



Bidirectional relationships of comorbidity with obstructive sleep apnoea

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Obstructive sleep apnoea (OSA) is an independent risk factor for comorbidity, especially cardiometabolic. However, some comorbidities may be risk factors for OSA, supporting a bidirectional relationship that may have important implications for treatment.

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Abstract

Obstructive sleep apnoea (OSA) is frequently associated with comorbidities that include metabolic, cardiovascular, renal, pulmonary and neuropsychiatric. There is considerable evidence that OSA is an independent risk factor for many of these comorbidities but, more recently, there is evidence that some of these comorbidities may predispose to the development of OSA. Thus, there is growing evidence of a bidirectional relationship between OSA and comorbidity, especially for heart failure, metabolic syndrome and stroke. Potential mechanisms of bidirectional relationships differ in individual comorbidities with fluid retention and redistribution being especially important in heart failure and end-stage renal disease, whereas neural mechanisms may be more important in diabetes mellitus and stroke. The evidence for other comorbidities, such as hypertension and atrial fibrillation, support these being more a consequence of OSA with limited evidence to support a bidirectional relationship. The present review explores the evidence for such bidirectional relationships with a particular perspective on comorbidities that may predispose to OSA. The impact of therapy in bidirectional relationships is also reviewed, which highlights the clinical importance of accurate diagnosis. This aspect is especially true of COPD, where the identification of co-existing OSA has important implications for optimum therapy.

Introduction

Obstructive sleep apnoea (OSA) is highly prevalent [1] and there is growing evidence to support an independent association of OSA with a wide range of comorbidities including metabolic, cardiovascular, renal, pulmonary and neuropsychiatric [2]. The evidence is greater for some comorbidities than others, and, in cardiovascular disease, is strongest for hypertension and atrial fibrillation [3]. The demonstration of independent associations between OSA and comorbidity may be more difficult because of the very high prevalence of sleep-disordered breathing (SDB) in the general population, in addition to the confounding effect of shared risk factors such as obesity. Furthermore, there is evidence of a bidirectional relationship between OSA and several comorbidities that include heart failure (HF) as a result of nocturnal fluid accumulation in the neck, in addition to stroke and the metabolic syndrome.

Possible mechanisms relating to OSA contributing to comorbidity include intermittent hypoxia, fluctuating intrathoracic pressure and recurring micro-arousals that are integral features of obstructive apnoea, which generate cell and molecular consequences that include sympathetic excitation, systemic inflammation and oxidative stress, in addition to metabolic and endothelial dysfunction [4–7]. Different mechanisms may predominate in specific comorbidities. For example, sympathetic excitation appears to be the principal mechanism in the development of hypertension, especially nocturnal [8], whereas inflammation and oxidative stress are likely to be more important in the development of atherosclerosis and coronary artery disease [3]. Other factors such as obesity may be linked to both OSA and other comorbidities, especially



cardiometabolic, which confound the assessment of independent relationships between OSA and comorbidity [1]. Furthermore, there is evidence of interaction between the intermittent hypoxia that is a core feature of OSA and adipose tissue in the development of cardiometabolic comorbidity [9, 10].

The present review explores the relationships between OSA and comorbidity with a specific perspective on comorbidities that show evidence of a bidirectional relationship. Potential benefits of therapy will also be discussed, which have recently been questioned, especially relating to cardiovascular outcomes [11–13].

Metabolic syndrome

The metabolic syndrome includes systemic hypertension, insulin resistance, hyperlipidaemia and central obesity and has been linked to OSA [14, 15]. The relationship between OSA and the metabolic syndrome is complex and likely bidirectional in nature [7, 16]. OSA has been shown to cause or worsen several metabolic disorders, especially hypertension and insulin resistance [16], but several metabolic disorders predispose to OSA by mechanisms that include anatomic and neural effects on the upper airway [7].

Obesity

Many patients with OSA are obese and most research has focussed on obesity as a risk factor for OSA, although there are grounds to propose that the relationship is bidirectional.

Obesity predisposing to OSA

There is a strong link between OSA and obesity, and the contribution of central obesity to OSA and comorbidity occurs at several levels. The accumulation of fat in the neck contributes to oropharyngeal narrowing, which increases the collapsibility of the upper airway, and abdominal obesity reduces traction on the upper airway, further predisposing to increased collapsibility [17]. Furthermore, intermittent hypoxia, which is a central feature of OSA, elicits a pro-inflammatory response in visceral adipose tissue and contributes to insulin resistance [9]. In epidemiological terms, 70% of those with OSA are obese [18] and, conversely, 50% of those with a body mass index (BMI) >40 have OSA with an apnoea–hypopnoea index (AHI)>10 [19]. A higher BMI typically results in more severe OSA, most notably in males and in the younger population.

Impact of therapy

Major weight reduction, especially following bariatric surgery, improves OSA [20], whereas a recent report showed only modest benefit to OSA from weight loss by dietary intervention alone over a 10-year follow-up period [21]. Weight loss shows the highest benefit to OSA in patients with a small pre-existing maxillomandibular volume, indicating an important interaction between upper airway anatomy and the impact of obesity [22].

OSA predisposing to obesity

Although lifestyle effects of OSA, such as reduced activity levels and a tendency to snack with high calorie foods to boost energy, should promote weight gain, there has been limited research on this subject. Obese men with OSA lose less weight in response to a 1-year dietary and exercise programme compared with similarly obese men without OSA [23]. While continuous positive airway pressure (CPAP) therapy is highly effective in controlling OSA, paradoxically, some patients gain weight after commencing CPAP, especially females and nonobese patients [24].

Overall, the relationship between obesity and OSA is synergistic in terms of cardiometabolic risk with a variety of potential intermediate mechanisms including inflammation, endothelial dysfunction, and insulin resistance being amplified by the concurrence of both disorders [15].

Diabetes mellitus

Diabetes and OSA frequently coexist and there is growing evidence of a bidirectional relationship [7].

OSA predisposing to diabetes

There is growing evidence that OSA represents an independent risk factor for diabetes mellitus [25]. Several cross-sectional cohort studies have demonstrated an independent relationship with type 2 diabetes and insulin resistance, including the European Sleep Apnea Database (ESADA) [26, 27], and a pooled estimate of relative risk for diabetes from nine original studies was 1.69 (95% CI 1.45–1.80) [25]. Mechanisms of diabetes and insulin resistance include intermittent hypoxia and sleep fragmentation leading to sympathetic excitation and inflammation. There are fewer long-term studies on this risk. One community-based study of middle-aged men found an odds ratio for incident diabetes of 4.4 (95% CI 1.1–18.0) comparing those with and without OSA after 10-years follow-up after adjusting for confounders, and

AHI was inversely related to insulin sensitivity index at follow-up [28]. Another historical cohort study involving 8678 adults investigated for OSA reported that those with severe OSA had a 30% higher risk of developing diabetes than those without OSA after a mean follow-up of 67 months after controlling for confounding factors [29].

Impact of therapy

CHIRINOS *et al.* [30] reported that CPAP alone for 24 weeks did not benefit insulin sensitivity in nondiabetic patients with OSA in contrast to weight reduction. Randomised control studies of CPAP in diabetic patients with OSA have produced mixed results, some showing no benefit to diabetic control or insulin sensitivity, whereas others reported benefit [25]. Good compliance with CPAP was a factor in decreasing the risk of incident diabetes in a US Veterans Affairs study, despite weight gain during the follow-up period [31].

Diabetes predisposing to OSA

Some consequences of diabetes mellitus could predispose to OSA, including neuropathy affecting the upper airway muscles, and disturbances in ventilatory control. A retrospective primary care cohort study involving over 1 million subjects found an adjusted incidence rate ratio of OSA in patients with type 2 diabetes compared with those without of 1.48 (95% CI 1.42–1.55; $p < 0.001$), and identified insulin use, diabetic foot disease, male sex, obesity and cardiovascular disease as significant factors [32]. Another prospective study of almost 300 000 healthcare professionals found that OSA was an independent risk factor for incident diabetes, but conversely, insulin-dependent diabetes was an independent risk factor for OSA in women [33].

Thus, overall, there is good evidence for a bidirectional relationship between OSA and diabetes, but evidence of benefit from CPAP therapy to glycaemic control is limited.

Hypertension

While hypertension is very common in patients with OSA, the great majority of research on this topic has focussed on OSA as a risk factor for hypertension [34].

OSA predisposing to hypertension

There is strong evidence across many population-based epidemiological studies that OSA is a risk factor for systemic hypertension, often with a nondipping nocturnal blood pressure (BP) profile. Data from the Sleep Heart Health Study indicated a dose-dependent relationship with prevalent hypertension [35] and the Wisconsin Cohort study reported a higher presence of hypertension associated with OSA after 4 years follow-up [36]. A meta-analysis of seven prospective studies confirmed an independent relationship with incident hypertension in a dose-dependent fashion [37], particularly resulting in the loss of nocturnal dipping and high diastolic BP [38], as well as resistance to conventional antihypertensive treatment [39]. Indeed, nondipping nocturnal BP is highly predictive of OSA, independent of symptom profile [40], and rapid eye movement (REM)-associated OSA is independently associated with incident nondipping BP [41]. Sympathetic excitation appears to be the principal pathogenic mechanism [8, 42] with possible additional involvement of renin-angiotensin-aldosterone system (RAAS) dysfunction. Hypertension has also been associated with mild OSA. Data from the ESADA study involving 4372 subjects with mild OSA found an independent relationship with prevalent hypertension [43], and a prospective study involving 744 subjects with mild/moderate OSA and normotensive at baseline reported an association with incident hypertension after 9 years in subjects <60 years old [44].

Impact of therapy

While many studies indicate a reduction in BP with CPAP therapy, the effect is small at 2 mmHg in 24 h mean BP [45], although greater in younger subjects and those with uncontrolled hypertension or severe oxygen desaturation [46], and in more CPAP-compliant patients [47].

Hypertension predisposing to OSA

There is limited evidence that hypertension may predispose to OSA. Data from animal and small human studies suggest fluctuations in BP can influence upper airway tone by demonstrating inhibitory changes on electromyogram (EMG). This suggests that reduction in BP may improve airflow and reduce OSA severity [48]. Furthermore, a meta-analysis of 11 studies, including prospective and randomised trials, supports the concept that antihypertensives may reduce AHI, with a more pronounced effect when diuretics were used [49].

Heart failure

The bidirectional relationship between sleep apnoea and HF can be partly explained by shared risk factors including age, high BMI and sedentary lifestyle. Unifying mechanisms, particularly fluid retention and redistribution, result in a bidirectional relationship where it may be difficult to establish cause and effect [50]. HF is associated with both central and obstructive sleep apnoea, but for the purpose of this review, only the relationship with OSA will be discussed.

OSA predisposing to HF

Despite shared risk factors, large scale epidemiological studies have reported that OSA is independently associated with an increased risk of incidence and progression of coronary heart disease, congestive HF and cardiovascular mortality [51]. In the Sleep Heart Health Study, 4442 patients were followed prospectively and demonstrated a 58% increased risk of incident HF in those with severe OSA (AHI>30) compared with those without OSA [52], and the severity of OSA was directly proportional to incident HF risk.

Obstructive events lead to major swings in intrathoracic pressure, which alter cardiac haemodynamics resulting in increased preload, reduced left ventricular filling pressure, and increased afterload [17]. These effects stimulate the RAAS promoting sodium and water retention [53]. OSA may induce cardiac remodelling, contributing to HF, and may acutely impair cardiac function, thus worsening episodes of acute HF [54]. Patients with a higher AHI exhibit a greater degree of diastolic dysfunction [55].

Patients with no or mild OSA had a 50% less incidence of fatal events compared with those with untreated moderate or severe disease [56]. OSA can negatively impact the prognosis of HF and is associated with increased hospital readmissions and an increased rate of post-discharge mortality in patients diagnosed with OSA as an inpatient [57].

Impact of therapy

Treatment of OSA with CPAP improves intermediate cardiovascular end-points such as BP, heart rate and rhythm, and ejection fraction [58]. KANEKO *et al.* [59] found a 9% increase in left ventricular ejection fraction (LVEF) in addition to a daytime fall in heart rate and BP, which may reflect a reduction in nocturnal urinary excretion of epinephrine. However, while immediate physiological improvement has been shown with CPAP therapy, long-term reports on the benefit of CPAP have been inconsistent. Data supporting improved mortality and transplant free survival are lacking [60]. Studies have been limited by small sample sizes and short follow-up periods. Observational studies of long-term CPAP therapy have reported reduced cardiovascular morbidity and mortality over 10 years' follow-up compared with those who were noncompliant with CPAP [61, 62]. However, more recent randomised controlled trials of CPAP therapy such as the SAVE trial have failed to show benefits in the secondary prevention of cardiovascular diseases, including HF, although the study was limited to nonsleepy patients with OSA and compliance with CPAP was poor [63].

HF predisposing to OSA

Many observational studies have demonstrated a higher prevalence of SDB in HF than those without [50]. However, patients with HF and OSA report less hypersomnolence, thus making it harder to recognise [64]. In an outpatient clinic setting, 53% of patients with stable HF met the diagnostic criteria for OSA [64] and the degree of cardiac dysfunction relates to the severity of OSA [54]. A prospective study of 203 HF patients with LVEF <40% reported 71% having AHI >10 and 43% meeting the clinical diagnostic criteria for OSA [65].

A different clinical phenotype of OSA is common in patients with HF, with many having lower BMI, which supports the view that HF may predispose to, or exacerbate SDB, in the absence of other shared risk factors such as obesity [54]. Patients with HF have a lower stroke volume, which, through neurogenic and humoral mechanisms, promotes fluid retention. Nocturnal redistribution of fluid in the recumbent position to dependent areas of the body such as the parapharyngeal soft tissue increases upper airway resistance and collapsibility [66]. Dietary sodium intake is directly proportional to the severity of OSA in HF, likely due to effects on fluid retention and redistribution [67]. Furthermore, nonobese men with venous insufficiency who wore compression stockings during the day to prevent fluid accumulation showed a reduction in AHI of 36% compared with no stockings [68]. A schematic representation of factors associated with fluid retention and redistribution to the neck region that predispose to pharyngeal collapse is given in figure 1.

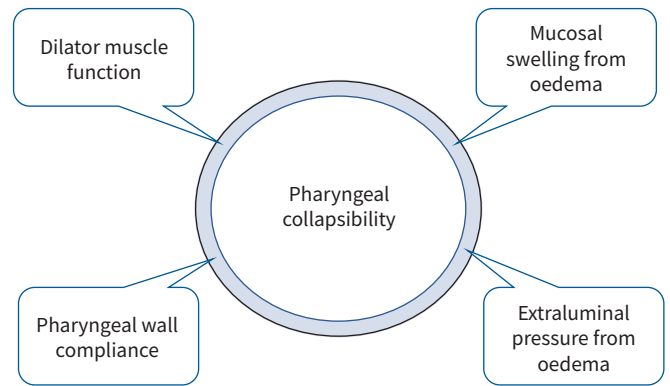


FIGURE 1 Potential mechanisms of increased pharyngeal collapsibility resulting from fluid accumulation in the neck region.

Impact of therapy

As the severity of OSA can fluctuate in response to the degree of fluid redistribution, it is plausible to propose that OSA should respond to treatment of HF. However, in a randomised control trial (RCT) of patients with severe OSA, sodium restriction and diuretic therapy resulted in only a limited improvement in AHI, suggesting that fluid accumulation only partially explains the aetiology of OSA in HF [69]. In an acute exacerbation of hypertensive diastolic HF, diuretic therapy resulted in a reduction in body weight, increased pharyngeal calibre, and a fall of 17 in AHI [70]. Conversely, in an observational study, diuretic therapy improved OSA in overweight patients or those with hypertension but no significant improvement was seen in OSA severity in patients with HF [71]. While beneficial in central sleep apnoea, cardiac resynchronisation therapy has been little studied in OSA, although in small sample sizes has been reported to reduce AHI [72].

Renal dysfunction

Current evidence suggests that renal disease and sleep apnoea have a bidirectional relationship. Patients with renal impairment have an increased risk of SDB, with both OSA and central sleep apnoea (CSA) more common than in those with normal renal function, independent of confounders [73]. End-stage renal disease (ESRD) can also lead to worsening of OSA. It is increasingly recognised that OSA increases the risk of kidney injury and is associated with progressive decline in renal function [74].

Renal disease predisposing to OSA

The prevalence of OSA is up to ten times higher in patients with chronic kidney disease (CKD) than in the general population [75] but OSA remains under-recognised in CKD, which may reflect atypical presentations and a higher threshold for symptom recognition. The occurrence of OSA increases proportionally to the severity of CKD, supporting its role in pathogenesis. A clinic-based study reported a prevalence for OSA of 27%, 41% and 57% in patients with eGFR >60, patients with eGFR <60 but not on renal replacement therapy, and those on haemodialysis respectively [76].

Factors contributing to OSA in CKD include increased chemoreflex sensitivity, reduced clearance of uraemic toxins, and hypervolaemia [77]. Changes in chemoreflex responsiveness in response to metabolic acidosis in ESRD can enhance the responsiveness to carbon dioxide tension (P_{CO_2}), thus affecting ventilation and the apnoeic threshold. Accumulation of uraemic toxins and related myopathy can increase upper airway collapsibility [77]. AHI scores correlate negatively with urea and peritoneal creatinine suggesting improved uraemic clearance can improve symptoms. Fluid accumulation with associated nocturnal redistribution in the recumbent position with consequent pharyngeal narrowing, as with HF, is also likely to play an important role (figure 1). In a group of 40 patients on haemodialysis, 70% had an AHI >15 as well as a greater total body extracellular fluid volume, including neck, thorax and leg volumes despite no difference in BMI compared with those with an AHI <5 [78].

Impact of therapy

Increased fluid overload predicts a worsening of OSA and aggressive treatment of ESRD may reduce the severity. Daily dialysis, nocturnal dialysis and nocturnal peritoneal automated dialysis have been addressed in observational studies with benefits to OSA associated with reduced AHI, reduced airway congestion,

and improved uraemic clearance [79, 80]. Additional removal of 2.2 L of fluid during a single ultrafiltration session induced a 36% reduction in AHI that correlated with the amount of fluid removed [81]. Renal transplantation reverses many of the metabolic complications in ESRD and slows the progression of associated comorbidities but its role in benefiting OSA remains inconclusive. In one report, 18 patients with ESRD having polysomnography (PSG) before and 3 months after transplantation demonstrated a significant improvement in the prevalence and severity of OSA after surgery [82].

OSA predisposing to renal disease

While OSA can occur as a result of CKD, there is evidence that OSA can contribute to CKD and progressive decline in GFR [83]. OSA has also been associated with a higher morbidity and mortality in patients with ESRD, which may relate to the compounding effects of comorbidities such as cardiovascular and cerebrovascular disease, including dysrhythmia, coronary disease and stroke. However, retrospective data analysis from the Wisconsin Sleep Cohort reported that OSA did not accelerate kidney function decline over time compared with those without OSA [84]. A large retrospective review in Taiwan showed an increased risk, similar to that of hypertension, of incident CKD in those with newly diagnosed OSA [85].

OSA induced renal disease can be explained by two primary mechanisms, hypertension and intra renal hypoxia with glomerular hyperfiltration [77]. The renal medulla is particularly sensitive to hypoxia, triggering oxidative stress, systemic inflammation, and endothelial dysfunction and resulting in tubulointerstitial injury, which is the hallmark of CKD. Apnoeic episodes stimulate the sympathetic nervous and RAAS systems, leading to systemic and glomerular hypertension, vascular damage and arterial wall stiffness, culminating in renal ischaemia.

Impact of therapy

CPAP has been shown to positively impact renal haemodynamics in patients with normal renal function at baseline, suggesting a benefit in slowing renal injury [76]. However, the role of CPAP in attenuating the progression of renal impairment in OSA is uncertain with studies reporting differing results, and there are few studies focusing on patients with established CKD.

The ESADA cohort study reported a slower decline in eGFR in patients using fixed CPAP compared with auto-adjusting CPAP in patients without CKD [86]. CPAP treatment in patients with moderate to severe OSA has been reported to positively impact kidney filtration in the short term [77]. Another uncontrolled observational study reported a significant reduction in serum creatinine and increase in eGFR in males with AHI >20 after 3 months of CPAP [87]. A longer follow-up study again showed positive short term benefits but, after 8 years, patients with higher AHI had higher serum creatinine levels, despite CPAP treatment [74]. An RCT of patients with Stage 3 and 4 CKD showed no statistically significant difference in eGFR between CPAP and usual care over a 1 year follow-up, while demonstrating some improvement in renal function in those at a lower risk of CKD progression [88]. Furthermore, a post hoc analysis of 200 patients from the SAVE trial reported that CPAP treatment of OSA in patients with cardiovascular disease does not alter renal function or the occurrence of renal adverse events [89].

Stroke

SDB is common in patients after stroke. Whether OSA reflects a provoking factor by potentiating known vascular risk factors such as hypertension, or a consequence of stroke-related brain injury, remains unclear. With increasing research, it is evident that the complex relationship between stroke and sleep is bidirectional [90].

OSA predisposing to stroke

OSA is a risk factor for stroke and confers approximately a two-fold increase in stroke incidence [91]. A meta-analysis of six systemic reviews identified an increased occurrence of stroke in those with untreated OSA, even considering potential confounders such as age, BMI, diabetes and high BP [91]. The Sleep Heart Health Study prospectively demonstrated a direct relationship between OSA and subsequent risk of stroke [92]. Moreover, it reported a connection between OSA severity and stroke risk in younger men, with a rise of 6% for every unit rise between 5 and 25 events per hour. In the Wisconsin Cohort study, there was an increased stroke risk (OR 4.3) in those with an AHI >20 [93]. Initial studies identified 25% of strokes as occurring during sleep, suggesting a circadian influence on the pathophysiology [94]. The phenomenon of wake-up stroke led to a particular focus on REM sleep and highlighted arousal as a possible trigger. The Sleep Tight study reported that men with wake-up strokes had significantly higher AHI scores [95]. Dysautonomia, circadian activation of RAAS and fluctuations in BP result in changes in cerebral blood flow. This, in turn, stimulates intermediary mechanisms such as platelet aggregation, hypercoagulability and endothelial damage. Additionally, accelerated atherosclerosis, impaired glucose

tolerance and cardiac dysrhythmias, particularly refractory atrial fibrillation, are more common in untreated OSA, resulting in a higher risk of stroke. The presence of OSA has been reported to increase the risk of recurrent or repeated stroke [96].

Impact of therapy

CPAP's role in patients with OSA is controversial, with variable results from cohort studies to date. Observational studies indicate a reduction in stroke risk in patients with OSA, particularly in treatment compliant patients [97]. RCTs suggested compliance >4 h with treatment may provide some benefit [98]. Although the SAVE trial reported no reduction in stroke rate with CPAP therapy [63], a more recent post hoc analysis of this trial identified self-reported snoring as a risk factor for incident stroke [99]. Potential benefits of treatment are more convincing and easier to demonstrate in OSA patients post-stroke despite a relative paucity of studies in this setting [100]. Post-stroke rehabilitation in untreated OSA can be adversely affected, especially with reduced executive function, attention, sleepiness and psychomotor ability. Randomised trials support an improvement in both short and long-term functional outcomes with CPAP therapy [101] while others report no difference in neurological outcome based on intention to treat analysis, although some improvement was observed in CPAP-compliant patients [102]. Treatment aims to target the alterations in cerebral autoregulation and to protect the ischaemic penumbra area. Many of these studies are limited by methods of measuring outcomes, including the unreliability of patient-reported symptoms post-stroke. Patient selection (stroke severity, disability, and complications such as delirium or depression), in addition to difficulty with recruitment and adherence, can confound results, thus contributing to inconsistent outcomes. Furthermore, it is likely that improvements in glycaemic and BP control also reduce the risk of recurrent stroke.

Stroke predisposing to OSA

The prevalence of OSA is high in stroke, with one-third of survivors documenting an AHI >30 [96, 103], although it is possible that stroke may unearth pre-existing OSA [104]. Post-stroke sleep architecture may impair breathing control mechanisms at a central level, but more specifically, stroke may adversely affect upper airway muscle function, thus increasing collapsibility. Further evidence for OSA as a consequence of stroke is the fall in frequency of events from the acute to the subacute phase of recovery. OSA is a predictor of poor outcome post-stroke, and has been associated with increased cerebrovascular morbidity, including worse functional and cognitive outcomes, and longer hospitalisation and rehabilitation times [105]. Patients with OSA presenting with acute stroke also tend to have higher National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale scores on discharge [106]. The mechanism through which these detrimental effects occur is proposed to be a further insult to the ischaemic penumbra by an arterial blood flow steal situation that has been described post-stroke, whereby apnoea-induced hypercapnia redirects blood flow from the already ischaemic region in a "reverse Robin Hood" phenomenon. A prospective study found 1.8 times increased risk of death in a 10-year follow-up of those with stroke and OSA [107].

COPD

COPD has a complex relationship with OSA with some factors such as hyperinflation being protective against OSA, whereas other factors such as fluid retention promoting OSA. These considerations likely explain at least some of the reported differences in the epidemiology of this relationship [108].

COPD predisposing to OSA

Most reports evaluating the relationship of COPD with OSA have focussed on COPD as a contributing factor for OSA. Data from the Sleep Heart Health Study found no increased prevalence of SDB in patients with mild COPD [109], although oxygen desaturations during sleep were more pronounced in patients with both disorders compared with those with either disorder alone. However, more recent studies have reported a relatively high level of OSA in patients with moderate-to-severe COPD [110, 111]. The reasons for these conflicting results are unclear but may reflect the different populations under investigation. It is notable that increasing BMI and smoking history positively correlate with the likelihood of OSA in patients with COPD [111].

COPD includes a spectrum of clinical phenotypes ranging from the hyperinflated patient with low BMI (predominant emphysema phenotype) to the patient with higher BMI and right HF (predominant chronic bronchitis phenotype). The predominant emphysema phenotype has a lower likelihood of OSA as demonstrated by a more negative critical closing pressure of the upper airway during sleep [112]. However, the predominant chronic bronchitis phenotype may predispose to OSA due to a higher BMI and a higher prevalence of right HF with fluid retention. Rostral fluid shift during sleep in the recumbent position predisposes to upper airway obstruction by airway narrowing similar to HF (figure 1) [66]. Data from the COPDGene study indicate that the chronic bronchitis phenotype has a higher prevalence of OSA even in the absence of differences in BMI and lung function [113]. Upper airway inflammation associated with cigarette smoking may also contribute to OSA [114] in addition to skeletal myopathy affecting the upper airway muscles.

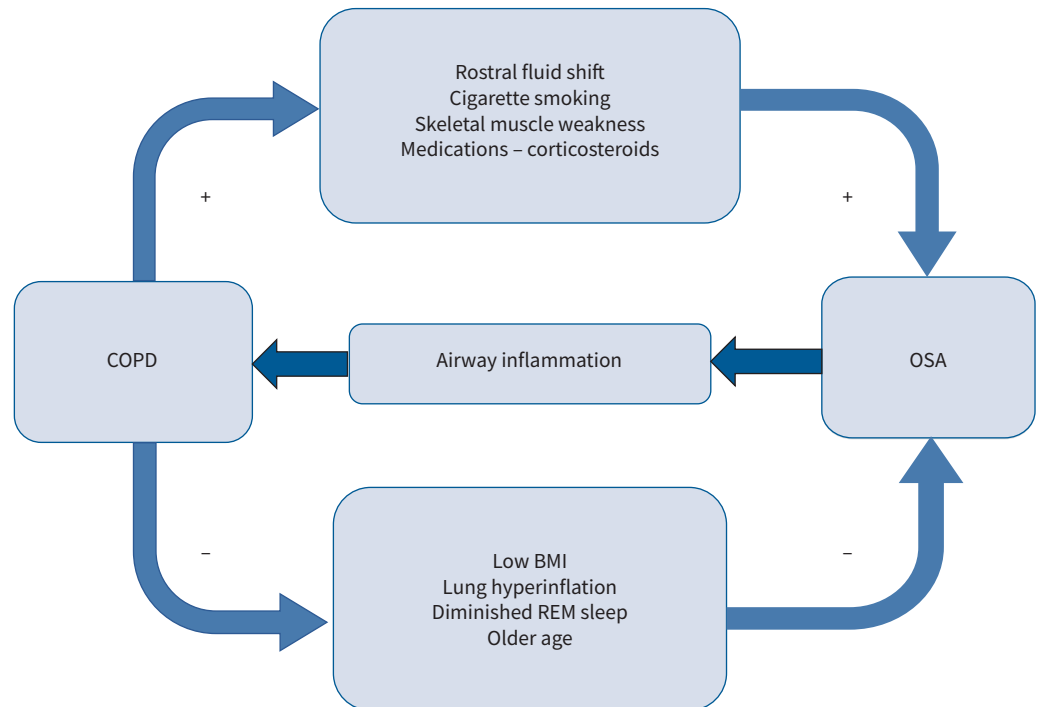


FIGURE 2 Inter-relationships between COPD and OSA demonstrating COPD-related factors that increase or decrease the likelihood of OSA, and OSA-related factors that may promote COPD. BMI: body mass index; OSA: obstructive sleep apnoea; REM: rapid eye movement.

OSA predisposing to COPD

Reports of OSA as a risk factor for COPD have produced varying findings [115]. GREENBERG-DOTAN *et al.* [116] reported a higher prevalence of COPD and asthma in patients with OSA compared with a matched control population, especially among females. However, ZHAO *et al.* [117] reported a lower prevalence of COPD in subjects with SDB compared with those without SDB in a community-based study of 853 community-dwelling older men. OSA also appears to exacerbate lower airway inflammation in patient with COPD [118] and animal studies report that chronic intermittent hypoxia contributes to lung damage in mice by inducing inflammation and oxidative stress [119].

Thus, the epidemiological relationship of COPD and OSA and related outcomes remain an important topic for further research comparing different clinical phenotypes and across the age spectrum. Factors that impact the interrelationship between the two disorders are illustrated in figure 2.

Impact of therapy

Patients with COPD-OSA overlap treated with long-term CPAP have a survival similar to patients with COPD alone, whereas overlap patients not treated with CPAP have a higher mortality and rate of hospitalisation with acute exacerbations [120, 121]. These findings emphasise the importance of recognising co-existent OSA in patients with severe COPD so that optimum therapy can be selected.

Depression

Depression and OSA may exhibit similar symptoms, including poor concentration, memory and fatigue, which complicate their clinical assessment and diagnosis (figure 3). Sleep disturbance is a frequent self-reported symptom of depression, and may represent a predictive symptom for the later development of depression [122]. A more recent theory is that those with depression are at a higher risk of OSA later in life [123]. Proposed mechanisms underlying each process include sleep fragmentation, frequent arousals and intermittent hypoxic episodes resulting in cerebral hypoperfusion and neurotransmitter dysfunction. Despite biologic plausibility, there is little research in possible bidirectional relationships, and findings have been inconsistent.

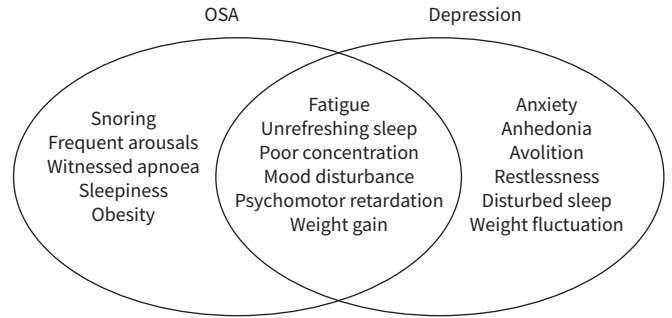


FIGURE 3 Clinical features in obstructive sleep apnoea (OSA) and depression demonstrating shared features in the overlap of both disorders.

A study of nearly 19 000 participants of all ages reported that in patients with OSA or depression, almost one-fifth also had the other disorder, supporting a mutual relationship [124]. A prospective study from Taiwan reported that patients with OSA had an increased risk of subsequent physician-diagnosed depression [125], and there was a reciprocal link with an increased risk of incident OSA at follow-up for those with depression at baseline, independent of sociodemographic factors and comorbidities.

OSA predisposing to depression

In clinical cohorts, the prevalence of depression in OSA ranges from 20–40% [126] and there appears to be an increased odds ratio of depression with increasing severity of SDB [127]. However, other smaller studies reported that the presence or severity of OSA were not independent predictors of depression scores or subsequent hospitalisation [128, 129].

Impact of therapy

A meta-analysis of 22 RCTs involving CPAP and mandibular advancement device (MAD) therapy of OSA reported a modest benefit and, more importantly, a clinically relevant improvement in depressive symptomatology using recognised depression scales [130]. The analysis demonstrated a dose-dependent

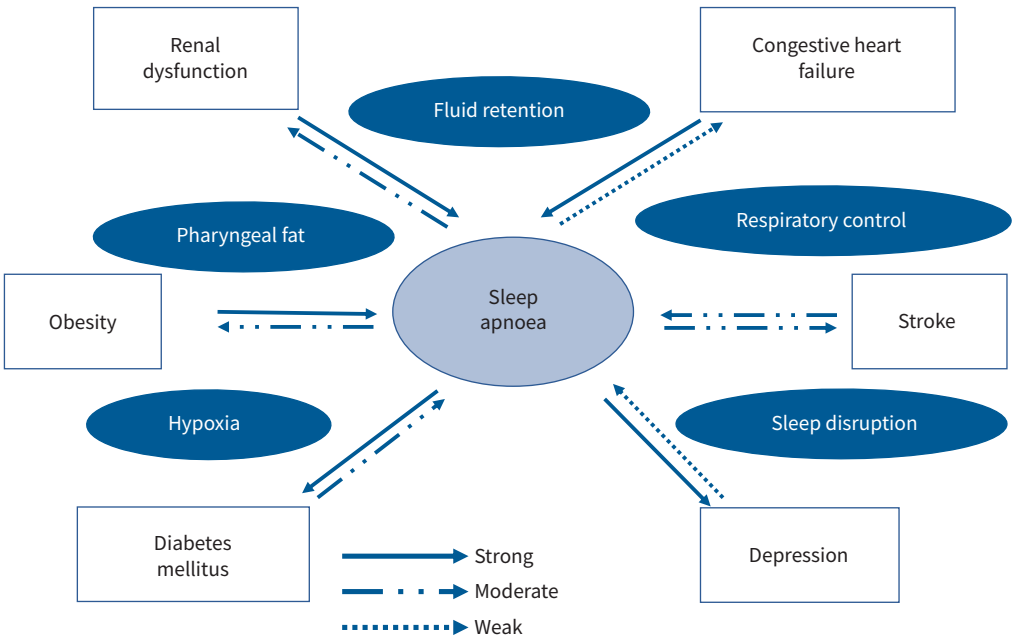


FIGURE 4 Proposed bidirectional relationships between obstructive sleep apnoea and comorbidity. The levels of evidence favouring inter-relationships ranging from strong to weak are the authors’ opinions based on the available evidence.

response whereby those with worse depressive symptoms at the onset of treatment yielded the most benefit. Treatment of OSA with CPAP for 5 or more hours nightly for at least 3 months improved depressive symptoms, including suicidal ideation [131], which was independent of the use of antidepressants.

Depression predisposing to OSA

Depression as a potential cause of OSA has not been well studied. Prevalence reports indicate that 15% of psychiatric inpatients with major depressive disorder (MDD) have increased AHI on overnight polysomnography, and 18% of patients with MDD also met the diagnostic criteria for OSA [132, 133]. Another study found a higher prevalence of 39% and suggested that insomnia contributed to this increased prevalence [123]. The exclusion of diagnosed and probable patients with OSA strengthens the findings of this study.

Impact of therapy

A review of prospective studies looking at five different antidepressants found only two had a positive impact on reducing AHI but did not affect sleepiness or sleep quality [134]. Furthermore, undiagnosed OSA may worsen with some pharmacological treatments targeting depression, with weight gain as one potential factor [135]. Benzodiazepines can increase the frequency and duration of apnoeic events by affecting upper airway tone and alteration of the arousal threshold

Points for clinical practice and questions for future research

- The association of comorbidity with OSA may be bidirectional and, thus, does not necessarily imply a causative association for OSA in the relationship.
- Comorbidities associated with fluid retention are especially likely to predispose to OSA by rostral distribution of fluid in the recumbent position.
- Clinicians involved in the care of patients with metabolic, cardiovascular, renal and neuropsychiatric disorders should be alert to the possibility that many of these disorders may predispose to OSA.
- Cross-sectional reports of independent associations of OSA and selected comorbidities do not imply causality, and greater emphasis should be placed in future research on prospective outcome studies to clarify the nature of such relationships.

Conclusion

OSA may occur in association with many comorbidities, some of which may represent risk factors for OSA by differing mechanisms. While there has been substantial research on the role of OSA as an independent risk factor for comorbidity, the reverse relationship has been less well studied and represents an important area for future research. The authors' assessment of the putative bidirectional relationships between OSA and comorbidities is given in figure 4.

Provenance: Commissioned article, peer reviewed.

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