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The association between asthma and obstructive sleep apnea (OSA): A systematic review

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ABSTRACT

Objective: Bronchial asthma and obstructive sleep apnoea (OSA) are common respiratory disorders that can co-exist. The strength of this association, and also the impact of OSA on asthma-related clinical outcomes remain unclear. **Data Sources:** Literature review was performed in EMBASE and MEDLINE databases. Studies up to and including 2016 were selected. **Study Selection:** Studies were included if they contained; 1) a population with asthma AND 2) a prevalence of OSA reported using either polysomnography or validated questionnaires such as the Sleep Apnoea Scale of the Sleep Disorders Questionnaire (SA-SDQ), STOP BANG or the Berlin questionnaire. **Results:** Nineteen studies were identified. Thirteen questionnaire-based studies met the inclusion/exclusion criteria and twelve of these demonstrated a prevalence of OSA in asthma of 8–52.6%, with one study showing no association between the two conditions. Six studies using polysomnography demonstrated a high prevalence of 19.2–60%; which was higher at 50–95% in severe asthma. Two polysomnography and four questionnaire studies found worse asthma-related clinical outcomes with co-existing OSA. One polysomnography and two questionnaire studies showed no difference. **Conclusion:** This systematic review suggests that there is a high prevalence of OSA in asthma, particularly within severe asthma populations and that co-diagnosis of OSA in asthma patients is associated with worse clinical outcomes. However this outcome was not uniform and the number of studies using polysomnography to confirm OSA was small. This weakens the conclusions that can be drawn and prompts the need for adequately powered and well-designed studies to confirm or refute these findings.

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Asthma; obstructive sleep apnoea; OSA; prevalence

Introduction

Asthma is a common respiratory condition, with 5.4 million people in the United Kingdom requiring treatment (1). Approximately 5%–10% of the asthma population has refractory asthma that remains uncontrolled despite optimal medical therapy (2). This group experiences frequent exacerbations, hospital admissions, and health-care utilization and are often dependent on high doses of inhaled corticosteroids (ICS) or maintenance oral corticosteroids (OCS) (3).

OSA with sleepiness (OSA syndrome) has been shown to have a prevalence of 2% in women and 4% in men. OSA without associated daytime sleepiness has a higher prevalence of 9% in women and 24% in men (4). This condition is strongly associated with obesity, and has independent

associations with hypertension, stroke, diabetes, and cardiovascular disease (5–7). Treatment with continuous positive airway pressure (CPAP) reduces long-term mortality, particularly cardiovascular mortality in patients with severe OSA (8).

Asthma and OSA overlap with similar comorbidities and underlying pathophysiology potentiating the two conditions (Figure 1). Gastro-esophageal reflux disease (GORD), rhinosinusitis, and obesity are associated with both. The pathophysiology connecting these conditions is complex with a high likelihood for central role played by systemic and local inflammation (9).

Asthmatics have poor sleep quality, reduced sleep time, and reduced slow wave sleep (10–12). In addition to this, many epidemiological studies have shown

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Guarantor Statement: All content in this article is accurate, to the best of my knowledge. SD

Author Contributions: SD designed the article, reviewed and interpreted the relevant data/results and drafted content of final version. AB was the second reviewer of data for the systematic review and involved in interpretation of data and results. SW and AT reviewed the methodology and article content. AM was involved in design, and review of the methodology, relevant data/results, and overall content.

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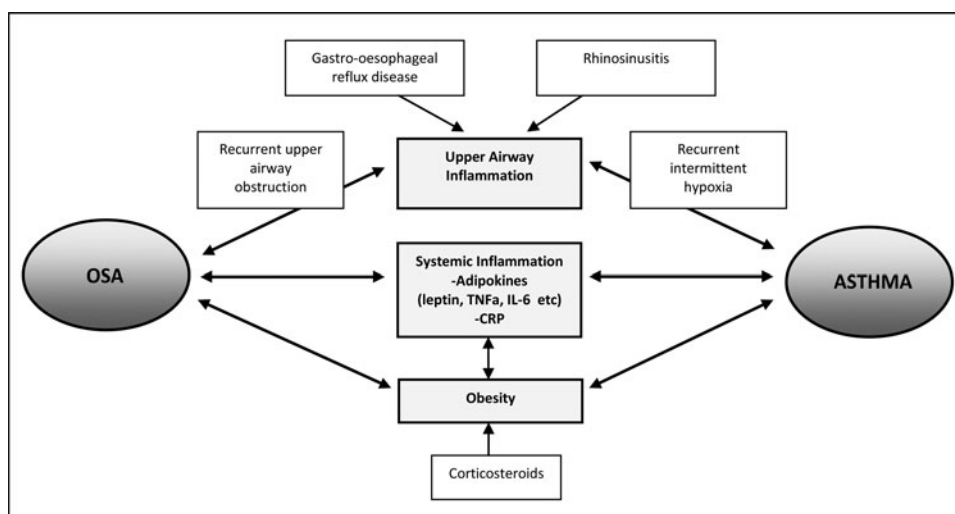


Figure 1. Pathophysiological interplay in asthma-OSA overlap.

asthmatics have increased incidences of symptoms of sleep-disordered breathing (13–14, 16–18).

The symptoms of poorly controlled asthma and OSA have similar clinical features. Given the associated morbidity and mortality of both conditions, a review of the literature is warranted to determine the current state of knowledge on the strength and direction of any relationship between OSA and asthma, and to highlight any gaps in the literature that require further research.

Materials & methods

A qualitative systematic review of the literature was performed with MEDLINE and EMBASE databases using the following search terms: Asthma AND (incidence OR prevalence OR odds OR risk) AND (Obstructive Sleep Apnoea OR Obstructive Sleep Apnea OR OSA OR sleep OR apnoea OR apnea OR snoring OR sleep-disordered breathing). All studies up to and including the year 2016 were included.

Inclusion/exclusion process

Studies were selected for full text review if they fulfilled the criteria of examining 1) a population with asthma and 2) an outcome focusing on OSA/sleep/sleep-disordered breathing or symptoms of sleep-disordered breathing or 3) comorbidities relating to either condition. Studies were excluded if not in the English language or were carried out on a pediatric population (<18 years of age).

The gold standard for diagnosis of OSA is an overnight polysomnography (PSG) test (19). Limited channel-sleep studies are a well-recognized clinical alternative to PSG. The Sleep Apnoea-Scale of Sleep Disorders Questionnaire (SA-SDQ), the Berlin Questionnaire, and STOP-BANG are validated screening questionnaires used to assess risk of OSA. Questionnaires used in the assessment of severity

Table 1. Sensitivity and specificity of detecting OSA (AHI ≥ 5).

Test/Questionnaire	Sensitivity	Specificity
Limited-channel sleep study (LCSS) (19,20)	32%–100%	33%–100%
Overnight oximetry (19,20)	87% (SE 4%, CI 36%–100%)	65% (SE 7%, CI 23%–99%)
Questionnaires (pooled data that includes STOP-BANG, SA-SDQ, and Berlin) (20,21)	77.0% (95% CI: 73.0–80.0%; $I^2 = 78.1\%$)	53.0% (95% CI: 50%–57%; $I^2 = 88.8\%$)

of symptoms, such as daytime sleepiness (e.g., Epworth sleepiness score), were not included unless known to have specific validation for prediction of obstructive sleep apnea risk. The sensitivity and specificity of the accepted diagnostic tests and validated questionnaires are reported in Table 1. All studies that involved formal overnight sleep tests were found to use PSG rather than limited-channel sleep studies or overnight oximetry, but were not excluded on this basis. This review included studies that have demonstrated OSA diagnosis (using PSG) or OSA risk through the use of validated questionnaires. Table 2 illustrates how the included studies have made the diagnosis of OSA and also if robust asthma

Table 2. Method of asthma/OSA diagnosis.

OSA diagnosis	ATS/GINA asthma diagnosis	
	Yes	No
PSG	2	4
Validated questionnaire (SA-SDQ, STOP-BANG, Berlin)	8	5

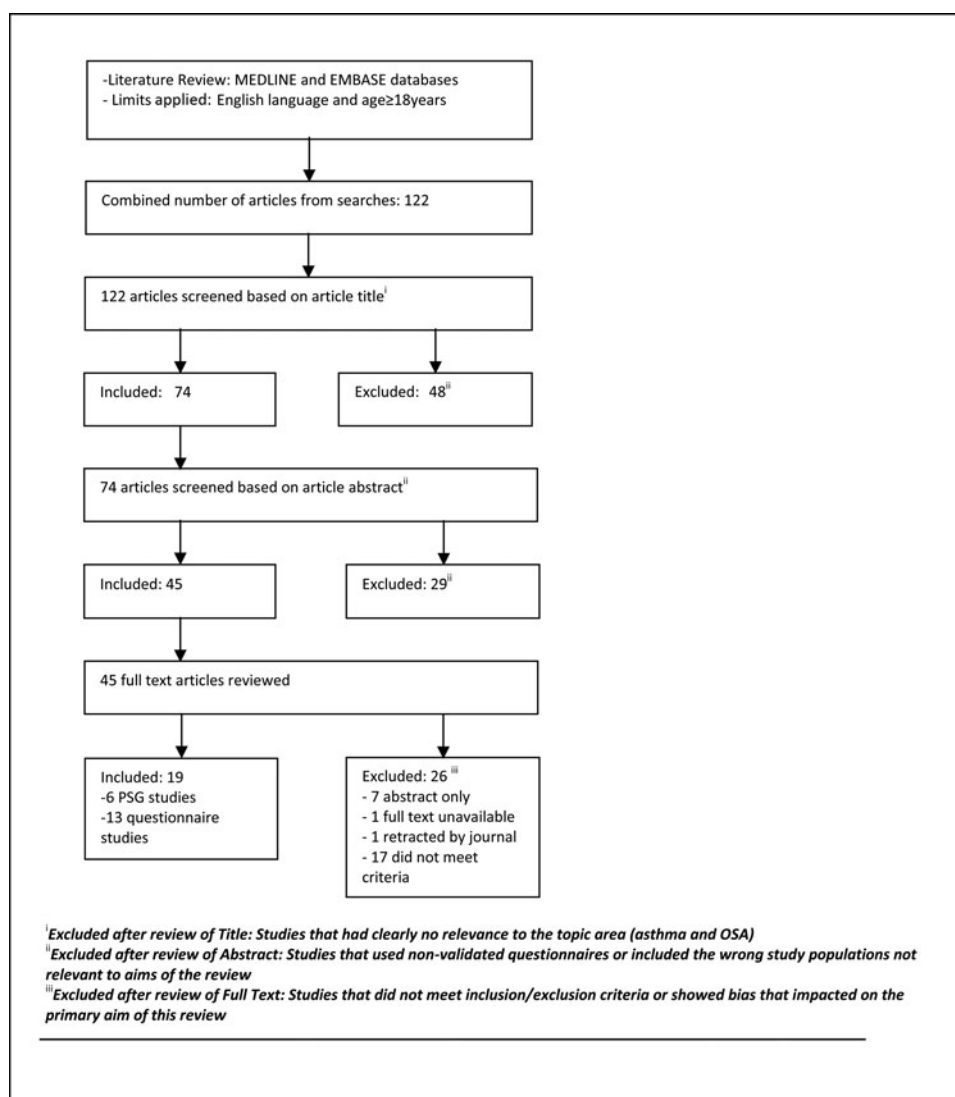


Figure 2. Preferred reporting items for systematic review and meta-analyses (PRISMA).

diagnostic criteria were used. Studies using nonvalidated questionnaires were excluded. Studies were also excluded if they showed clear bias in the selection of asthma patients based on symptoms of sleep-disordered breathing. Studies that report OSA diagnosis (PSG) and OSA risk (validated questionnaires) are presented separately in Tables 3 and 4, respectively.

Secondly, to evaluate asthma-related clinical outcomes in patients with coexisting OSA, included studies were reviewed to determine if measures including the Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ), and Asthma Control Questionnaire (ACQ) were reported (22–24). Alternative clinical measures such as the number of emergency department visits/hospital admissions/intensive care admissions, frequency of OCS requiring exacerbations and persistent daytime and night-time asthma symptoms were also included. The impact of OSA treatment with CPAP is beyond the scope of this systematic review, and is not included in the results.

Data synthesis/extraction

Data were extracted from studies by one reviewer (SD) and checked by a second (AB) to determine if the inclusion/exclusion criteria were met (see Figure 2). Studies were then re-reviewed to evaluate clinical outcomes in OSA versus no-OSA.

Assessment of bias

Bias was assessed using the Briggs scale (27) by two reviewers independently, with any disagreement resolved by discussion.

Results

The progression of the studies through the selection process is summarized in the preferred reporting items for systematic review and meta-analyses (PRISMA) diagram in Figure 2. Abstracts were excluded as sufficient review of the study methodology was not possible. Other reasons for exclusion included the following: one selected study

Table 3. Table of characteristics - Studies that include diagnostic sleep test (PSG) for OSA.

Study	Study design	Population	Asthma diagnosis	OSA diagnosis	Outcomes
1. Julien et al. J Allergy Clin Immunol 2009;124(2):371–376 (30)	Cross-sectional	N = 26 severe asthma N = 26 moderate asthma N = 26 controls	ATS guidelines	PSG	19/52 (36.5%) of total asthma population had OSA vs. 3/26 (12%) of control group. 13/26 (50%) with severe asthma had OSA, 6/26 (23%) with moderate asthma had OSA and 3/26 (12%) of control group had OSA ($p = 0.007$). AHI did not correlate with asthma severity or other clinical outcomes (FEV_1 , %pred or AQLQ scores).
2. Shaarawy et al. Egypt J Chest Dis Tuberc 2013;62(1) (28)	Cross-sectional (with additional prospective interventional component)	N = 60 with asthma Centre for allergy and respiratory disease	“Proven reversible airway obstruction” and “long history of bronchial asthma”	PSG	15/60 (25%) of asthma subjects had OSA. Mean AHI 23.5 ± 10.9 . No significant change in FEV_1 or ACT after 6/52 treatment with CPAP.
3. Teodorescu et al. JAMA 2015;313(2):156–164 (26)	Prospective cohort study	Asthma: $n = 81$ No asthma: $n = 466$ (Total $n = 547$) Taken from Wisconsin Sleep Cohort Study	Self-reported (on 2 occasions)	PSG every 4 years (All had negative PSG at baseline.)	22/81 (27%) (95%CI, 17%–37%) of asthma subjects experienced incident OSA compared to 75/466 (16%) (95%CI, 13%–19%) of non-asthma subjects observed over 4 year intervals ($p = 0.02$). Asthma duration was related to incident OSA (RR 1.07 per 5yr increment in asthma duration, 95%CI, 1.26–5.89), ($p = 0.045$).
4. Yigla et al. J Asthma. 2003;40(8):865–871 (32)	Cross-sectional	N = 22 (all with asthma) Continuous OCS:14 OCS burst: 8 Tertiary care centre in Israel)	Reversibility > 15% + For severe (daily symptoms > 6 m, ICS + LABA, OCS > 2/year or continuous)	PSG	21/22 (95.5%) prevalence of OSA Significantly higher prevalence of OSA in patients receiving continuous OCS compared to short bursts of OCS ($p < 0.05$)
5. Wang et al. Sleep Med.2016;(26)1–5 (29)	Prospective cross-sectional cohort study	N = 146 asthma N = 157 controls Asthma follow up outpatient clinics	Physician diagnosed	PSG	28/146 (19.2%) of asthma subjects had OSA compared to 15/157 (9.6%) of controls, $p = 0.016$. RR 2.25 (95%CI, 1.15–4.40), ($p = 0.016$). Annual number of severe asthma exacerbations was significantly higher in the OSA group compared to the no-OSA group ($p < 0.001$). AHI significantly correlated with the number of exacerbations ($p < 0.001$).
6. Zidan et al. Egypt J Chest Dis Tuberc. 2015;64(2):425–430 (25)	Cross-sectional	N = 30 with asthma N = 12 healthy controls Asthma outpatient clinic	Physician diagnosis. GINA to assess control	PSG	18/30 (60%) of asthmatics had OSA vs. 2/12 (17%) of controls, $p < 0.001$. Presence of OSA associated with worse asthma control ($p < 0.001$) (using FEV_1 , %pred).

Table 4. Studies that include validated questionnaires to assess OSA risk.

Study	Study design	Population	Asthma diagnosis	OSA diagnosis	Outcomes
1. Auckley, D. et al. Sleep Med. 2008;9(5):494–499 (35)	Cross-sectional	Asthma N = 177 Control N = 328 (Nonasthma patients recruited from general medical outpatient clinics)	Physician diagnosed. Recruited from asthma and internal medicine clinics	Berlin Questionnaire	Risk of OSA was higher in the asthma group compared to controls: 70/177 (39.5%) vs. 89/328 (27%), ($p = 0.004$). In the asthma group, risk for OSA did not correlate with asthma severity ($p = 0.183$).
2. Braidto, F. et al. Respir Care 2014;59(12):1851–1856 (14, 15)	Cross-sectional	Total N = 1,941 Asthma alone = 740 Asthma + Allergic rhinitis = 1,201 (Recruited by general practitioners during a control visit)	Physician diagnosis as per GINA guidelines	STOP-BANG	1020/1941 (52.6%) of all asthma subjects were high risk for OSA.
3. Ferguson, S. et al. Lung. 2014;192(5): 675–683 (41)	Cross-sectional	N = 812 asthma (Routine follow up at allergy and asthma clinics)	American Thoracic Society (ATS)	SA-SDQ	140/887 pre-existing OSA diagnosis, with 75/140 on CPAP and excluded 239/812 (29%) had high OSA risk.
4. Karachaliou, F et al. Prim Care Respir J. 2007;16(4):222–228 (31)	Cross-sectional	N = 1501 Asthma = 218	2 respiratory physicians: (a) longstanding history of asthma from childhood or adolescence (b) a history of atopy was considered indicative of asthma; (c) significant reversibility of airway obstruction on spirometry (i.e. increase of at least 12% and 200 mL in baseline FEV ₁ after administration of 400 µg salbutamol)	Berlin Questionnaire and Epworth Sleepiness Scale	Subjects with a diagnosis of asthma were more likely to be obese (OR = 1.50; CI: 1.12–2.04), but there was no association with snoring (OR = 1.01; CI: 0.76–1.35), breathing pauses (OR = 1.22; CI: 0.79–1.88), and excessive daytime sleepiness (OR = 1.39; CI: 0.83–2.35).
5. Kim, M. Y. Ann Allergy Asthma Immunol. 2013;110(4):253–257 (40)	Cross-sectional	Total N = 217 (with asthma) Controls = 0 Randomly recruited from tertiary care clinic	1. Airway reversibility with FEV ₁ > 12% and 200 mL post SABA or methacholine provocation causing 20% fall of 16 mg/ml or less 2. Persistent symptoms 3. Physician diagnosis of asthma (need all 3)	Berlin Questionnaire	89/217 (41.0%) were high risk for OSA. The high OSA risk group had a lower ACT score than the low OSA risk group, but it was not statistically significant: 20.9 ± 3.6 vs. 21.5 ± 3.3 ($p = 0.091$).
6. Kumar, R et al. J Assoc Physicians India. 2013 Sep;61(9):615–618 (42)	Cross-sectional	N = 328 with asthma Outpatients of Vallabhbhai Patel Chest Institute	GINA guidelines (reversibility of more than 12% or increase of 200 ml in FVC or FEV ₁ after 200 micrograms of inhaled salbutamol)	Berlin Questionnaire (and ESS). Subgroup had home PSG	BQ was positive 60/328 (18.29%) of asthmatic patients. ESS was positive in 35/328 (10.67%) of asthma patients. (Only 17/60 patients had home PSG - 6 mild, 7 moderate, 4 severe OSA). (Continued on next page)

Table 4. (Continued)

Study	Study design	Population	Asthma diagnosis	OSA diagnosis	Outcomes
7. Tay, T.R et al. Respirology 2016;21(8):1384–1390 (39)	Cross-sectional	N = 90 asthma	Specialist physician diagnosis after review of investigations (76 had variable airflow obstruction)	Clinical symptoms and Berlin questionnaire (17) score ≥ 2 OR Previous positive PSG	OSA or high OSA risk in 35/90 (38.9%). No significant difference in number of exacerbations in OSA vs. no OSA: 19 (48.7%) vs. 16 (31.4%), $p = 0.094$. Univariate analysis showed asthmatics with OSA to have worse ACT ($p = 0.034$) and worse AQLQ ($p = 0.029$) but not in multivariate analysis.
8. Teodorescu, M et al. J Allergy Clin Immunol Pract. 2015;3(4):566–575 (33)	Cross-sectional	Severe asthma (SA) = 94 Nonsevere asthma (NSA) = 161 Normal controls (NC) = 146 (Substudy to the observational Severe Asthma Research Program –SARP II)	Episodic respiratory symptoms, reversible airflow obstruction (documentation of variability of FEV ₁ and/or FVC by 12% and 200 cm ³ either spontaneously or after two puffs of inhaled albuterol), and/or a positive methacholine test	SA-SDQ	24/94 (26%) of severe asthma, 26/161 (16%) of non-severe asthma and 4/146 (3%) of controls had high OSA risk ($p < 0.0001$). There was a significant difference for SA vs NC ($p = 0.04$) and NSA vs NC ($p = 0.02$) but not for SA vs NSA. (Patients with history of OSA or CPAP use excluded) High OSA risk related to worse AQLQ scores ($p < 0.0001$), ED visits ($p = 0.001$), hospital stays ($p = 0.005$) and ITU admissions ($p = 0.01$)
9. Teodorescu, M et al. Sleep Disord.2013;25:1567 (36)	Cross-sectional	N = 813 –154(19% elderly) –659 (81% young) N = 140 (Previous OSA diagnosis) Recruited from outpatient respiratory clinics	Diagnosed by specialist Asthma severity as per NAEPP guidelines	SA-SDQ	High OSA risk in 20/154 (13%) older patients compared to 45/659 (7%) younger patients ($p = 0.01$). Therefore overall prevalence 65/813 (8%) OSA was associated with nearly 7 times greater likelihood of severe asthma in an older individual (OR = 6.67). This relationship was of greater magnitude than in younger subjects (OR = 2.16).
10. Teodorescu, M et al. J Asthma. 2012;49(6):620–628 (37)	Cross-sectional	N = 828 subjects with asthma Allergy and Pulmonary subspecialty clinics	ATS guidelines. Asthma diagnosed and managed by academic specialist	SA-SDQ and review of medical notes for historical diagnosis.	136/828 (16%) had established OSA-75/136 (55%) of these were on CPAP and excluded from analysis. Of the remaining 752, 212 (28%) had high OSA risk High OSA risk associated with persistent daytime (odds ratio(OR)1.96(95% CI = 1.31–2.94)) and night-time (1.97(1.32–2.94)) asthma symptoms

11. Teodorescu, M et al. Chest. 2010;138(3):543–550 (38).	Cross-sectional	N = 472 with asthma From tertiary care clinic visits	Asthma or allergy specialist at tertiary centre - using ATS guidelines. ACQ for control	SA-SDQ	Total of 511 asthmatics recruited, 63 had pre-existing OSA and the 39 receiving treatment were excluded 109/472 (23%) categorised as high risk for OSA. High OSA risk associated with 2.87x higher odds for having poorly controlled asthma (95%CI, 1.54–5.32, $p = 0.0009$) using ACQ full version.
12. Teodorescu, M et al. Chest. 2009;135(5):1125–1132 (34)	Cross-sectional	N = 244 asthma Asthma patients from routine clinical visits to the asthma-airways centre	Physician diagnosis, after medical records review Asthma severity measured using National Asthma Education and Prevention Program guidelines	SA-SDQ	75/284 (26%) had known OSA diagnosis and 40/75 (53%) of these patients were receiving CPAP and excluded from further analysis. 97/244 (39.7%) had high OSA risk. Asthma severity step was predictive of OSA risk OR 1.60(95%CI 1.26–2.03), $p < 0.0001$ High OSA risk associated with daytime ($p < 0.0001$) and night-time ($p = 0.0006$) asthma symptoms. There was a significant inverse relationship with FEV ₁ pred ($p = 0.002$). 135 included, 40 (29.6%) had pre-existing OSA and 20/40(50%) were being treated for OSA and excluded. High OSA risk in 39/79 (49%) of women and 12/36 (33%) of men. ESS correlated with SA-SDQ ($p < 0.0001$) and asthma severity step ($p = 0.04$) (but did not correlate with asthma severity step in multiple regression model).
13. Teodorescu, M et al. Sleep Med 2006;7(8):607–613 (10)	Cross-sectional	N = 115 asthmatic patients (Routine asthma follow up visits)	Physician diagnosis Severity as per NAEPP guidelines	SA-SDQ	

was not available in full text after a search of the British Library and one selected study had a retraction printed by the journal after publication. Other reasons for exclusion at each step are summarized in the PRISMA diagram. A total of 19 studies were identified for inclusion in this systematic review (6 PSG and 13 questionnaire based).

Association between asthma (non-severe) and OSA

a) Studies using PSG for OSA diagnosis (Table 3)

The prevalence of OSA was reported at 19.2%–60% (26–29). Julien et al. reported a prevalence of 6/26 (23%) in moderate asthma was compared to 3/26 (12%) in the control group, but this did not reach statistical significance ($p = 0.303$) (30). Zidan et al. demonstrated an OSA prevalence of 18/30 (60%) in asthma compared to 2/12 (17%) of controls ($p < 0.001$) (25). A prospective cohort study by Shaarawy et al. demonstrated a prevalence of OSA of 15/60 (25%) in patients with asthma (28). Wang et al. demonstrated a significantly higher prevalence of OSA in asthma subjects of 28/146 (19.2%) versus matched controls of 15/157 (9.6%), ($p = 0.016$) (29). Teodorescu demonstrated incident OSA of 22/81 (27%) in asthma compared to 75/466 (16%) in controls over multiple 4 year intervals ($p = 0.02$) (26).

b) Studies using questionnaires to assess OSA risk (Table 4)

Thirteen questionnaire-based studies met the inclusion/exclusion criteria, of which twelve demonstrated increased prevalence of OSA in asthma at a range of 8%–52.6%, while one study showed no association. In the latter study by Karachalioua et al., there was no association between asthma and snoring [odds ratio (OR) = 1.01; CI: 0.76–1.35], apneas (OR = 1.22; CI: 0.79–1.88) or excessive daytime sleepiness (OR = 1.39; CI: 0.83–2.35) (31).

Association between severe/difficult to treat asthma (SDTA) and OSA

a) Studies using PSG for OSA diagnosis (Table 3)

Two studies looked at the association between severe/difficult-to-treat asthma (SDTA) and prevalence of OSA (30, 32). Julien et al. (30) reported a prevalence of OSA of 50% (13/26) in severe asthma (SA) and 6/26 (23%) in moderate asthma compared to 3/26 (12%) in controls. There was significantly more OSA in severe versus moderate asthma ($p = 0.044$) and severe versus controls ($p = 0.003$), but not when comparing moderate to controls ($p = 0.303$). A study of 22 difficult-to-treat asthma patients by Yigla et al. showed a particularly high prevalence of OSA at 21/22 (95.5%) (32).

b) Studies using questionnaires to assess OSA risk (Table 4)

Only four of the thirteen studies reported asthma severity in relation to OSA risk. Teodorescu et al. showed a significant difference in OSA risk in SA versus normal controls (NC, 24/94, 26% vs. 4/146, 3%, $p = 0.04$) and non-severe asthma (NSA) versus NC (26/161, 16% vs. 4/146, 3%, $p = 0.02$). However, there was no significant correlation for OSA risk in SA compared to NSA (33). A study of asthmatic patients from a tertiary care center demonstrated a prevalence of 97/244 (39.7%) of high OSA risk and additionally that asthma severity step was predictive of OSA risk (OR 1.6[95% CI: 1.26–2.03], $p < 0.0001$) (34). However, a study of 177 asthmatic patients by Aukley et al. showed a similar prevalence of OSA risk in asthma of 70 (39.5%) but did not show a correlation between OSA risk and asthma severity ($p = 0.183$) (35). A study of 115 asthmatics found 39/79 (49%) of women and 12/36 (33%) of men had high OSA risk. This study included 38 (33%) asthmatics on treatment severity Step 4; however, correlation between asthma severity and OSA risk was not clearly presented (10). Teodorescu et al. looked at OSA risk in the elderly (20/154, 13%) compared to the young (45/659, 7%). OSA was associated with an almost 7 times greater likelihood of SA in older individuals, which was of greater magnitude than the younger population (OR = 2.16) (36).

OSA and asthma-related clinical outcomes

a) Studies using PSG for OSA diagnosis (Table 3)

Only three of the six included PSG-based studies reported on asthma-related clinical outcomes. Of these, two showed worse clinical outcomes with coexisting OSA. A recent prospective cross-sectional cohort by Wang et al. demonstrated that subjects with OSA had an increased prevalence of SA exacerbations when compared to asthmatics without OSA ($p < 0.001$). The Apnoea Hypopnoea Index (AHI) significantly correlated with the number of severe exacerbations (OR: 1.322, 95% CI: 1.148–1.523, $p < 0.001$) (29). Zidan et al. used FEV₁% as a marker of asthma severity to demonstrate this as a significant predictor for the development of OSA, $p < 0.001$ (25). Julien et al. showed that AHI did not correlate with asthma severity or other clinical outcomes, including FEV₁% and AQLQ scores (30).

b) Studies using questionnaires to assess OSA risk (Table 4)

Only 6/13 questionnaire studies evaluated OSA risk in relation to asthma-related clinical outcomes. Of these, 4 studies reported worse clinical outcomes in patients with high OSA risk, with a further 2 studies reporting no significant difference in clinical outcomes. Teodorescu et al.

demonstrated that high OSA risk was related to worse AQLQ scores ($p < 0.0001$), increased number of emergency department (ED) visits ($p = 0.001$), increased number of hospital admissions ($p = 0.005$) and increased number of admissions to the intensive care unit (ITU) ($p = 0.01$) (31). A cross-sectional study by Teodorescu et al. showed an association between high OSA risk and both persistent daytime ([OR] 1.96[95% CI = 1.31–2.94]) and night-time (1.97[1.32–2.94]) asthma symptoms (37). A further study of 427 asthma patients showed high OSA risk was associated with 2.87 times higher odds for having poorly controlled asthma (95% C, 1.54–5.32) (38). A cross-sectional study of 244 asthmatics demonstrated that high OSA risk was associated with both daytime ($p < 0.0001$) and night-time ($p = 0.0006$) asthma symptoms (34). Tay et al. demonstrated in a univariate analysis that asthmatics with OSA to have worse ACT ($p = 0.034$) and worse AQLQ ($p = .029$), but this was not shown in multivariate analysis of the same study. This study also showed no significant difference in the number of exacerbations in the OSA group versus no-OSA group (39). A cross-sectional study by Kim et al. showed the high risk OSA group to have lower ACT scores than the low risk OSA group, however this did not reach statistical significance ($p = 0.091$) (40).

Discussion

In this systematic review, we observed a high OSA prevalence in asthma, of 19%–60%. This was higher in SDTA populations at 50%–95%. OSA risk assessed using validated questionnaires reports a prevalence of 8%–52.6%. Clinical outcomes were worse in asthma patients with coexisting OSA. This prevalence is similar to that reported in a meta-analysis by Kong et al. (43), who demonstrated a prevalence of OSA of 49.5%, and OSA risk of 27.5%. However, the latter study did not analyze asthma severity or report on associated clinical outcomes.

All studies reported an increased prevalence of OSA when using PSG diagnosis. Only one study reported data refuting the relationship between asthma and OSA risk (31), and this was a questionnaire-based study. The latter study did have robust asthma diagnostic criteria, so the conflicting results are notable. However, asthma severity measures were not reported and it is possible that this population represents a milder asthma subgroup followed up in primary care.

The concomitant diagnosis of OSA and asthma was associated with worsened asthma-related clinical outcomes. However, this finding was not universal between studies. Two PSG studies demonstrate worse clinical outcomes in OSA (29) and (25), whereas one PSG study

showed no significant difference (30). All six questionnaire studies that looked at clinical outcomes showed worse outcomes in OSA. However, although Tay et al. demonstrated worse ACT and AQLQ in the OSA group using a univariate analysis; this was not reproduced in a multivariate analysis (39). Kim et al. demonstrated a worsening of ACT scores in the OSA that failed to reach significance (40).

Only two PSG studies reported a prevalence of OSA in SA. The study by Yigla et al. demonstrated a particularly high OSA prevalence of 95%, but this population had above-normal body mass index (BMI) and neck circumference (32). Additionally, steroid use could be an independent predictor of OSA due to local myopathic effects in the upper airways (44). Julien et al. found an increased prevalence of OSA in SA (50%) and also in moderate asthma (23%), with a prevalence of 12% in controls, although this was not significant in moderate asthma compared to controls (30). A questionnaire-based study reported a prevalence of OSA in SA as 26% compared to 16% in NSA and 3% in controls (33). Both studies used robust asthma and SA criteria. Questionnaires to diagnose OSA rely on OSA symptoms, and it may be that the OSA prevalence in this study is more reflective of the symptomatic general population at 2% in women and 4% in men (4), which is matched more closely in the study control group (3%). Julien et al. used PSG to diagnose OSA, which does not rely on symptoms and this may explain higher prevalence in the control group (12%) (30), which is closer to that of the asymptomatic general population of 9% of women and 24% of men (4).

All studies were systematically reviewed by two independent reviewers and only those that used either a PSG or validated questionnaire were included in this review. A pooled systematic analysis that included the SA-SDQ, and the Berlin and STOP-BANG questionnaires reported sensitivity and specificity to be 77% and 53%, respectively (21).

There are limitations to this review, particularly concerning the diagnostic criteria of both clinical conditions. Although the questionnaires are validated for the detection of OSA risk, there is still potential for error as an overnight sleep study is required for diagnosis with full PSG being recognized as the gold standard. Alternative methods such as limited-channel sleep studies are often recognized alternatives but interestingly none of the studies used this method. It should also be noted that the questionnaires have not been specifically validated in asthma populations and clinical symptoms of OSA and asthma can overlap. Participants were also included in studies without consistent confirmation of asthma diagnosis. It is notable that of the six PSG studies, two of these studies relied on a previous physician diagnosis of

asthma, one study used self-reported asthma and one study used unquantified reversible airway obstruction. Only two studies had criteria similar to the American Thoracic Society (ATS) or Global Initiative for Asthma (GINA) guidelines. Of the questionnaire-based studies, only eight of the thirteen studies demonstrated evidence of robust asthma diagnostic criteria.

It is reasonable to assume that many of the participants in the questionnaire-based studies by Teodorescu et al. could overlap. The cross-sectional study in 2012 (37) has reported that it is an expansion of other studies included in this review (10, 34, 38). The impact of this should be considered, particularly given the limited number of studies available.

The effects of confounders such as BMI are not adequately accounted for in all studies. Yigla et al. found an unexpectedly high prevalence of OSA in SA at 95% (32), which could be attributed to steroid use. However the average BMI and neck circumference were both higher than normal in this population, both of which are independent risk factors for OSA. Without a control group it is difficult to ascertain the cause of this unexpectedly high prevalence of OSA. The population studied by Shaarawy et al. (28) also had a mean BMI that would fall within obese range, but the prevalence of OSA in this group is lower than other PSG-based studies with lower BMI populations. Zidan (25) and Julien et al. (30) also had overweight populations, but mean BMI was not significantly different from the control groups. Obesity is an important comorbidity to consider, not only because it increases the likelihood of OSA but also due to its association with asthma. The interplay between obesity, asthma, and OSA is complex (Figure 1) and it would be ideal to ascertain the direction of this relationship, but given the cross-sectional nature of the majority of studies, this is beyond the scope of this review.

Despite the discussed limitations, we have systematically reviewed the current evidence and found an association between OSA and asthma, which is stronger than that of the general population (4). Further well-designed studies using overnight PSG and robust asthma diagnostic criteria are required.

Conclusion

This review of the current literature demonstrates a consistently high prevalence of OSA in asthma, particularly SA. Studies using questionnaires to assess OSA risk have reported similar findings. Coexisting OSA may adversely impact on asthma-related clinical outcomes. However, there is a lack of PSG-based studies, and further evidence is required before firm conclusions on this topic can be made.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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