (95%CI -2.6%, 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 (see online supplement).

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 in 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, awaking with asthma) regardless of whether those with NAS had current-asthma or not. 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 presence or absence of NAS. In contrast, BHR was not associated with OSA-risk or NAS. Our findings suggest that nocturnal asthma-like symptoms in some asthmatics may be symptoms of OSA.

Treatment for OSA helps 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 responds 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 is 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 questionnaire 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 generalisability 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] which 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 in place 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 is likely to have under-powered our statistical estimates. Use of medications could have influenced BHR but the findings were consistent when those who were on respiratory medication during past one 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 nocturnal asthma-like symptoms who have other clinical features that predispose to OSA should be screened for potentially undiagnosed OSA, in addition to optimising 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 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.

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Author Contributions:

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Table 1. Socio-demographic 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-<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)

‡ % out of the valid responses; BMI=body-mass index; OSA=obstructive sleep apnoea; NAS=nocturnal asthma symptoms; LDRS= log dose-response slope for MCh bronchial challenge test (per %change in FEV_1 per MCh(mg); BHR=bronchial hyper-reactivity (PD_{20} < 2mg MCh; see text); SD=standard deviation; ¥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.

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[ǂ]	**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)**

NAS= nocturnal asthma symptoms; OSA=obstructive sleep apnoea; [¥]contribution of individual NAS symptoms to this category was 32% tightness in the chest, 17% shortness of breath and 51% perceived asthma; [ǂ]contribution of individual NAS symptoms to this category was 47% tightness in the chest, 47% shortness of breath and 6% perceived asthma

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

Current-asthma-NAS subgroup	OSA-risk[‡] OR (95%CI)	Likelihood of more severe OSA[§] OR[ø] (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) **

NAS= nocturnal asthma symptoms; OSA=obstructive sleep apnoea; [‡]Defined as STOP-Bang score ≥3; [§]Defined as ordinal increase in the STOP-Bang score from 0 to 8; [ø] per one-unit increase in the Stop-Bang score; OR=odds ratio; CI=confidence interval; *=p<0.05; **=p<0.01