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CLINICAL REVIEW

# Asthma and obstructive sleep apnoea in adults and children – an up-to-date review

Ran Wang [a, b], Stefan Mihaicuta [c, *], Angelica Tiotiu [d], Alexandru Corlateanu [e], Iulia Cristina Ioan [f, g], Andras Bikov [a, b]

[a] North West Lung Centre, Wythenshawe Hospital, Manchester University Foundation Trust, Manchester, United Kingdom
[b] Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester, United Kingdom
[c] Center for Research and Innovation in Precision Medicine of Respiratory Diseases, Department of Pulmonology, "Victor Babes" University of Medicine and Pharmacy Timisoara, Timisoara, Romania
[d] Department of Pulmonology, University Hospital of Nancy, France
[e] Department of Respiratory Medicine, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[f] Lung Function Testing Lab, University Children's Hospital of Nancy, France
[g] DevAH, University of Lorraine, France

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SUMMARY

Obstructive sleep apnoea (OSA) and asthma are two common respiratory disorders in children and adults. Apart from common risk factors, such as obesity, gastroesophageal reflux disease and allergic rhinitis, emerging evidence suggest that the two diseases may complicate the clinical course of each other. On one hand, OSA modifies asthmatic airway inflammation and is associated with poor asthma control. On the other hand, asthma and its medications increase the collapsibility of the upper airways contributing to the development and worsening of OSA. The overnight respiratory symptoms of OSA and asthma are often similar, and an inpatient polysomnography is often necessary for a proper diagnosis, especially in children. Continuous positive pressure, the gold standard treatment for OSA can improve asthma control in patients suffering from both diseases. However, there is limited evidence how anti-asthma medications act in the same patients. Nevertheless, adenotonsillectomy seems to be effective in children with concomitant asthma and OSA. This review summarises the evidence for the bidirectional link between asthma and OSA, focuses on diagnostic and therapeutic challenges and highlights the need for further research.



## Introduction

Whilst asthma is a chronic inflammatory disease of the airways that is characterised by variable expiratory airflow limitation [1], obstructive sleep apnoea (OSA) is characterised by repetitive complete or partial collapse of the upper airways during sleep [2]. The co-existence of asthma with OSA is common, partly due to the high prevalence of both diseases, but also the shared risk factors and genetic background [3].

In this review, we will update the epidemiological and pathophysiological link between the two diseases and focus on diagnostic and clinical challenges in both children and adults when assessing co-existent asthma and OSA. We also summarise the clinical and research recommendations for this area.

## Epidemiology

### *Prevalence of asthma and OSA*

There are mounting evidence showing a bidirectional link between asthma and OSA where each adversely influence the other [4]. Whilst asthma is the most common chronic disease of the airways affecting both adults and children worldwide [5], OSA is the most prevalent (yet under-recognised) chronic sleep-related breathing disorder. More than 339 million people worldwide are

* Corresponding author. Center for Research and Innovation in Precision Medicine of Respiratory Diseases, Department of Pulmonology, "Victor Babes" University of Medicine and Pharmacy Timisoara, E. Murgu Sq. no. 2, 300041, Timisoara, Romania. Fax: +40256706437.
*E-mail address:* Stefan.mihaicuta@umft.ro (S. Mihaicuta).

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**Abbreviations**

| | |
|---|---|
| AHI | apnoea-hypopnoea index |
| AT | adenotonsillectomy |
| BHR | bronchial hyperresponsiveness |
| BMAL1 | brain and muscle ARNT-Like 1 |
| BMI | body mass index |
| cACT | children asthma control test |
| CIH | chronic intermittent hypoxaemia |
| CPAP | continuous positive airway pressure |
| ESS | Epworth sleepiness scale |
| FeNO | fractional exhaled nitric oxide |
| $FEV_1$ | forced expiratory volume in 1 s |
| GINA | global initiative for asthma management and prevention |
| GORD | gastro-oesophageal reflux disease |
| HIF | hypoxia inducible factor |
| ICS | inhaled corticosteroid |
| IL | interleukin |
| LTRA | leukotriene receptor antagonist |
| MMP | matrix metalloprotease |
| NF-κB | nuclear factor-κB |
| OCS | oral corticosteroid |
| OSA | obstructive sleep apnoea |
| OVA | ovalbumin |
| PEFR | peak expiratory flow rate |
| PSG | polysomnography |
| REM | rapid eye movement |
| RBM | reticular basal membrane |
| SARP | severe asthma research program |
| VEGF | vascular endothelial growth factor |

currently diagnosed and treated for asthma, and almost one billion people are affected by OSA [2]. Both conditions each poses a substantial health-economic burden [5,6], but the long-term sequelae of untreated OSA further causes increased risks of cardiovascular diseases, metabolic syndrome disorders, reduced quality of life and premature deaths, and therefore further negatively impact on disease-related morbidity and mortality [6].

In a meta-analysis, the prevalence of objectively confirmed OSA in patients with asthma is as high as 50%, approximately 2-fold higher compared to those who has OSA risks (from validated questionnaire-based evaluations) (20–28%) [4]. This was confirmed by a subsequent systematic review, but a significant heterogeneity between studies was also highlighted [7]. There is a clear link between increasing OSA risk and asthma severity [8,9], poor asthma control [10,11], the frequency of severe asthma exacerbations [12,13], longer hospital stay [13] and long-term mortality [14] with the prevalence of OSA symptoms in severe asthma is almost 9-fold higher than in non-asthmatic individuals [15]. The link between OSA and asthma is stronger in females than in males [16,17] and the association between OSA risk and asthma severity is stronger in older than in younger subjects [18].

On the other hand, asthma also seems to be more prevalent in patients with OSA than in healthy subjects. The prevalence of asthma in patients with OSA varies between 5% and 20% [17,19,20]. Asthma was associated with worse sleep quality and increased daytime sleepiness in the severe asthma research program (SARP) II study [9], however another study investigating a Central European population did not find a link between asthma and Epworth sleepiness scale (ESS) [19].

The associations are not merely observed in cross-sectional studies. Investigating subjects without OSA, with or without self-reported asthma in the Wisconsin Sleep Cohort Study, Teodorescu et al. reported that a higher proportion of patients with asthma developed OSA within 4 years (27%) than of non-asthmatic subjects (17%). The relative risk for OSA incidence was 1.39 after adjusting for gender, age and body mass index (BMI) [21]. However, disease severities were not investigated bi-directionally and the findings have not yet been confirmed by any other studies to date. In another prospective observational study, patients with asthma were three times more likely to develop habitual snoring regardless of BMI or weight changes over 14 years [22]. This is further confirmed in a larger but retrospective cohort study of >38,000 patients with newly diagnosed asthma [23]. Although evidence remains lacking due to predominant questionnaire-based studies, existing data may indicate that the two conditions may be related and have diagnostic and therapeutic implications.

*Common risk factors*

Several common risk factors have been associated with both OSA and asthma, including obesity, rhinitis, smoking, systemic corticosteroid treatment and gastro-oesophageal reflux disease (GORD) [24]. Most importantly, obesity is a rapidly growing global health concern affecting 1.9 billion adults and 650 million children [25]. It is a major risk factor for OSA, and with the simultaneous increase in asthma prevalence, the asthma-obesity link has been well-established in both children and adults [26,27]. Losing weight in obese asthmatics improves ventilation mechanics and asthma related quality of life [28]; whilst, weight loss in patients with OSA improves nocturnal oxygenation, reduces day-time somnolence and apnoea-hypopnoea index (AHI) [29].

Sleep disturbances are also commonly reported in asthma, owing to prevalent nocturnal symptoms reported in up to three quarters of patients with asthma [30]. Recently, Maidstone et al. demonstrated clear associations between asthma acquisition and severity and shift working using data collected from >280,000 UK Biobank participants [31]. Importantly, whilst permanent night shift workers had higher risk of moderate-severe asthma than day workers, participants with morning chronotype (who gets up early and sleep early) but working irregular shifts (including night shifts) had an even higher risk after adjustment for major confounding factors. Shift working is an important circadian rhythm modulator, which cause misalignment of circadian timing system. Therefore, sleep disruption and misalignment of circadian rhythm may potentially add to our previous knowledge of the asthma-OSA bidirectional relationship [32,33].

## The bidirectional link between OSA and asthma

*The circadian clock*

OSA may modulate asthma by affecting airway immunity and bronchial hyperresponsiveness (BHR). On the other hand, asthma may lead to upper airway narrowing contributing to development of OSA (Fig. 1). Of note, many patients with asthma report nocturnal symptoms without any evidence of OSA [30,34]. Peak expiratory flow rate (PEFR) and forced expiratory volume in 1 s ($FEV_1$) are the lowest at night in these patients accompanied by the greatest BHR to methacholine and histamine at 4:00 AM. Bronchial eosinophil, lymphocyte, neutrophil and total leukocyte counts also peak at 4:00 AM in asthma [34]. In addition, using murine models, the deletion of core clock gene Brain and Muscle ARNT-Like 1 (BMAL1)

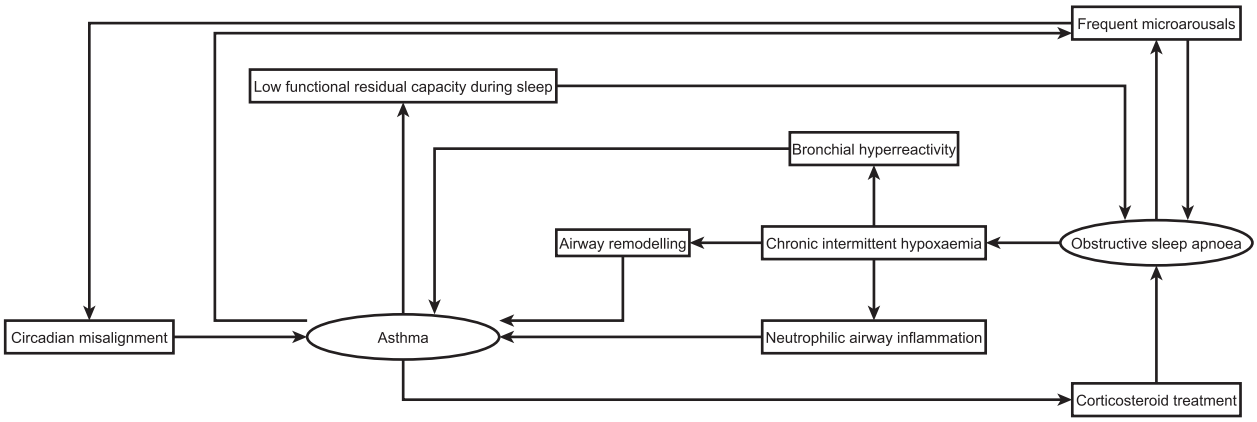


**Fig. 1.** The bidirectional relationship between OSA and asthma.

and chronic jet lag exacerbate acute viral-induced bronchiolitis and BMAL1 knockout mice developed heightened asthma-like airway changes post infection [35]. Mice lacking BMAL1 in myeloid cells showed increased lung inflammation, markedly higher number of eosinophils and increased interleukin (IL)-5 levels in lung and serum following ovalbumin (OVA)-induced sensitisation [36]. Circadian differences in airway hyperresponsiveness are also gated by clock gene REV-ERBα in mouse models [37]. Using bronchial washings of patients with severe asthma, Ehler et al. demonstrated loss of clock gene expressions such as BMAL1, PER2 and REV-ERBα in asthmatics compared to the controls. Children with respiratory syncytial virus bronchiolitis and persistent wheeze also demonstrated deficient BMAL1 expression in nasal washings [35]. Recently, Scheer et al. studied patients with asthma who were untreated with steroids using a constant routine and a forced desynchrony protocol and confirmed that the intrinsic circadian system plays a significant role in modulating pulmonary function and asthma severity, independent of sleep and other behavioural/environmental cycles [38]. Notably, intermittent hypoxaemia in OSA may also lead to circadian misalignment potentially contributing to the link between asthma risks in OSA [39]. Using leukocytes of peripheral blood collected in patients with OSA and healthy controls, Yang et al. demonstrated that three core clock genes were disrupted, and eight clock genes, including BMAL1, were down-regulated at midnight in patients with severe OSA [40]. Combined clock genes CRY1 and PER3 were associated with severe OSA [40].

### *Airway inflammation*

Chronic intermittent hypoxaemia (CIH) in OSA induces various alterations in airway inflammation [41] (Fig. 2). These changes are primarily mediated by bronchial epithelial cells and alveolar macrophages. Hypoxaemia induces bronchial epithelial, most particularly club cell proliferation via hypoxia inducible factor (HIF)-2α [42]. In addition, it leads to the production of matrix metalloproteinase (MMP)-2, MMP-9, IL-8, platelet derived growth factor-AA and vascular endothelial growth factor (VEGF) [43] by the epithelial cells. It is not clear if epithelial permeability is also increased, as although hypoxaemia leads to increased permeability of the nasal epithelial cells [44] small airway epithelial cells expressed higher levels of epithelial junction protein following hypoxaemia [45]. Hypoxaemia also leads to increased IL-6 production by alveolar macrophages via HIF-1α and nuclear factor (NF)-κB [46]. Furthermore, hypoxia may induce cell necrosis in the airway cells which leads to IL-1α release from the dying cells inducing NF-κB expression by alveolar macrophages [47]. Interleukin-8 produced by epithelial cells and macrophages upon CIH leads to neutrophil influx [43] which is accelerated by bronchial vasodilation induced by VEGF excess from epithelial, bronchial smooth muscle and bronchial epithelial cells [43]. Furthermore, hypoxaemia contributes to neutrophil survival which is mediated by HIF-1α-dependent NF-κB activity [48]. In line with this, higher sputum neutrophil counts were demonstrated in patients with OSA [49,50]. Increased levels of multiple inflammatory molecules reflecting on Type1 inflammation in sputum and exhaled breath condensate were also reported [41,51]. In OVA-sensitised rats, Broytman et al. also demonstrated that CIH alters immune response to allergen towards a Th-1-predominant cellular phenotype with collagen deposition and matrix degradation, leading to medium and large airway obstruction [52]. Ohta et al. demonstrated that CIH decreases IL-5, IL-13 levels, and eosinophil numbers in bronchoalveolar lavage fluid in OVA-sensitised mice [53]. Furthermore, CIH exposure suppressed glucocorticoid sensitivity by activating the p38 MAPK signalling pathway in OVA-challenged mice [54].

Higher risk for OSA based on a questionnaire was independently associated with sputum neutrophilia in patients with asthma participating in the SARP study [9]. The effect of OSA on asthmatic airways has been investigated directly by Taille et al. who reported that severe asthmatic patients with OSA had higher sputum neutrophils and lower sputum macrophages, higher sputum IL-8 and MMP-9 levels than those patients with asthma who did not have OSA. The reticular basal membrane (RBM) was significantly thinner in bronchial biopsies from patients with OSA with a significant inverse relationship between RBM thickness and AHI. The airway smooth muscle area and number of vascular sections were similar for OSA and non-OSA patients. The number of eosinophils, neutrophils, mast cells and lymphocytes in biopsies was similar between the two groups, despite the number of neutrophils being higher, although not significantly, in OSA than non-OSA patients with asthma [55]. These changes imply that OSA may be disease modifying in asthma as neutrophilia contributes to steroid resistance and increased disease severity in asthma [56].

### *Upper and lower airway physiology*

It is known that hypoxaemia worsens BHR [57] which is likely to be mediated via carotid chemoreceptors [58]. In addition, high risk of OSA was associated with more rapid lung function decline in general population and this was steeper among patients with

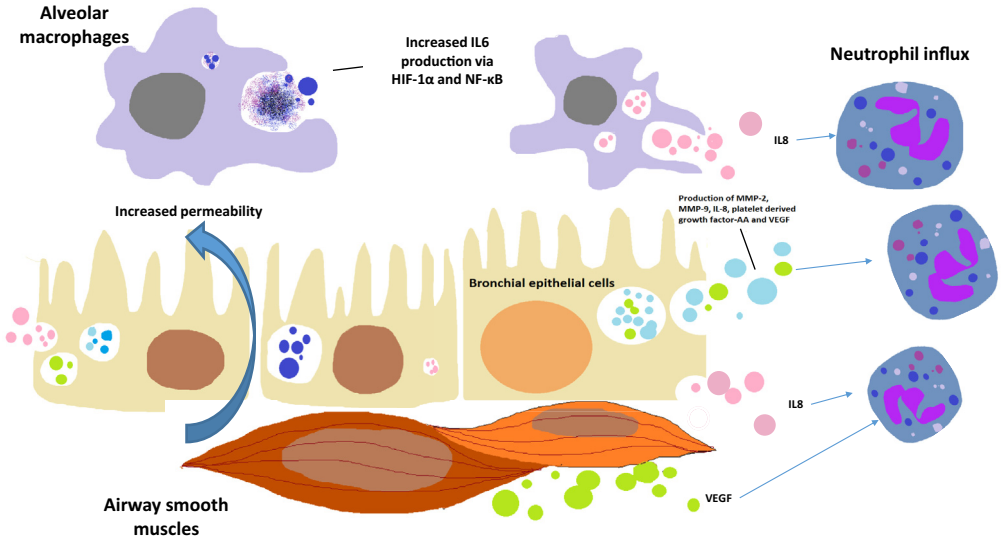


**Fig. 2.** The effect of intermittent hypoxaemia in the airways.

asthma [59]. In patients with asthma, OSA accelerated $FEV_1$ decline, and its pace was related to OSA severity [60].

Asthmatic patients frequently report poor sleep quality irrespective from nocturnal breathlessness which is related to worse asthma control [30]. Sleep fragmentation [61] and sleep deprivation [62] caused by nocturnal asthma may lead to increased collapsibility of the upper airways. In addition, bronchoconstriction may lead to glottal narrowing [63,64].

Smaller lung volumes could also contribute to increased collapsibility of the upper airways during sleep [41]. It has been noticed that patients with asthma express a greater reduction in functional residual capacity than healthy volunteers [65]. In line with this, $FEV_1$ and forced vital capacity were related to OSA severity in non-asthmatic subjects [66]; however there was no relationship between $FEV_1$ and OSA risk in patients with asthma [67]. Moreover, when lying supine, fluid shifting from the legs to the chest causes increased airway resistance and stiffness [68] and asthmatics with narrower small airways may be more sensitive to this effect during sleep [69]. Using Muller manoeuvres to simulate the effects of OSA, Cao et al. found that exaggerated negative intrathoracic pressure against occluded pharynx during obstructive apnoeas drew blood into the thorax, increasing the intrathoracic fluid and caused increased airway resistance in asthmatics [70].

The bidirectional link between asthma and OSA are clearly multifaceted. Understanding the contributing mechanisms will have therapeutic implications for both conditions.

## Diagnostic challenges

The symptoms of OSA are heterogenous and the clinical presentation varies from a completely asymptomatic individual to patients reporting snoring, nocturnal choking, nocturia, excessive daytime sleepiness and cardiovascular, metabolic and cognitive comorbidities [2].

Symptoms of OSA such as nocturnal dyspnoea, non-restorative sleep and daytime fatigue are often difficult to separate from asthma-related symptoms. Nocturnal dyspnoea may be described by the patient as nocturnal choking, gasping, coughing, or shortness of breath. Patients with asthma suffer from night-time coughing, wheezing and breathlessness that disturb their sleep [34] and they report more daytime sleepiness [17,20]. Some of these symptoms perceived as asthma may be related to OSA and therefore, should be considered for sleep study [71]. On the other hand, investigation for asthma should be considered for patients with symptoms suggestive of OSA and a normal sleep study.

Obesity, rhinitis and nasal polyposis are frequent in both diseases, and may complicate asthma, therefore assessment for OSA is advised [72]. Patients who have allergic and non-allergic rhinitis should be screened for common comorbidities such as asthma and OSA, therefore a sleep test and a lung function test are needed [72]. The 2020 update of the global initiative for asthma management and prevention (GINA) document incorporates the recommendation that a broad range of differential diagnoses for both nocturnal and daytime symptoms need to be considered. In severe asthma with obesity there is a need to distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction and/or sleep apnoea [1].

The “gold standard” for the diagnosis of OSA is PSG which provides detailed information on sleep stages, arousals from sleep, and respiratory abnormalities. A previous systematic review highlighted that most studies assessing OSA and asthma used cardiorespiratory polygraphy that is a less sensitive method to diagnose OSA and often underestimates disease severity [7]. Asthma may modify the results of a sleep study. It has been reported that patients with asthma and OSA may have deeper drops in oxygen saturation compared to patients with OSA but without asthma [73], especially in rapid eye movement (REM) sleep [74]. However, asthma alone is not associated with obstructive respiratory events [74] or desaturations [75]. On the other hand, patients with asthma have shorter total sleep time, higher proportion of N2 and lower proportion of N3 sleep [17] as well as longer sleep latency [20].

Asthma diagnosis is primarily based on demonstrating the evidence of variability of airflow obstruction [1] but OSA itself is not associated with this [49,50]. Fractional exhaled nitric oxide (FeNO) is a surrogate breath biomarker for airway inflammation. Whilst a high level of FeNO supports asthma diagnosis [1], this is also increased in patients with OSA [51].

## The effect of asthma therapy on OSA

Pharmaceutical treatment of asthma includes inhaled corticosteroids (ICS), long-acting β2-agonists, tiotropium, leukotriene receptor antagonists (LTRA), biologics and oral corticosteroids (OCS) [1].

Increasing evidence suggests that patients with asthma treated with ICS are more at risk to develop OSA (the estimated risk varies between 1.33 and 4.05) [8,11,23]. In a clinical survey including 244 patients with asthma, the use of ICS was dose-dependent with an increased risk for habitual snoring and OSA, independent of asthma severity and being overweight. The OSA risks were 129% higher for those treated by low-dose, 267% higher for medium-dose and 443% higher for high-dose ICS compared to those without ICS use [8]. The hypothetical mechanisms include myopathy with a decrease in contractility of the upper airway dilator muscles and the centripetal fat accumulation/redistribution in the neck raising the surrounding tissue pressure, well-known side-effects of ICS, particularly at higher doses [11]. Indeed, the administration of high-dose inhaled fluticasone propionate (1760 μg/day) for 16 wk in corticosteroid-naive subjects with mild asthma increased genioglossus muscle strength at wakefulness and decreased endurance, in a comparable pattern to untreated patients with OSA [76]. The treatment affected the passive upper airway collapsibility during sleep which was related to age, male gender, less controlled asthma, and higher AHI. In another subset of participants whose weight and upper airway collapsibility did not change during the study, the fat content in the neck (measured by magnetic resonance imaging) increased by 20.6% from baseline [76]. These findings confirm that high-dose ICS alter the structure and the collapsibility of upper airway during sleep. In line with this, ICS destabilise tongue muscle hydrostat properties leading to increased collapse potential in rats [77]. A very recent study showed that the use of ICS increased the risk of OSA independently of asthma control (odds ratio, OR 1.58) and this risk was different according to the size of particles [11]. Most ICS containing inhalers have particles with a mass median aerodynamic diameter between 2 and 4.5 μm, therefore result in more deposition in the upper airways. ICS with extra-fine particles of <2 μm distribute more uniformly across the lower airway. While those who used ICS with standard size particles had increased odds for OSA compared to non-users (OR 1.56), this risk for OSA was not observed when extra-fine particle ICS users were compared to patients who did not use ICS (OR 1.11) [11].

The prevalence of OSA was extremely high in patients with severe asthma who were treated with long-term OCS (95.5%) [78]. The mean respiratory disturbance index in the group requiring continuous therapy with OCS was significantly higher compared to the group receiving bursts. However, these studies are limited by small sample size and the findings must be confirmed by largest studies. A course of systemic corticosteroids significantly increases BMI [78,79] and leads to peri-pharyngeal fat deposition and upper airways myopathy [79]. Corticosteroids may also shorten REM sleep latency and increase REM density [79] contributing to higher propensity of OSA.

A randomized, double-blind, placebo-controlled study analysed the effects of salmeterol during sleep in 20 patients with OSA [80]. All patients underwent full polysomnography at baseline and after the administration of placebo or 50 μg salmeterol at 7PM. There were no differences in total sleep time, sleep stages, apnoea index, AHI, and nadir oxygen saturation between the placebo and salmeterol groups [80]. A double-blinded, placebo-controlled study showed that the administration of montelukast 10 mg/day for several weeks in patients with perennial allergic rhinitis improved daytime somnolence and fatigue compared to placebo. However, there was no difference in the ESS between the groups [81]. A case report suggests a possible role of omalizumab in improving OSA (decrease in AHI from 72.7/h to 21.9/h) without weight loss in a patient with severe asthma [82].

Therefore, the potential adverse effects of asthma therapy on OSA are predominantly due to inhaled and oral corticosteroid use, and not bronchodilator or leukotriene receptor antagonist treatment. The effects of use of biologics on OSA remains unclear.

## The effect OSA therapy on asthma

Continuous positive airway pressure (CPAP) is the first line therapy in OSA, especially for moderate-to-severe patients. Potential beneficial mechanisms of CPAP in OSA and asthma can be mechanical and neuromechanical effects, suppression of GORD, local and systemic anti-inflammatory effects, cardiac function improvements, leptin level suppression, weight reduction and sleep restoration [83].

In their seminal study in 1988, Chan et al. demonstrated that CPAP improved asthma control and PEFR in nine patients with asthma and OSA [84]. In 16 patients with asthma 7-day CPAP therapy improved BHR compared to a sham challenge [85]. In 20 patients with coexisting asthma and OSA 6 mo of CPAP treatment improved asthma quality of life without changing lung function or BHR [86]. In a larger, subsequent study involving 99 patients, 6 mo of treatment with CPAP led to improvement of bronchodilator reversibility, a decrease of FeNO and a reduction in the score of the Asthma Control Questionnaire [87]. Those patients who used their device for more than 4 h/night benefited from the treatment [87]. In addition, CPAP decelerated $FEV_1$ decline in asthmatic patients [60]. In a cross-sectional study, where OSA was related to increased asthma severity, CPAP treatment attenuated this risk, especially in older subjects [18]. In contrast, bilevel positive airway pressure therapy did not change asthma control or BHR [88]. Finally, CPAP therapy reduced 10-yr mortality in patients with co-existing asthma and OSA [14]. A meta-analysis summarising studies with CPAP in asthma concluded an improvement in asthma quality of life, but no change in lung function [89].

The effect of CPAP on airway biology is contradictory, likely because this therapy may increase BHR in subjects without asthma [49]. On the other hand, humidified sham and CPAP challenge reduced BHR in patients with asthma without difference between sham and CPAP, suggesting that dry air rather than positive airway pressure affects BHR [90].

It is not clear how CPAP affects airway inflammation. Irrespective of asthma, CPAP decreased the airway levels of IL-6, 8-isoprostane, tumour necrosis factor-α, nitrotyrosine and increased IL-10 and sirtuin one concentrations as well as pH. However, other studies did not show any change in exhaled carbon monoxide, or airway IL-6, $H_2O_2$, 8-isoprostane, nitrate, leukotriene B4, or pH values [41,51]. There was a significant decrease in FeNO following CPAP treatment in some, but not all studies [51]. CPAP had no effect on sputum neutrophilia in OSA [49,50]. However, most of these studies did not take into consideration asthma. Nevertheless, the adherence to CPAP therapy in patients with OSA and concomitant asthma is low [90].

It is important to note that weight loss is another effective treatment for both OSA and asthma and should be encouraged in all patients [28,29].

There is no evidence how second line treatment for OSA, including mandibular advancement device or upper airways surgery improves asthma outcomes in adults.

## OSA and asthma in children

Similarly to adults, children with asthma have poor sleep quality as they experience nocturnal symptoms such as cough or wheeze,

which cause sleep disturbance [91]. Moreover, children with poorly controlled asthma have more frequent and longer nocturnal awakenings than those with well-controlled or no asthma [92] and this contributes to daytime sleepiness with negative effect on academic performances [93]. Asthma may affect the PSG results as it is associated with longer sleep latency, lower N3 ratio, higher N1, N2 and REM ratio, higher leg movement index and arousal index [94] in children.

The significant association between OSA and asthma has been demonstrated in several studies included in a meta-analysis on 45,155 children with mean age 8.6 ± 2.5y which showed evidence that children with asthma have a significantly higher risk for OSA (OR 1.9 [1.7; 2.2]) and OSA is significantly more frequent in these children compared with non-asthmatics, 23.9% vs 16% ($p < 0.01$) [95]. Nevertheless, the main limitation of paediatric studies is that asthma and OSA are usually defined by subjective measures based on questionnaires or clinical history and not by objective PSG or lung function testing. By analysing the studies that used PSG or polygraphy for OSA diagnosis, the overall risk of OSA was also high [96,97]. The evidence of an independent association between OSA and asthma was further established in a recent large cross-sectional survey of 20,672 school-aged children in whom asthma and OSA were evaluated by questionnaires. The prevalence of OSA was 12.0% and 3.5% for asthma. The symptoms of OSA, such as habitual snoring and apnoea, were found to be significantly associated with asthma after adjusting for demographic and socioeconomic characteristics, obesity and allergy [98]. In addition, OSA is more frequent in severe than in mild to moderate asthmatic children [99], thus contributing to poorer asthma control and need for higher dose of systemic corticosteroids.

The recent GINA recommendations list OSA as a comorbidity of asthma in children 6–11 yr of age [1] and the 2016 European Respiratory Society statement on paediatric OSA recommends that children be screened for comorbidities [100]. However, there are no specific recommendations to address when to refer asthmatic children for sleep studies or what screening method to use or when to perform a lung function testing for a child with OSA. Nonetheless, asthmatic children with uncontrolled asthma or frequent nocturnal symptoms should be referred for a PSG to rule out an underlying sleep condition. Future research should focus on protocols for systematically, objectively assessing these conditions and their association to avoid serious irreversible consequences.

There is no study on effects of asthma therapy on OSA in children with both conditions. However, two prospective randomised double-blind studies reported improvement in overnight respiratory indices in children with OSA following montelukast treatment [101,102].

A large database study that identified 13,506 children with asthma who underwent adenotonsillectomy (AT) and 27,012 age-, sex- and geographically-matched children with asthma without AT showed that the surgical procedure was associated with significant reductions in acute asthma exacerbations, acute status asthmaticus, asthma-related emergency room visits and asthma-related hospitalizations in the year following AT in comparison with the year preceding AT. AT was as well associated with significant reductions in most asthma prescription refills, including bronchodilators, ICS, LTRA and systemic corticosteroids [103]. Another recent study has demonstrated a significant improvement in childhood asthma control test scores (cACT) in asthmatic children after AT compared to asthmatic control children not undergoing surgery with 47% of the asthmatics having uncontrolled asthma before AT compared to only 15% at follow-up, whereas in controls, the proportion of subjects with uncontrolled asthma did not change (37% at entry vs 32% at follow-up). The multivariate analysis identified baseline score at paediatric sleep questionnaire as a significant predictor of improvement in cACT, the additional variables in the model (i.e., prematurity, ethnicity, allergy and BMI) being non-significant [104].

The impact of asthma on the need for CPAP therapy in children with severe OSA was investigated in a cross-sectional study on 400 children, 133 (33%) of them being asthmatics, and it was found that significantly more asthmatics with severe OSA need CPAP than children with OSA alone (29% vs 14%, $p < 0.01$) [105]. Moreover, the association between asthma and the need of CPAP was independent of demographics, OSA severity, obesity and history of AT ($p < 0.01$) [105]. In contrast to adults, asthma was not associated with poor adherence in children [106].

## Summary and recommendations

Several lines of evidence suggest that OSA and asthma may complicate each other contributing to worsening disease severity. Despite multiple studies investigating how asthma influences the function of the upper airways and how OSA contributes to airway inflammation, the number of translational studies directly assessing patients with OSA and asthma is low. There is good evidence that CPAP and adenotonsillectomy, first line treatment for OSA in adults and children, respectively, improves asthma control. However, it is less clear, how treatment of asthma influences OSA in patients suffering from both diseases.

**Practice points**

- Referral for a PSG is recommended in adult and paediatric patients with non-fully controlled asthma who show daytime sleepiness or nocturnal symptoms or those who have risk factors for OSA (obesity, comorbidities), reflux or ear, nose, and throat symptoms.
- Assessment for asthma is recommended in those who complain about nocturnal respiratory symptoms and have a normal PSG, or those who continue having nocturnal symptoms despite optimal OSA management.
- CPAP coupled with a humidifier should be offered as a first line treatment for adult patients suffering from concomitant OSA and asthma.
- Montelukast, adenotonsillectomy and CPAP could be offered in children with OSA and asthma.

**Research agenda**

- We suggest conducting human studies investigating airway pathology in patients with concomitant asthma and OSA using invasive and non-invasive techniques.
- We suggest clinical trials comparing different ICS treatments on upper airways collapsibility.
- We suggest clinical trials assessing the effect of montelukast in patients with asthma and concomitant OSA.
- We suggest including sleep studies to assess OSA in clinical trials using biologics in severe asthma to better define the impact of OSA on treatment outcomes in this special group.

## Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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