

## INVITED REVIEW

# Integrating the overlap of obstructive lung disease and obstructive sleep apnoea: OLDOSA syndrome

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## ABSTRACT

Obstructive lung diseases (OLD) such as asthma and chronic obstructive pulmonary disease (COPD) are very prevalent conditions. Disease phenotypes (e.g. chronic bronchitis, emphysema, etc.) often overlap, and significant confusion exists about their optimal nosologic characterization. Obstructive sleep apnoea (OSA) is also a common condition that features bidirectional interactions with OLD. OSA appears to be more commonly seen in patients with OLD, perhaps as a result of shared risk factors, for example obesity, smoking, increased airway resistance, local and systemic inflammation, anti-inflammatory therapy. Conversely, OSA is associated with worse clinical outcomes in patients with OLD, and continuous positive airway pressure therapy has potential beneficial effects on this vicious pathophysiological interaction. Possible shared mechanistic links include increased parasympathetic tone, hypoxaemia-related reflex bronchoconstriction/vasoconstriction, irritation of upper airway neural receptors, altered nocturnal neurohormonal secretion, pro-inflammatory mediators, within and inter-breath interactions between upper and lower airways, lung volume-airway dependence, etc. While the term overlap syndrome has been defined as the comorbid association of COPD and OSA, the interaction between asthma and OSA has not been integrated yet nosologically; in this review, the latter will be called alternative overlap syndrome. In an effort

to bolster further investigations in this area, an integrated, lumping nomenclature for OSA in the setting of OLD is proposed here—OLDOSA (obstructive lung disease and obstructive sleep apnoea) syndrome.

**Key words:** asthma, chronic obstructive pulmonary disease, obstructive sleep apnoea, respiratory function test.

**Abbreviations:** AHI, apnoea-hypopnoea index; BHR, bronchial hyperresponsiveness; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; FEV<sub>1</sub>, forced expiratory volume in 1 s; IL, interleukin; OLD, obstructive lung diseases; OR, odds ratio; OSA, obstructive sleep apnoea; QOL, quality of life.

## INTRODUCTION: ASTHMA, COPD AND OSA—THREE COMMON CHRONIC CONDITIONS

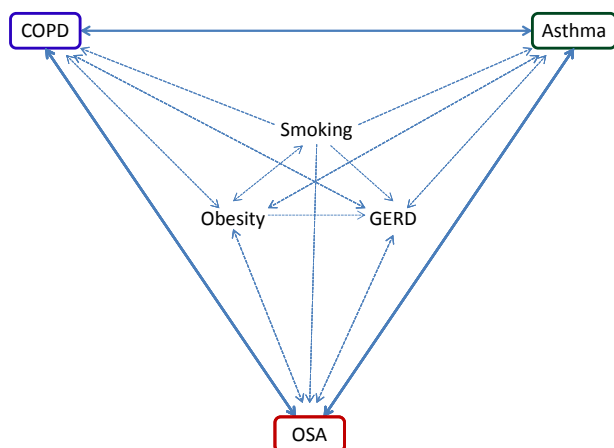
Asthma and chronic obstructive pulmonary disease (COPD) are frequent chronic respiratory disorders and important causes of impaired health-related quality of life (QOL), disability and death worldwide.<sup>1,2</sup> Obstructive sleep apnoea (OSA) is also a common condition, and its effect on health is increasingly being recognized, including its adverse cardiovascular consequences.<sup>3</sup> Mounting evidence suggests bidirectional interactions between OSA, asthma and COPD, beyond random coexistence due to high prevalence. The term overlap syndrome has been used for the coexistence of OSA and COPD; while such an interaction clearly exists with asthma, it has not been rigorously validated so far (we will call this clinical scenario alternative overlap syndrome).

We will examine here each side of the triangle COPD–asthma–OSA and will discuss several of the pathophysiological and clinical interactions between them (Fig. 1). We will start by discussing current nosologic and pathophysiological conundrums related to obstructive lung diseases (OLD), review the existent epidemiological and pathophysiological data for the said overlap syndromes and will finish with the arguments for incorporating OLD and OSA into a more general entity (OLDOSA syndrome). The intent of this

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**Figure 1** Complex interactions between asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea (OSA)—outer triangle, and the contribution of obesity, smoking (or inflammation) and gastro-oesophageal reflux disease (GERD)—inner triangle (see text for further details of these interactions).

endeavor is nosologic ‘re-lumping’ for future, better ‘re-splitting’, based on more precise definitions and phenotyping, pathophysiological interactions and, hopefully, personalized therapies. Arguments for defining this new syndrome are multiple: (i) asthma and COPD often coexist and sometimes are difficult to be differentiated based on current clinical and functional criteria; (ii) OSA seems to be more prevalent in both COPD and asthma populations; (iii) OSA is relevant to disease control/mortality of both asthma and COPD patients; (iv) inspiratory and expiratory flow limitation tend to potentiate each other; (v) OLD and OSA share common risk or aggravating factors such as ageing, obesity, smoking, gastro-oesophageal reflux disease, etc.; and (vi) OSA is associated with worse OLD outcomes, which improve when OSA is treated.

## OLD: ASTHMA AND COPD

### Definition conundrum

OLD are a heterogeneous group of disorders with distinct subphenotypes (e.g. chronic bronchitis, emphysema, small airway disease, asthma with airway hyperreactivity, asthma with remodelling and no airflow reversibility, etc.). It is likely that each phenotype emerges from the interaction between different genetic backgrounds and environmental exposures, through different pathophysiological pathways. Thus, without adequate phenotyping, any therapeutic approach may lack the level of individualization needed to ‘tackle’ the specific pathophysiological pathway. OLD are operationally defined by diagnostic criteria that are not mutually exclusive and very different in nature, that is anatomical, biological, functional or clinical criteria. Global Initiative for Asthma defines asthma as an airway disease [anatomical criterion], emphasizing its inflammatory nature [biological criterion] and characterized by airflow

limitation reversibility and bronchial hyperresponsiveness (BHR) [functional characteristics].<sup>4</sup> On the other hand, the two major phenotypes of COPD are defined as follows: (i) chronic bronchitis—cough and sputum production for >3 months, for  $\geq 2$  consecutive years [clinical criterion]; and (ii) emphysema—permanent enlargement and destruction of distal airspaces established tomographically or by pathologic examination [anatomical criterion]. Furthermore, Global Initiative for Chronic Obstructive Lung Disease describes COPD such as non-reversible [functional aspect] and usually progressive airflow limitation [historical component], and defines it as a post-bronchodilator forced expiratory volume in 1 s ( $FEV_1$ ) to forced vital capacity ratio ( $R$ ) < 0.70 [functional definition].<sup>5,6</sup>

There are several pitfalls to these definitions: (i) they span different domains (clinical, functional, anatomical, etc.); (ii) they are not mutually exclusive (not partitioning unequivocally the spectrum of OLD); (iii) because  $R$  tends to decrease with age, a fixed threshold of 0.70 leads to underestimation of COPD in the young and overestimation in the elderly;<sup>7,8</sup> (iv)  $R$  is generally higher in women, and this can underestimate the disease frequency in females; (v) defining airflow obstruction by lower limit of normal may result in a larger number of young asthmatics being diagnosed with COPD; and (vi) post-bronchodilator [vs pre-bronchodilator]  $R$  may reduce the prevalence of COPD by about 25% in general population, especially in younger individuals.<sup>8,9</sup> While the intent of using post-bronchodilator ratio was to specifically exclude patients with asthma, the latter can at times have less reversible airway limitation, and hence be misclassified.<sup>10</sup> Various studies have evaluated the prevalence of OLD based on the earlier definitions and found an astonishing high number of patients with COPD who never smoked (>30%), that asthma accounted for >50% of COPD cases, that high percentage of patients with these diagnoses had  $R > 0.70$  and that a large proportion of the OLD population did not meet criteria for any phenotypic characterization (e.g. asthma, chronic bronchitis or emphysema).<sup>11</sup>

Furthermore, small airway disease, a frequently forgotten OLD, can be the harbinger of both asthma and COPD. It is typically defined as a disorder of the airways with a calibre <2 mm, which leads to an increased overall airway resistance, expiratory flow limitation and symptoms of breathlessness. It is typically defined as normal  $FEV_1$  and  $R$ , and reduced ‘mid-expiratory flows’.

Recently, there have been several attempts to explore OLD phenotypes with newer methodologies (e.g. cluster analysis, genomics, metabolomics, interactomics, reactome, etc.) which do not rely on *a priori* assumptions about the best way to split disease categories into clinical groups.

In conclusion, current definitions do not provide sufficient discriminating ability between these conditions. Given the discussed limitations of the present OLD definitions, the use of more advanced clustering and characterization techniques is imperatively needed.

### Classification conundrum

The central conundrum of OLD nosology and classification schemes has been a long-lasting conflict between 'splitting' and 'lumping' approaches (e.g. 'British hypothesis' vs 'Dutch hypothesis', respectively).

A group of British investigators in the 1960s posited that recurrent bronchial infections were the reason why only some smokers developed progressive airways disease, although asthma and COPD were considered distinct disorders ('British hypothesis').<sup>12</sup> Fletcher and Peto tested this hypothesis by examining the frequency of respiratory infections, sputum amount and quality in relation to the decline in lung function in a group of working male subjects, but found no correlation between these parameters.<sup>13</sup> More recently, it was found that sputum bacterial load<sup>14</sup> and recurrent respiratory infections or COPD exacerbations<sup>15,16</sup> are in fact associated with an accelerated decline in lung function in patients with COPD.

The 'Dutch hypothesis', proposed by Orie *et al.* more than 50 years ago,<sup>17</sup> stated that asthma and COPD are different expressions of the same disease (lumping approach, potentially useful in epidemiologic studies). The theory is based on three important components: (i) different OLD have overlapping clinical features and phenotypes (e.g. cough, dyspnoea, environmental allergies/susceptibility and/or BHR); (ii) development of OLD is influenced by specific genetic factors and environmental triggers, (e.g. allergenic exposures, infections, smoking, fossil fuel pollution, etc.); and (iii) OLD is 'fluid', that is asthma can lead in time to COPD in the 'right' environmental context (e.g. cigarette smoke exposure). In support of this hypothesis, BHR has been found an important predictor of progression of airway limitation in patients with early COPD who continue to smoke, independent of the baseline level of obstruction,<sup>18</sup> and was predictive of higher COPD mortality.<sup>19</sup> In fact, in a more recent study,<sup>20</sup> BHR was found to be second only to smoking in predicting functional deterioration in COPD (population-attributable risk of BHR for development of COPD was 15%, while cigarette smoking has a population-attributable risk of 39%).<sup>20</sup>

### Pathophysiological conundrum

Although significant controversy still surrounds the natural history and the pathogenic connection between these two major 'phenotypes' of OLD (i.e. asthma and COPD), several pathophysiological arguments can be made for the 'lumping approach'. Both are inflammatory conditions, and their pathologic correlates may have common pathways. Nevertheless, a 'splitting approach' happens almost invariably when pathophysiology comes into discussion. For example, asthma is generally a disease of the airways characterized by eosinophilic inflammation, CD4+ lymphocytic infiltration and humoral factors such as interleukin (IL)-4, IL-5, IL-13 (T helper 2 mediators). On the flip side, more severe disease phenotypes seem to resemble COPD, with more neutrophilic, CD8+ lymphocytic infiltration and being less responsive to steroids.<sup>21,22</sup> COPD is a disease affecting both

large and small airways and distal parenchyma, and is generally characterized by neutrophilic and CD8+ lymphocytic infiltration and chemokines such as IL-6, IL-8, IL-1 $\beta$ , tumour necrosis factor- $\alpha$  (T helper 1 mediators).

More recently, and in addition to (or in support of) the 'Dutch hypothesis', some suggested that patients with OLD (or COPD) suffer from abnormal tissue repair in response to smoking-induced injury (the 'American hypothesis').<sup>23,24</sup> As such, emphysema may arise from abnormal repair of alveolar structures, while small airway remodelling may result from over-exuberant, fibrotic repair of peri-bronchiolar tissues and/or bronchial wall hypervascularization (as seen in asthma). In support of this paradigm is the finding that reduced serum fibronectin levels (which is a critical mediator in injury repair) is associated with rapid disease progression and higher mortality in patients with COPD.<sup>25</sup>

Additionally, shared genes such as A disintegrin and metalloprotease 33, seem to be correlated not only with asthma severity and presence of BHR, but also with susceptibility to develop COPD in the general population and to the rate of lung function decline in both asthma and COPD.<sup>26,27</sup> Last, both disorders seem to respond to similar therapeutic agents, affecting common inflammatory pathways.

## COPD AND OSA: OVERLAP SYNDROME

### Epidemiology

Epidemiologic studies show a prevalence of overlap syndrome of approximately 1% in adult males, but the coexistence of asymptomatic COPD and OSA is likely much higher.<sup>28–31</sup> COPD is characterized by expiratory flow limitation which is typically not fully reversible, usually progressive and associated with a local and systemic inflammatory response triggered by tobacco smoke and other environmental noxious particles or gases. OSA syndrome (i.e. OSA *and* excessive daytime sleepiness (EDS)) affects at least 4–5% of middle-aged persons.<sup>32</sup> More than 80% of men and 90% of women with OSA remain undiagnosed and untreated.<sup>33</sup> Well-recognized risk factors include excess bodyweight, nasal congestion, alcohol, smoking and menopause.<sup>34</sup> Typical symptoms include snoring, witnessed apnoeas and EDS. OSA is diagnosed by polysomnography, based on an apnoea-hypopnoea index (AHI) of  $\geq 5$  events/h of sleep.<sup>35</sup>

One study found a high prevalence (~11%) of OLD in patients with OSA, exceeding the disease frequency in the general population.<sup>36</sup> Conversely, sleep apnoea symptoms among patients with COPD are very common. For example, more than 25% of the COPD participants in the Tucson Epidemiologic Study of Obstructive Airways Disease reported EDS.<sup>37</sup> Additionally, COPD was found to be associated with a higher likelihood of snoring (odds ratio, OR = 1.34), apnoeas (OR = 1.46) and EDS (OR = 2.04).<sup>38</sup> In a clinic population of COPD patients, a high risk for OSA, as assessed by validated questionnaires, was highly prevalent relative to controls (50% vs 7.5%).<sup>39</sup> A high

prevalence of OSA has also been reported in patients with OLD.<sup>40</sup> However, Sanders *et al.* found no increase in OSA prevalence in OLD compared with non-OLD participants.<sup>28</sup> They examined a cohort of 1138 participants in the Sleep Heart Health Study with home-based sleep studies, using oronasal thermistor for airflow monitoring. These participants had OLD defined by  $R < 0.70$ , and were on average of mild severity (mean  $R = 0.63$ ). In this study, the authors' ability to diagnose OSA may have been hampered by reduced sensitivity of thermocouples as opposed to newer methods of assessing airflow, and by limited representation of participants with more severe OLD (e.g.  $R < 0.60$ ). A retrospective analysis of 73 patients studied with lab-based polysomnography and pulmonary function testing revealed that, while overall severity of OSA was not different in subjects with COPD versus no COPD, during rapid eye movement sleep, patients with  $FEV_1 < 80\%$  predicted had higher respiratory disturbance indices than those with higher  $FEV_1\%$  ( $P = 0.01$ ).<sup>41</sup> These discrepancies can be explained by: (i) definition differences for SDB events (hypopnoeas, respiratory effort-related arousals, 4% vs 3% oxygen desaturations, with or without arousals, etc.); (ii) lower sensitivity of the airflow technology (thermistor/thermocouple vs nasal pressure transducer); (iii) classification schema (respiratory disturbance index vs AHI; AHI cut-offs of 5, 10, 15, etc.; with or without symptoms, etc.). Most recently, in a pulmonary clinic-based population, high risk for OSA, as assessed by Berlin Questionnaire, was significantly more common than in OLD patients versus controls (55.2% vs 7.5%).<sup>39</sup>

## Outcomes

Patients with overlap syndrome have increased morbidity and mortality compared with COPD or OSA alone. The degree of nocturnal hypoxaemia is increased in overlap syndrome compared with COPD or OSA alone, as patients with COPD do not typically return to normal baseline oxygen saturation levels. This, in turn, leads to pulmonary hypertension and *cor pulmonale*. The prevalence of *cor pulmonale* in patients with overlap syndrome was estimated at 80%, with a dismal 30% 5-year survival.<sup>42</sup> Moreover, OSA adds economic burden to patients with COPD. In an analysis of Medicaid claims, beneficiaries with overlap syndrome had significantly more medical service claims and, on average, \$US 4155 excess medical costs than those with COPD alone.<sup>43</sup>

Patients with overlap syndrome tend to be more hypoxic during sleep (especially in rapid eye movement sleep).<sup>44</sup> Predictors of gas exchange abnormalities during sleep are oxygenation during wakefulness (arterial partial pressure of oxygen  $< 65$  mm Hg) and daytime hypercarbia (arterial partial pressure of carbon dioxide  $\geq 45$  mm Hg).<sup>45</sup> Hypercarbia has been shown to be a better predictor of nocturnal hypoxaemia than exercise<sup>46</sup> and has been associated with more severe nocturnal hypoxaemia as compared with normocapnic patients.

Continuous positive airway pressure (CPAP) therapy appears to improve pulmonary-related out-

comes in overlap syndrome. In an earlier study of hypoxaemic COPD patients with moderate-severe OSA, 5-year survival was 71% in those on CPAP plus oxygen versus 26% in those on oxygen alone, independent of baseline post-bronchodilator  $FEV_1$ .<sup>47</sup> Recently, Marin *et al.* have shown that patients with overlap syndrome have a higher general and cardiovascular mortality (vs COPD alone), and that CPAP reduces this mortality and the number of hospitalizations for COPD exacerbations.<sup>48</sup> Furthermore, very little is currently known about the effect of untreated OSA on the rate of lung function decline. In a small study, one night of sleep loss resulted in a slight reduction in  $FEV_1$  ( $-60$  mL) and in forced vital capacity ( $-130$  mL) in 15 men with COPD ( $R < 0.60$ ),<sup>49</sup> however, the clinical significance of this finding is not clear.

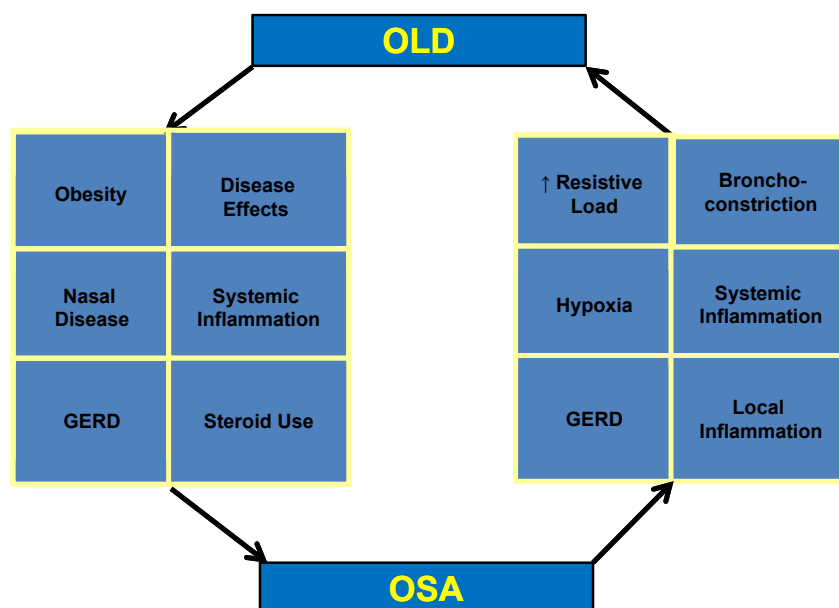
While improved outcomes with long-term positive airway pressure therapy for overlap syndrome were noted, it is currently unclear if such therapy for COPD patients without OSA impacts outcomes. One study randomized 122 COPD patients hospitalized with respiratory failure to long-term oxygen therapy versus non-invasive nocturnal ventilation (positive airway pressure) plus oxygen therapy. There was an improvement in health-related QOL and reduction in length of intensive care unit stay in the non-invasive ventilation group, but no difference in mortality or subsequent hospitalizations.<sup>50</sup> There is no clear evidence of a survival benefit attributable to the use of nocturnal positive airway pressure in stable, hypercarbic COPD patients without OSA, despite improved daytime gas exchange.<sup>51,52</sup>

In summary, the overlap syndrome may represent a condition with important phenotypic characteristics, which could explain the frequent association, symptomatic load and mortality consequences. The use of positive airway pressure in overlap syndrome needs further evaluation.

## Pathophysiology

There are at least several mechanisms explaining how COPD and OSA might cause or exacerbate each other (Fig. 2). This bidirectional relationship could be related to several factors: (i) ageing, because both conditions are getting worse with advancing age; (ii) smoking, which is a shared risk factor; (iii) both conditions are associated with local and systemic inflammatory state, protease-antiprotease imbalance and redox disequilibrium in the lungs; (iv) increased vagal tone; (v) gastro-oesophageal reflux; (vi), hypoxia; (vii) pulmonary hypertension; and (viii) endothelial dysfunction, etc.<sup>30</sup>

Smoking is a shared risk factor for both conditions. Both smoking and COPD can lead to impaired sleep quality in direct correlation with the expiratory flow limitation severity,<sup>53</sup> which can in fact lead to higher collapsibility of the upper airway<sup>54,55</sup> and development of obesity.<sup>56,57</sup> Patients with frequent COPD (or OLD) exacerbations tend to receive more frequent corticosteroid courses, which may put them at risk to develop upper airway closure due to fat deposition in the neck, abdominal fat effect on the diaphragm and



**Figure 2** The dual relationship between obstructive lung disease (OLD), that is asthma or chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA). For example, shared putative pathways leading from OLD to OSA include: disease-specific effects, represented by frequent nocturnal awakenings, decreased cross-sectional area of the airways, lung volume effects; disease-related systemic inflammation leading to a reduction in respiratory muscle force generation; gastro-oesophageal reflux disease (GERD), which could lead to pharyngeal muscle spasm and/or neurogenic inflammation; corticosteroid use, which can mediate its effects through steroid-induced myopathy and/or local fat deposition; hypoxia may lead to suppressed cough reflex, reduced symptom perception and/or higher arousal threshold, etc. Conversely, OSA may influence OLD in similar ways: augmenting the resistive load on the lower airways; vagally mediated bronchoconstriction via stimulation of upper airway receptors during the Mueller manoeuvres; it can promote GERD, via effects of hypoxia on arousal thresholds, cough and symptom perception; and through a neutrophilic lower airway inflammatory phenotype (see text for details).

on functional residual capacity, or through a steroid-induced myopathy.<sup>58–60</sup> Elevated airway resistance leads to more negative intrapleural pressure which, with the added effect of reclined position, can lead to more collapsible upper airway.

Prior studies have shown significant interdependence between upper and lower airway flows and resistance; for example, prior to an apnoeic event, there seems to be a progressive increase in expiratory airflow resistance<sup>61</sup> and decrease in upper airway cross-sectional area,<sup>62</sup> which may play significant roles in the described nosologic interactions. Additionally, increased end-expiratory lung volume has the potential to improve upper airway mechanics (tracheal tug theory),<sup>63</sup> but this effect may be counterbalanced by the loss of elastic recoil seen in emphysema (similarly to severe acute exacerbations of asthma). Consequently, the decreased tethering of the lower airways by emphysema may lead to more collapsible upper airway, especially during sleep. In severe COPD, with associated *cor pulmonale*, cephalad fluid redistribution due to supine position during sleep can also contribute to OSA.<sup>64</sup>

Conversely, OSA can also exacerbate COPD (Fig. 1). In an animal model, repetitive upper airway collapse increased lower airway resistance.<sup>65</sup> Patients with clinically significant OSA have EDS and/or fatigue, which may lead to higher smoking intensity versus those without OSA. Additionally, systemic inflammatory ‘overspill’ in OSA may have a significant effect on

the redox equilibrium of the lower airways.<sup>30</sup> Upper–lower airway interdependence has been proven by many investigators, and these interactions may explain how expiratory and inspiratory flow limitation are connected in the overlap syndromes.

## ASTHMA AND OSA: ALTERNATIVE OVERLAP SYNDROME

### Epidemiology

In large population-based studies, asthmatics report more often OSA symptoms. In a UK community-based random population, asthmatics of all ages snored more often than other responders ( $P < 0.01$ ), which was not explained by differences in body mass index (BMI).<sup>66</sup> In the European Community Health Respiratory Survey, self-reported habitual snoring and apnoea were significantly more prevalent in asthmatics as compared with non-asthmatics (14.7% vs 9.2% and 3.8% vs 1.2%, respectively).<sup>67</sup> Moreover, the associations of asthma with snoring (OR = 1.7) and apnoeas (OR = 3.7) were independent of BMI, age, gender and smoking.<sup>67</sup> In a cohort of 677 young atopic women, the prevalence of habitual snoring was 20.5% and symptomatic asthma almost doubled the risk of snoring (OR = 1.8), independent of upper respiratory symptoms (e.g. rhinitis), cigarette smoking or race.<sup>68</sup> Similarly, in the Busselton study—a prospective cohort Australian study, asthma emerged as an inde-

pendent risk factor for development of habitual snoring (relative risk = 2.8), after adjusting for potential confounders, such as BMI at baseline and BMI change during the 14-year follow-up period.<sup>69</sup>

Clinic-based studies provide further support for a link between asthma and OSA. Higher prevalence of self-reported OSA symptoms such as snoring (86%), habitual snoring (38%) and witnessed apnoea (31%) were reported in one study, in which 44% of the subjects met a high risk for OSA.<sup>70</sup> In this cohort, OSA symptoms were up to 4.4 times more common than reported in general population, when using similar survey methodology.<sup>70</sup> Similar results were reported in three other cohorts of asthmatics.<sup>39,71,72</sup> When compared with internal medicine clinic patients, asthmatics were more likely to report habitual snoring (18% vs 8%) and witnessed apnoeas (11% vs 6%).<sup>71</sup>

Polysomnographic studies report a high prevalence of OSA with more severe asthma, regardless of the methodology used. In an earlier study of 22 difficult-to-control asthma patients studied with laboratory-based polysomnography with recording of airflow via thermocouples, 21 (95.5%) were diagnosed with OSA (respiratory disturbance indices  $\geq 5$  with associated fatigue and EDS), and 9 (41%) had moderate-severe OSA (respiratory disturbance indices  $\geq 20$ ).<sup>73</sup> In a more recent report using home-based complete overnight polysomnography (airflow recorded with both thermistor and nasal pressure transducer), OSA (AHI  $\geq 5$ , hypopnoea defined with  $\geq 4\%$  desaturation) was significantly more prevalent among those with severe asthma (50%) versus moderate disease (23%) or controls (12%).<sup>74</sup> When corroborated with an abnormal Epworth Sleepiness Scale score ( $\geq 11$ ) (OSA syndrome), the same pattern was noted (42% vs 15% vs 4%), with a prevalence in the control group similar to previous reports.<sup>32</sup> However, when hypopnoea was scored based on either arousal or  $\geq 4\%$  desaturation, and an AHI  $\geq 15$  was used, the group differences were even more striking (88% vs 58% vs 31%). In both studies, the very high prevalence of OSA in severe asthmatics was unexpected for the degree of excess bodyweight observed (mean BMI 29 and 27 kg/m<sup>2</sup>, respectively).<sup>73</sup>

## Outcomes

OSA is generally linked to worse asthma outcomes. In a large clinic sample, having a high risk for OSA was associated with poorly controlled asthma, as assessed with a validated questionnaire.<sup>75</sup> Furthermore, in 752 asthma clinic patients, high OSA risk and historical diagnosis were each associated with persistent daytime asthma symptoms, to an extent that matched or exceeded associations with night-time asthma symptoms,<sup>76</sup> suggesting the nocturnal sleep-related breathing disorder impacts asthma around the clock. OSA has also been linked to a higher risk (OR = 3.4) of frequent asthma exacerbations.<sup>77</sup> In a population-based study that included 2713 subjects with asthma-related symptoms, health-related QOL was adversely related to snoring and witnessed apnoeas.<sup>78</sup> Lastly, in 63 difficult-to-treat asthma patients, OSA emerged as an important risk factor (OR = 3.4) for frequent exacerbations in the prior year.<sup>77</sup>

Treatment of OSA with CPAP appears to improve asthma control. Cross-sectionally, in asthmatic patients with clinically diagnosed OSA, CPAP use was associated with a lower likelihood of persistent daytime asthma symptoms.<sup>76</sup> Results from prospective, interventional studies further extend this observation. In nine severe nocturnal asthmatics with polysomnography-diagnosed OSA, Chan *et al.*<sup>79</sup> found that 2 weeks of CPAP therapy decreased the frequency of asthma symptoms during the day and night, reduced bronchodilator use and improved peak expiratory flow rates. Cessation of CPAP returned peak expiratory flow rates to levels prior to therapy. Guilleminault *et al.* studied 10 men with OSA and predominantly nocturnal asthma. Six to nine months of CPAP treatment abolished nocturnal asthma attacks.<sup>80</sup> Additionally, five subjects with nocturnal and daytime asthma, regular snoring and deep negative inspiratory oesophageal pressure swings during sleep (indicative of increased upper airway resistance) were studied. For them, 6 months of CPAP eliminated nocturnal asthma and reduced daytime attacks. In 16 patients with nocturnal asthma symptoms, Ciftci *et al.* found that 2 months of CPAP treatment for coexistent OSA resulted in significant reduction in nocturnal asthma, but no changes in FEV<sub>1</sub>.<sup>81</sup> Lafond *et al.* reported improved asthma-specific QOL after 6 weeks of CPAP for OSA, but no reduction in bronchial reactivity in 20 stable asthma patients.<sup>82</sup>

In summary, there is increased recognition that a dual interaction between asthma and OSA exists. On one hand, there is increased prevalence of OSA in asthma, perhaps related to its unique features, such as disease severity, comorbidities, glucocorticosteroid medication usage, aside from obesity and other traditional risk factors. Conversely, data suggest worse asthma outcomes and QOL in patients with coexistent OSA.

## Pathophysiology

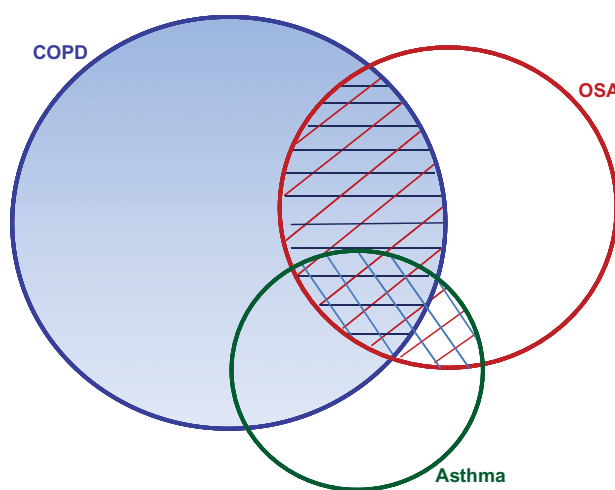
### Asthma → OSA

Many pathways could contribute to OSA pathogenesis in asthma<sup>83</sup> (see also Fig. 2). Among the traditional factors, certainly excess weight and obesity play a significant role. Obesity is a known major risk factor for OSA.<sup>84</sup> The epidemic is more rampant among asthmatics<sup>85,86</sup> and its association with OSA risk, specifically in asthmatics was recently demonstrated.<sup>39,59</sup> Furthermore, nasal disorders, such as rhinitis, chronic sinusitis, nasal polyps are common among asthmatics.<sup>87</sup> The nose represents the primary route of breathing during sleep and can influence the oropharyngeal mechanics. Increased nasal resistance results in more negative oropharyngeal pressure during inspiration, predisposing to collapse.<sup>88</sup> A prospective study of patients with seasonal allergic rhinitis found higher AHI and nasal resistance during allergen season than during asymptomatic periods.<sup>89</sup> Nasal congestion is also an established risk factor for snoring.<sup>90</sup> Its association with habitual snoring has also been reported in asthmatics.<sup>59</sup>

Additionally, asthma patients have a unique set of predisposing characteristics for OSA. As suggested by a recent study of 244 asthma clinic patients,<sup>59</sup> disease severity (OR = 1.6), gastro-oesophageal reflux (OR = 2.7) and use of inhaled corticosteroids (OR = 4.1) were each associated with high OSA risk, independent of other traditional risk factors.<sup>59</sup> Asthma itself could detrimentally impact the upper airway patency in several ways: (i) if uncontrolled, it can result in sleep loss and fragmentation which can increase upper airway collapsibility;<sup>54,55</sup> (ii) bronchoconstriction reduces total airway cross-sectional area and is associated with expiratory oropharyngeal and glottic constriction, possibly as a result of intrapulmonary and chest wall reflexes;<sup>91,92</sup> (iii) alterations of lung volumes during sleep, as asthmatics suffer greater reduction in functional residual capacity during sleep, with values during rapid eye movement nearly identical to those seen in healthy controls,<sup>93</sup> as a result of a loss of airways–parenchyma mechanical coupling,<sup>94</sup> which would attenuate the stiffening effect of tracheal tug on the pharyngeal upper airway segment;<sup>95,96</sup> (iv) asthma is associated with a chronic low-grade systemic inflammation,<sup>97</sup> which could affect the force generation properties of the respiratory muscles,<sup>98</sup> including the upper airway dilator muscles; (v) gastro-oesophageal reflux disease is commonly encountered in asthma, in many cases being asymptomatic<sup>99</sup> and its therapy seems to somewhat improve the AHI.<sup>100</sup> Pharyngeal spasm and mucosal exudative neurogenic inflammation occurring as a result of proximal migration of gastric acid and prolonged acid clearance during sleep<sup>101</sup> could render the upper airway dysfunctional and prone to collapse during sleep; and (vi) a potential detrimental effect of corticosteroids on pharyngeal upper airway patency was initially suggested by the observation of a high OSA prevalence (50%) in patients with Cushing's disease or syndrome,<sup>102</sup> conditions characterized by a sustained state of hypercortisolism. In asthmatics, Yigla *et al.* found higher respiratory disturbance indices with continuous use as opposed to intermittent bursts of oral steroids for exacerbations.<sup>73</sup> All patients were concomitantly on high doses of inhaled corticosteroids, precluding analysis of their potential association with AHI. A potential pathogenic role of inhaled corticosteroids is suggested by the aforementioned clinic-based cross-sectional study, which found a dose-dependent association of inhaled corticosteroids with high OSA risk, although no relationship with AHI was found in a smaller sample of asthma patients who were using  $\geq 200$   $\mu\text{g/day}$  of fluticasone or equivalent.<sup>74</sup> Presumed mechanisms for an inhaled corticosteroids effect on pharyngeal upper airway patency include local myopathy of its dilators (muscle fibre atrophy), similar to the one leading to dysphonia<sup>103</sup> and regional fat accumulation around the upper airway as a result of systemic absorption.<sup>104,105</sup>

#### OSA $\rightarrow$ asthma

Several pathways may connect OSA to asthma: (i) OSA increases the resistive load on the lower airways,<sup>106</sup> fact superimposed on an already challenged airway, especially during sleep;<sup>107</sup> (ii) stimulation of upper



**Figure 3** Venn diagram illustrating the clinical syndromes discussed: chronic obstructive pulmonary disease (COPD); obstructive sleep apnoea (OSA); obstructive lung disease and obstructive sleep apnoea (OLDOSA). Each overlap syndrome is discussed in more details in the text.  $\equiv$ , Overlap Syndrome;  $\equiv$ , Alternative Overlap Syndrome;  $\equiv$ , OLDOSA Syndrome.

airway receptors during the Mueller manoeuvres of obstructive events could augment the vagally mediated bronchoconstriction observed in asthmatics<sup>80,108</sup> and worsen BHR through alteration of the chemical arousal threshold or through resistive loading;<sup>80</sup> (iii) OSA promotes gastro-oesophageal reflux disease,<sup>109</sup> which is a well-recognized trigger of asthma;<sup>99</sup> (iv) hypoxia could impair arousal thresholds to resistive loading,<sup>110</sup> cough,<sup>111</sup> and asthma symptom perception,<sup>112</sup> all defences important for these patients during sleep; and (v) inflammatory links. Intermittent hypoxia and distally transmitted mechanical stress from snoring may exacerbate the lower airway inflammation in these patients. In OSA patients, inflammation of the upper airway has been well characterized,<sup>113</sup> while in the lower airway, a neutrophilic type of inflammation has been demonstrated in OSA patients, well correlated with disease severity.<sup>114</sup> Systemically, OSA gives rise to a persistent state of inflammation, which underlies its cardiovascular morbidity<sup>115</sup> and also shares features with the systemic inflammation of asthma.<sup>116</sup> These observations raise the possibility that OSA, through local airway or systemic effects, may promote a non-eosinophilic phenotype, which is seen in up to 60% of asthmatics with persistent symptoms,<sup>117</sup> is associated with greater asthma severity and risk for exacerbations and even with fatal asthma.<sup>118,119</sup>

#### COPD OR ASTHMA AND OSA: INTEGRATED OVERLAP OR OLDOSA SYNDROME

Although asthma and COPD are considered distinct disorders, there is significant overlap between them (Fig. 3), as in clinical practice patients frequently

**Table 1** Arguments in favour of an 'integrated' overlap or OLDOSA (obstructive lung disease and obstructive sleep apnoea) syndrome

| Criteria         | Arguments                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epidemiologic    | <p>OLD and OSA are frequent conditions and their overlap (COPD + asthma, OSA + COPD, OSA + asthma and OSA + COPD or asthma) seem to be more common than anticipated.</p> <p>High prevalence of snoring and OSA in clinical populations of asthma and COPD.</p> <p>Smoking, obesity, nasal disease and chronic inflammation are common risk factors.</p> <p>Asthma is a risk factor for snoring, independently of BMI.</p>        |
| Pathophysiologic | <p>OLD and OSA share one common functional denominator: dynamic flow limitation or increase in airway resistance, although at different levels.</p> <p>OLD is characterized by EFL, while OSA presents with IFL (the latter mainly during sleep).</p> <p>Complex functional interactions exist between upper and lower airways, which are also modulated by effects of corticosteroid medications and inflammatory pathways.</p> |
| Biological       | <p>OLD and OSA are inflammatory conditions with common pathways and biological cascades; nevertheless, their coexistence may lead to a different biologic phenotype than the individual components.</p>                                                                                                                                                                                                                          |
| Clinical         | <p>'Fuzzy' OLD phenotypes (in clinical practice patients frequently present with features of both asthma and COPD and respond to similar therapies).</p> <p>OLD patients more often have symptoms attributable to OSA.</p> <p>OSA has been associated with poor control of asthma, COPD morbidity and mortality.</p> <p>Improved outcomes of asthma and COPD with OSA treatment (CPAP).</p>                                      |
| Economic         | <p>Asthma, COPD and OSA are very frequent conditions, which pose significant burden to any health-care system, and likely the impact of a nosologic overlap magnifies the burden.</p>                                                                                                                                                                                                                                            |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; EFL, expiratory flow limitation; IFL, inspiratory flow limitation; OLD, obstructive lung diseases; OSA, obstructive sleep apnoea.

present with features of both and respond to similar therapies, hinting that these may be actually different phenotypes of the same condition (the 'Dutch hypothesis'). Additionally, there is increased recognition that a dual interaction between asthma or COPD and OSA exists beyond random coexistence. On one hand, there is increased prevalence of OSA in asthma/COPD. Furthermore, prospective studies find asthma as a risk factor for snoring, independent of possible confounders, such as BMI. These relationships may stem in part from a set of factors unique to these patients, related to disease severity, comorbidities, corticosteroid medications, aside from obesity and other traditional risk factors for OSA. Conversely, current data suggest worse asthma and COPD outcomes in patients with coexistent OSA, and that treatment for OSA improves disease control indices, reduces exacerbations and mortality. Again, several overlapping pathways may be at play in this direction as well. While the term overlap syndrome has been used for the association OSA–COPD, one has not been coined for OSA–asthma (we called it here alternative overlap syndrome), also a frequent interaction with significant clinical implications. When multiple disease or mechanistic features overlap, one successful approach to bolster research is to lump them and later 're-split' by using more refined technologies or techniques. Hence, a distinct, broader clinical entity or 'integrated' overlap syndrome, that is OLDOSA (obstructive lung disease and obstructive sleep apnoea) syndrome is proposed. We postulate here that the OLDOSA syndrome is an important distinct clinical entity, in favour of which there are multiple arguments, as summarized in Table 1.

## CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Complex, dual interactions between OLD and OSA have been described in the last decades. While considerable progress in asthma and COPD research has been made, many questions still remain. Based on the current clinical and functional criteria, asthma and COPD frequently coexist and/or overlap. The term overlap syndrome, used initially for the comorbid association COPD–OSA, does not include the interaction between asthma and OSA which also portends important clinical prognostic implications. We provided here several arguments for an integrated nomenclature of OSA in the setting of OLD, that is OLDOSA syndrome. We believe that better nosologic integration of these entities, in the era of exciting technological advances, will accelerate our understanding of these complex phenotypes and interactions.

Given the earlier considerations, we propose here that in daily clinical practice, one should: (i) perform a targeted evaluation for OSA in every patient with OLD (asthma, COPD or small airway disease) by using a detailed history and/or standardized questionnaires (e.g. Epworth Sleepiness Scale, Berlin Questionnaire, etc., albeit not validated in this setting) and sleep testing, when appropriate; it is likely that a *pre-bronchodilator* R (FEV<sub>1</sub>/forced vital capacity ratio) below the lower limit of normal on the pulmonary function testing should prompt a more thorough clinical evaluation for sleep apnoea; and (ii) obtain a focused clinical history and a functional assessment for possible OLD in all patients with established OSA, targeting smoking habits and intensity, episodic

dyspnoea and nocturnal symptoms, which, understandably, may be difficult to attribute to one condition or another. To what extent and/or in which subjects it would be useful to proactively assess for BHR remains to be elucidated.

With the compelling epidemiologic and clinical data accumulated linking OLD and OSA, we believe a concerted and focused effort from the research community is needed in this area, specifically: (i) in future prospective epidemiologic studies which commence earlier in life, to determine what is the direction of this association and how does each disease alters/ accelerates the progression of the other; (ii) in experimental investigations, to test the mechanisms proposed as links between OLD and OSA and find ways to reverse/mitigate them; and (iii) in carefully designed, longer-term clinical studies, to investigate the effects of OSA treatment on multiple outcomes of lung disease, including exacerbations, health-related QOL, health-care resource utilization, etc.

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