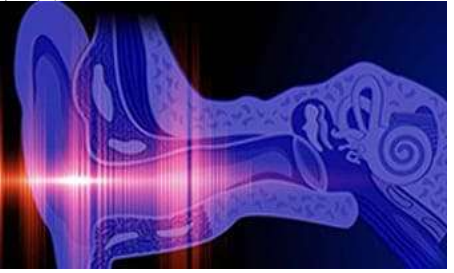


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## The bidirectional nature of the association between comorbidity and obstructive sleep apnoea

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### Abstract

Comorbidities of obstructive sleep apnea (OSA) includes metabolic, cardiovascular, renal, pulmonary, and mental disorders. Significant evidence indicates which OSA is an additional risk factor associated with numerous of these co-morbidities; however, there is also mounting evidence that several of these co-morbidities may lead to an occurrence of OSA. There is also mounting evidence of a two-way causality between OSA and comorbidities, particularly in the cases of heart failure, metabolic syndrome, and stroke. While retention of fluid and redistribution may play a larger role in comorbidities like heart failure and advanced renal disease, neurological processes may play a larger role in comorbidities like diabetic nephropathy and stroke. There is weak evidence to establish a two-way causal link between OSA and other comorbidities; instead, the data suggests that OSA primarily causes these conditions. This review focuses on co-morbidities that have been linked to an increased risk of OSA and examines the research supporting for such reciprocal interactions. Treatment's reciprocal effects are discussed to further emphasize the significance of precise diagnosis in clinical practice. This is particularly true of chronic obstructive pulmonary disease (COPD), where the detection of concurrent OSA has significant consequences for optimal treatment.

**Keywords:** OSA, relationship, comorbidity, hypertension, heart failure

### Introduction

There is accumulating evidence to show an independent link of obstructive sleep apnea (OSA) with a wide variety of comorbidities, particularly metabolic, cardiovascular, renal, pulmonary, and neuropsychiatric [2], and OSA is extremely common [1]. In the case of cardiovascular disease, the evidence is most robust for arterial hypertension and ventricular fibrillation [3]. The relatively high incidence of sleep-related breathing problems (SDB) in people of all ages, as well as the confounding influence of common risk factors like obesity, may make the proof of independent relationships between OSA and comorbidities more challenging. As a result of fluid buildup in the neck during sleep, OSA has been linked to an increased risk of heart failure (HF), as well as an increased risk of stroke and metabolic syndrome. Possible OSA-related mechanisms that contribute to co-morbidity include the sympathetic excitation, systemic inflammation, oxidative stress, metabolic, and endothelial dysfunction caused by temporary hypoxia, fluctuating intrathoracic pressure, and repeated micro-arousals [4]. Certain co-occurring disorders may have a predominance of one mechanism over another. Nocturnal hypertension appears to be driven by sympathetic excitation, whereas atherosclerosis and heart disease are more likely to result from inflammation as well as oxidative stress [3,4]. Comorbidities, especially cardiometabolic ones, may be associated with obstructive sleep apnea (OSA), which can make it difficult to establish the independent associations between OSA and comorbidities [1]. Intermittent hypoxia, a hallmark of OSA, has been shown to interact with adipose tissue in the progression of cardiometabolic comorbidity [5]. This study focuses on comorbidities that have been linked in both directions with OSA and provides an overview of the links between the two. The potential advantages of treatment, which have lately been called into doubt, will also be examined, with particular emphasis on cardiovascular outcomes [6].

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### Hypothalamic-pituitary-adrenal axis

Systemic hypertension, resistance to insulin, hyperlipidemia, and central obesity all contribute to the metabolic syndrome, which has been related to OSA [7]. There is likely a two-way street of causality between OSA and the metabolic syndrome [8]. However, various metabolic illnesses predispose to OSA through processes including morphological and neurological effects on the upper airway, and obstructive sleep apnea has been found to induce or aggravate several metabolic disorders, including hypertension and insulin resistance [8].

### Obesity

While many studies have focused on obesity as a potential risk reason for OSA, there is evidence to suggest that the association goes both ways.

### Causes of OSA include obesity

Central obesity contributes to OSA and comorbidities on several levels, strengthening the established relationship between the two. Excess fat in the abdomen lowers traction on the upper airway, further contributing to higher collapsibility [9]. Excess fat in the neck adds to oropharyngeal constriction, which enhances the collapsibility that occurs in the upper airway. In addition, visceral adipose tissue experiences intermittent hypoxia, a hallmark of OSA, which causes inflammation and aids in the development of insulin resistance. Epidemiologically speaking, 70% of people having OSA are obese, and 50% of those and a BMI >40 had OSA with an AHI >10 [10]. More severe OSA is commonly associated with a greater body mass index, especially in younger males and the general population.

### Effects of treatment

However, a recent analysis indicated relatively limited improvement to OSA following weight loss by dietary management alone during a 10-year further investigation period [11], contrasting with the substantial improvement of OSA after massive weight reduction, especially after bariatric surgery. There is a significant interplay between upper airway structure and the effects of obesity, and weight loss demonstrates the greatest benefit to OSA in individuals with an inadequate pre-existing maxillomandibular volume [12].

### Link between OSA and weight gain

Reduced physical activity and increased snacking on high-calorie meals to increase energy are two lifestyle impacts of OSA that, taken together, should lead to weight gain, however there is a lack of data to support this hypothesis. When compared to equally obese individuals without OSA, those with OSA lose fewer pounds after participating in a diet and exercise regimen for a year [13]. Despite the fact that CPAP (Constant positive airway pressure) treatment is very efficient in managing OSA, some patients, particularly females and nonobese individuals, gain weight after initiating CPAP [14]. Cardiometabolic risk is increased when obesity and OSA coexist due to a number of intermediary pathways. These mechanisms include inflammatory conditions, impaired endothelial function, and insulin resistance. Diabetic coma, there is emerging evidence of a two-way connection between diabetes and OSA [7].

### Obstructive Sleep Apnea and Diabetes

Increasing research suggests that OSA is an independent risk indicator for type 2 diabetes [15]. The European Sleep Apnea Database (ESADA) [16] is one of several cross-sectional cohort studies showing an independent association with type 2 diabetes and insulin resistance, and a pooled estimate of the proportional risk for diabetes to nine original studies was 1.69 (95% CI 1.45-1.80) [15]. Intermittent hypoxia and fragmented sleep, which cause sympathetic excitement and inflammation, contribute to the development of diabetes and insulin resistance. Fewer long-term research have been conducted on this possibility. After controlling for confounding factors, researchers in one community-based trial of middle-aged men identified a hazard ratio for accidental diabetes of 4.4 (95% CI 1.1- 18.0) between those who had or did not have OSA after 10 years of follow-up [17]. Additionally, they discovered an inverse relationship between AHI and insulin sensitivity index. Another retrospective cohort research of 8678 persons evaluated for OSA indicated that after 67 months of mean follow-up and after accounting for confounding variables, individuals having severe OSA had a 30% greater risk of acquiring diabetes compared to those without OSA [18].

### Effects of treatment

In contrast to weight loss, Chirinos *et al.* [19] found that 24 weeks of CPAP alone did not improve insulin sensitivity in non-diabetic individuals with OSA. There is conflicting evidence from randomized controlled trials using CPAP for OSA in people with diabetes; some have shown no improvement in glucose or insulin sensitivity, while others have found improvement [15]. In a research conducted by the US Department of Veterans Affairs, CPAP compliance was found to reduce the incidence of incident diabetes regardless of weight increase throughout the study's follow-up period.

### Obstructive Sleep Apnea and Diabetes

Neuropathy impacting the airway's upper muscles and abnormalities in ventilatory control are two diabetes mellitus-related complications that may increase the risk of obstructive sleep apnea. Insulin use, diabetic foot disease, male sex, obesity, and cardiovascular disease were identified as significant factors in a retrospective health care cohort study involving over 1 million subjects, yielding a modified incidence rate ratio of OSA among individuals with type 2 diabetes contrasted with those without of 1.48 (95% CI 1.42-1.55) [20]. OSA was revealed to be a distinct risk indicator for incident diabetes in another prospective cohort of over 300,000 healthcare workers, whereas insulin-dependent diabetes was found to be an important risk component for OSA in women [21]. Overall, there is strong evidence linking the two conditions, but less so linking CPAP therapy's efficacy in improving glycaemic management.

### Hypertension

Although hypertension occurs often in OSA patients, most studies have focused on OSA as a susceptibility factor for hypertension.

### A link between OSA and High Blood Pressure

Several population-wide epidemiological studies have found that obstructive sleep apnea is associated with an increased risk of systemic hypertension and a non-dipping midnight

blood pressure (BP) profile. Both the Sleep Heart Health Study [22] and the Wisconsin Cohort Study [23] found that OSA was related with a greater prevalence of hypertension after 4 years of follow-up. In particular, it causes a loss of nocturnal dipping, high diastolic blood pressure (BP), and resistance to standard antihypertensive medication, as supported by a systematic review of seven prospective investigations [24]. Indeed, rapid eye movement (REM)-related OSA is independently linked with recurrent nondipping BP, and nondipping nocturnal BP is significantly predictive of OSA regardless of symptom profile. Dysfunction of the renin-angiotensin-aldosterone system (RAAS) may play a role, although sympathetic excitement appears to be the primary pathogenic mechanism. Mild obstructive sleep apnea has also been linked to hypertension. A prospective study of 744 subjects with mild/moderate OSA and typical at baseline reported a connection with occurrence hypertension after 9 years in subjects 60 years old [25], and data about the ESADA study involving 4372 subjects in mild OSA found a distinct connection with prevalent hypertension [26].

### Effects of treatment

Numerous studies show that CPAP therapy lowers blood pressure, although the impact is minimal at 2 mmHg in 24 h mean BP, however it is larger in younger individuals, those with hypertension that is uncontrolled or severe oxygen desaturation, and in greater CPAP-compliant patients [27].

### Obstructive Sleep Apnea and Hypertension

Hypertension may increase the risk of obstructive sleep apnea, however the evidence is weak. Studies in animals and limited samples of humans show that blood pressure (BP) oscillations can affect upper airway tone, as seen by inhibitory changes in the corresponding electromyogram (EMG) reading. This shows that lowering blood pressure may increase airflow and lessen the severity of OSA. In addition, diuretics had a more noticeable effect on AHI, as shown by a meta-analysis of 11 research (including prospective and randomized trials) [28].

### Heart Failure

Sleep apnea and HF are linked in both directions, and they share risk factors such advanced age, obesity, and inactivity. Because of the two-way nature of the link between fluid retention and translocation and other unifying mechanisms [29], pinpointing a single reason for either phenomenon can be challenging. However, only the association between HF and OSA will be explored in this study. HF is linked to both central and obstructive sleep apnoea.

### Association between OSA and HF

Epidemiological investigations on a grand scale have shown that OSA is independently linked to an elevated risk of coronary heart disease, congestive HF, and cardiovascular mortality, despite the fact that these conditions share risk variables. Patients with severe OSA (AHI>30) were found to have a 58% higher risk of incident HF compared to patients without OSA in the Sleep Heart Health Study, which followed 4442 participants prospectively [30]. Large fluctuations in intrathoracic pressure brought on by obstructive events modify cardiac haemodynamics by raising preload, lowering left heart ventricular pressure, and raising afterload [9]. Sodium and retention of water are

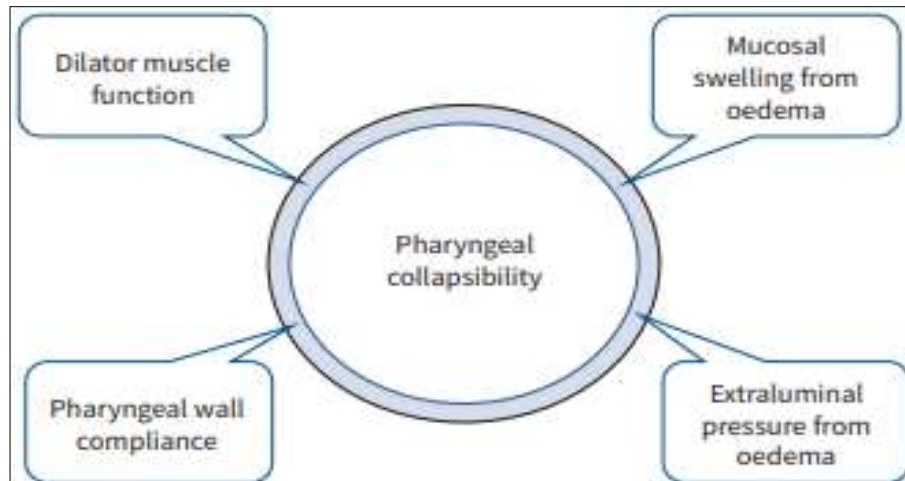
increased as a result of the RAAS being stimulated. OSA may immediately compromise cardiac function, making bouts of acute HF worse, and may cause cardiac remodelling, both of which contribute to HF. Diastolic dysfunction is more severe in those with a higher AHI. Compared to patients with uncontrolled moderate or severe illness, individuals who had no or moderate OSA had a 50% lower incidence of fatal events [31]. Patients who develop OSA while hospitalised have a higher risk of death after being released from the hospital, and their prognosis for recovery from HF is worse.

### Effects of treatment

Interim cardiovascular end-points such blood pressure, heart rate, and rhythm, and fraction of ejection are all enhanced by CPAP therapy for OSA. Heart rate and blood pressure dropped during the day, which may indicate less epinephrine was excreted in the urine overnight, as reported by KANEKO *et al.* [32]. While CPAP treatment has been found to offer short-term physiological benefits, reviews on its long-term effectiveness have been mixed. There is a dearth of evidence to support the claims of reduced mortality and transplant-free survival [33]. Research has been hindered by insufficient sample numbers and brief durations of observation. Long-term CPAP treatment has been shown in observational studies [34] to lower cardiovascular morbidity and death relative to noncompliant patients over a 10-year follow-up period. Although the SAVE trial was confined to non-sleepy individuals with OSA and adherence to CPAP was low, more recent randomized managed studies of CPAP therapy have failed to show improvements in the secondary avoidance of cardiovascular illnesses, including HF.

### The association between HF and OSA

The prevalence of SDB is greater in HF than in individuals without HF, as shown by several observational studies [29]. Hypersomnolence is more difficult to diagnose in individuals with heart failure and obstructive sleep apnea. The severity of OSA is correlated with the level of cardiac dysfunction, and 53 percent of patients having stable HF satisfied the criteria for diagnosis for OSA in a clinic for outpatient environment. Clinical diagnostic requirements for OSA were met by 43% of 203 individuals with HF and LVEF 10 in a prospective study [35]. Patients with HF tend to have a distinct clinical phenotype of OSA, in addition to having lower BMI; this finding lends credence to the theory that HF can contribute to, or worsen SDB, even without the presence of other common risk factors like obesity. As a result of a decrease in stroke volume, patients with HF are more likely to retain fluids via neurogenic and humoral pathways. Upper airways resistance and collapsibility are also impacted by the nighttime redistribution of fluid to dependent parts of the body, especially the parapharyngeal tissues. Because of the impact on retention of fluid and redistribution, dietary sodium consumption is inversely related to OSA severity in HF. Also, compared to not using stockings, nonobese males with venous insufficiency had a 36% decrease in AHI when they used stockings with compression during the day to avoid fluid collection. Pharyngeal collapse is facilitated by a number of circumstances, some of which are depicted in figure 1 as schematic representations.



**Fig 1:** Potential mechanisms of increased pharyngeal collapsibility resulting from fluid accumulations in the neck region

### Therapeutic Effects

It is reasonable to assume that treating HF will improve OSA, as the extent of OSA varies with fluid redistribution. While fluid buildup is thought to have a role in the development of OSA in HF, a randomized controlled trial (RCT) of patients having severe OSA found that sodium restriction and diuretic medication only resulted in a small improvement in AHI. The use of diuretics has been shown to reduce body weight, enhance pharyngeal calibre, and decrease AHI by 17 points in patients with an acute aggravation of hypertension diastolic HF. On the other hand, an observational trial found that diuretic medication reduced OSA severity among individuals with HF [36], but only in those who were overweight or hypertensive. Despite its usefulness in central sleep apnea, cardiac resynchronization treatment has received less research in OSA, despite preliminary reports that it can lower AHI.

### Renal Dysfunction

There is mounting evidence linking renal illness to sleep apnea, and vice versa. Both obstructive sleep apnea (OSA) and central sleep apnea (CSA) are more prevalent in patients having renal impairment than in those with adequate renal function, even after controlling for confounding factors. OSA might be made worse by end-stage renal disease (ESRD). Rapid deterioration in renal function and increased risk of kidney damage have both been linked to obstructive sleep apnea.

### OSA risk factors associated with renal disease

Patients with chronic kidney disease (CKD) have an incidence of OSA that is up to 10 times greater than the general population, however OSA is often misdiagnosed in this population. This may be due to unusual presentations and a greater threshold for symptom detection. Supporting its involvement in pathophysiology, the prevalence of OSA rises in tandem with the severity of CKD. The prevalence of OSA was 27% in those with an eGFR >60, 41% in those with an eGFR 60 who were not on renal replacement treatment, and 57% in those on haemodialysis, according to a clinic-based research. Higher chemoreflex sensitivity, reduced elimination of uraemic toxins, and hypervolemia all have a role in causing OSA in CKD. Metabolic acidosis in ESRD can cause changes in chemoreflex responsiveness, which in turn can increase the reactivity to carbon dioxide tension (PCO<sub>2</sub>), influencing breathing and the apnoeic

threshold. Upper airway collapsibility can be exacerbated by the buildup of uraemic toxins and the associated myopathy [37]. Reducing urea and peritoneal creatinine levels, which correlate inversely with AHI scores, may alleviate symptoms. Similar to HF, it is probable that fluid buildup and related nocturnal translocation in the recumbent state contribute to pharyngeal constriction. Seventy percent of 40 haemodialysis patients had an AHI >15, and those with an AHI >15 also had a greater overall body volume of extracellular fluid, including neck, thorax, and leg volumes, although having the same body mass index [38].

### Therapeutic Effects

The severity of OSA is likely to worsen as fluid overload increases, although it may improve with vigorous treatment of ESRD. Benefits to OSA have been linked to lower AHI, decreased airway congestion, and increased uraemic clearance [39] in observational studies comparing day dialysis, nocturnal dialysis, and nocturnal peritoneal mechanized dialysis. The volume of fluid extracted in an ultrafiltration session, in this case 2.2 L, coincided with a 36% decrease in AHI. It is unclear whether or not renal transplantation is beneficial for OSA, despite the fact that it cures most of the metabolic problems in ESRD and reduces the progression of related comorbidities. When comparing polysomnography (PSG) results from prior to and 3 months following transplantation in a group of 18 patients with ESRD, researchers found that both the incidence and severity of OSA decreased after surgery [40].

### Link between OSA and kidney disease

There are indications that OSA can influence CKD and the steady loss in GFR, as well as arise as an outcome of CKD. Comorbidities that include cardiovascular and cerebrovascular illness, including dysrhythmia, coronary disease, and stroke, may contribute to the increased risk of death and disability seen in individuals with ESRD who also have OSA. The loss in kidney function over time was not observed to be accelerated in those with OSA compared to those without OSA in a retrospective examination of data obtained from the Wisconsin Sleep Cohort. Newly diagnosed OSA patients had an elevated risk of incident CKD, comparable to that of hypertensive patients, according to a large retrospective analysis conducted in Taiwan [41]. The two basic mechanisms by which OSA causes renal illness are hypertension and intrarenal hypoxia accompanied

by glomerular hyperfiltration. The renal medulla is especially vulnerable to hypoxia, which leads to the hallmark of chronic kidney disease-tubulointerstitial injury-by way of oxidative stress, systemic inflammation, and endothelial dysfunction. Acute apnea causes systemic and glomerular hypertension, vascular damage, arterial wall stiffness, and ultimately renal ischaemia via activating the sympathetic nerve and RAAS systems.

### Impact of Therapy

In individuals with normal renal function at the starting point, CPAP has been demonstrated to affect renal haemodynamics favourably, suggesting a benefit in reducing renal damage. Studies have shown conflicting results on CPAP's ability to slow the course of renal impairment in OSA, and even less have focused on patients with already-present CKD. Patients without CKD who used fixed CPAP had a slower drop in eGFR compared to patients who used auto-adjusting CPAP, according to the ESADA cohort trial. It has been found that individuals with moderately to severe OSA who are treated with CPAP see an immediate improvement in renal filtration [24]. Another observational trial found that after three months of CPAP, serum creatinine decreased and eGFR increased in men with an AHI of >20. Another trial with a longer follow-up period also found short-term advantages, although patients with a greater AHI had higher blood creatinine levels even when CPAP therapy was continued for 8 years. Renal function improved in individuals at reduced risk of CKD development, but there was not a statistically significant difference in eGFR between CPAP and usual treatment after 1 year of follow-up in a randomized controlled trial of patients with Stage 3 and 4 CKD. Treatment of OSA with CPAP has not been shown to change renal function or increase the risk of renal adverse events among individuals with cardiovascular disease, according to a post hoc study of 200 patients from the SAVE trial [42].

Patients suffering from a stroke often have SDB. It is uncertain whether OSA is a result of stroke-related brain damage or a precipitating event that amplifies established vascular risk factors like hypertension. Stroke and sleep have been shown to have a complicated and mutually reinforcing connection [43].

### Risk factors for OSA-related stroke

Obstructive sleep apnea (OSA) is associated with a roughly twofold increase in the chance of having a stroke. Even after accounting for possible confounders such as age, BMI, diabetes, and high BP, a systematic review of six systematic studies indicated an elevated incidence of stroke in patients with untreated OSA [44]. A causal link between OSA and future risk of stroke was prospectively proven by the Sleep Heart Health Study [45]. It also found that the risk of stroke increased by 6% for every unit increase between 5 and 25 occurrences per hour in younger men with severe OSA. Those with an AHI >20 had a higher risk of stroke (OR 4.3) in the Wisconsin Cohort study. A quarter of all strokes occur when people are asleep, according to early research, which may indicate a circadian effect on the pathophysiology [46]. The phenomena of wake-up stroke directed attention to rapid eye movement (REM) sleep and brought attention to alertness as a potential cause. According to the Sleep Tight research, AHI was considerably greater in males who experienced wake-up

strokes. Alterations in cerebral blood flow are caused by dysautonomia, circadian activation of RAAS, and BP variations. Platelet aggregation, hypercoagulability, and endothelial injury are all intermediate pathways that are triggered by this. Untreated OSA also increases the risk of stroke due to factors like accelerated atherosclerosis, poor glucose tolerance, and cardiac dysrhythmias such refractory atrial fibrillation. There is evidence that obstructive sleep apnea (OSA) raises the probability of having a second stroke [47].

### Therapeutic Effects

Patients with OSA who use CPAP have had mixed results in cohort studies. Patients with OSA, and particularly those who adhere to therapy, have a lower risk of stroke, according to observational studies [48]. Randomized controlled trials (RCTs) revealed that treatment adherence of >4 hours may be beneficial. Post hoc analysis of the SAVE trial has linked self-reported snoring to an increased risk of incident stroke, notwithstanding the original conclusion that CPAP treatment had no effect on stroke rates. Despite a dearth of research, the potential advantages of therapy are more compelling and easier to establish in OSA patients who have suffered a stroke. Untreated OSA can have negative effects on stroke recovery, notably on executive function, concentration, drowsiness, and psychomotor abilities. However, some studies indicate no change in neurological result based on objective to treat analyses, despite some improvement being detected in CPAP-compliant individuals [49], while others find that CPAP therapy improves immediate as well as long-term functional outcomes. The goal of treatment is to prevent further damage to the ischemic penumbra and restore normal autoregulation in the brain. Methods of evaluating outcomes, such as the inaccuracy of patient-reported symptoms after stroke, restrict many of these research. Challenges with registration and adherence, as well as patient selection factors (stroke severity, impairment, and comorbidities like delirium or depression), can all obfuscate results and contribute to inconsistencies. In addition, better glycaemic and BP management are likely to minimize the risk of a second stroke.

### Causes of Obstructive Sleep Apnea

One-third of stroke survivors report an AHI >30 [47], suggesting that OSA is common in this population. However, stroke may also reveal latent OSA. Stroke may have a direct negative effect on the function of the muscles in the upper airway, increasing the likelihood of collapse, and post-stroke sleep patterns may exacerbate this problem. The decline in occurrence of OSA during the acute stage to the protracted phase of recovery is more evidence that OSA is a result of stroke. In addition to inferior functional and cognitive results and greater duration hospitalization and rehabilitation durations following a stroke, obstructive sleep apnea (OSA) has also been linked to increased cerebrovascular morbidity. When patients with OSA present with acute stroke, the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale scores are often greater than in patients without OSA [50]. These negative outcomes are thought to be caused by a "reverse Robin Hood" phenomenon wherein apnea-induced hypercapnia diverts blood flow away from the currently ischaemic region, adding insult to injury for the ischaemic penumbra.

Patients with both stroke and OSA had a 1.8-fold greater risk of mortality over a 10-year follow-up period [51] in a prospective trial.

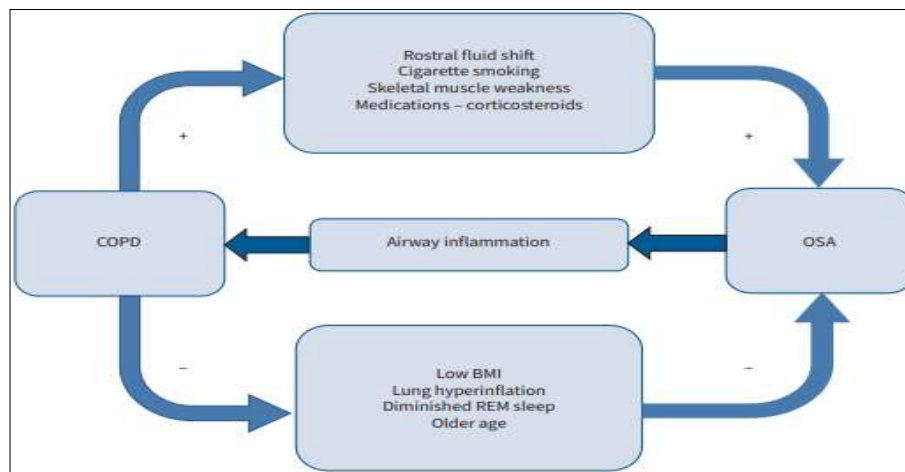
### COPD

The link between COPD and OSA is complicated, with certain characteristics, such as hyperinflation, protecting against OSA and others, like fluid retention, encouraging OSA. These factors probably account for some of the documented variations in this relationship's epidemiology.

### Link between OSA and COPD

When analyzing the connection between COPD and OSA, most studies have zeroed in on COPD as a potential cause of OSA. Patients with moderate COPD were not more likely to have SDB, according to findings obtained from the Sleep Heart Health Study [52], but they were more likely to experience oxygen desaturations during sleep if they also suffered from SDB. Newer investigations, however, have shown that individuals with moderate-to-severe COPD have an elevated risk of developing OSA [53]. The differences

between the populations studied may explain the contradictory findings. Notably, the prevalence of OSA in COPD patients increases with both body mass index and smoking history. From the hyperinflating patient with low body mass index (predominant emphysema phenotype) to the obese patient with right ventricular hypertrophy (predominant chronic bronchitis phenotype), COPD encompasses a wide range of clinical phenotypes. Lower critical closure pressure that occurs in the upper airway while sleep is associated with the emphysema phenotype that is most common. OSA is associated with obesity and right heart failure with fluid retention, both of which are more common in the chronic bronchitis phenotype. Recumbent sleepers are more likely to have HF-like airway constriction due to a change in the rostral fluid during sleep (figure 1). Despite no changes in body mass index or lung function, the COPDgene research found an increased frequency of OSA in the persistent bronchitis phenotype. Smoking-related upper-airway inflammation may have a role in obstructive sleep apnea, in alongside the skeletal myopathy that weakens the muscles that support the airway.



**Fig 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

There is conflicting evidence linking OSA to an increased risk of COPD. Patients with OSA, particularly women, have a greater risk of developing chronic obstructive pulmonary disease (COPD) and asthma compared to a control group. In contrast, a community-based research of 853 older men by ZHAO *et al.* [54] found a decreased incidence of COPD in participants with SDB in comparison to those without SDB. It has been shown in animal studies that persistent intermittent hypoxia leads to lung damage in mice by producing inflammation and oxidative stress, and obstructive sleep apnea appears to worsen lower airway inflammation in patients with COPD [55]. Further study is needed to compare different clinical phenotypes and age groups to better understand the epidemiological link between COPD and OSA and associated effects. Influencing factors on the link between the two illnesses are shown in figure 2.

### Therapeutic Effects

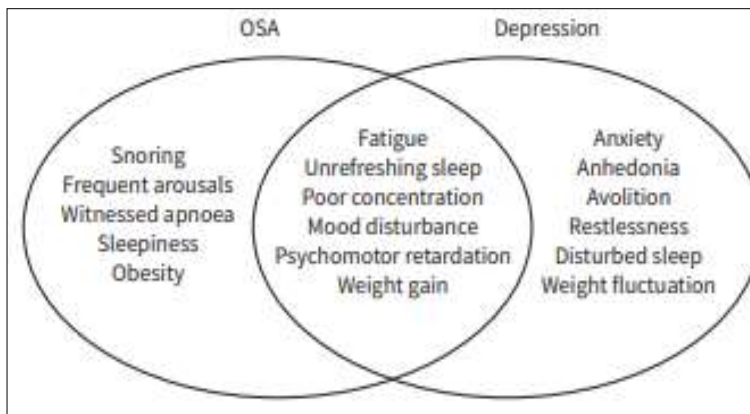
Long-term CPAP treatment improves survival for patients with COPD-OSA overlap, making them no different from patients with COPD alone. However, patients with overlap

who do not receive treatment with CPAP have a higher death rate and are more likely to be hospitalized for acute exacerbations. These results highlight the significance of identifying co-existing OSA for those with severe COPD to pick the most appropriate treatment.

### Depression

Similarities in symptoms between depression and OSA, such as forgetfulness and lethargy, might make a correct clinical diagnosis more challenging (Figure 3). Many people with depression report having trouble sleeping, and this complaint is often cited as a predictor of future depressive episodes. The link between depression and OSA has been theorised [56]. Sleep disruption, frequent awakenings, and brief periods of low oxygen levels that disrupt REM sleep have all been proposed as potential processes underpinning each process. Biologic plausibility Nonetheless, research into potential reciprocal interactions is limited, and results have been contradictory.

One research of almost 20,000 people of all ages found that individuals with OSA or melancholy were nearly equally likely to have the other illness.



**Fig 3:** Clinical features obstructive sleep apnoea (OSA) and depression demonstrating shared features in the overlap of both disorders

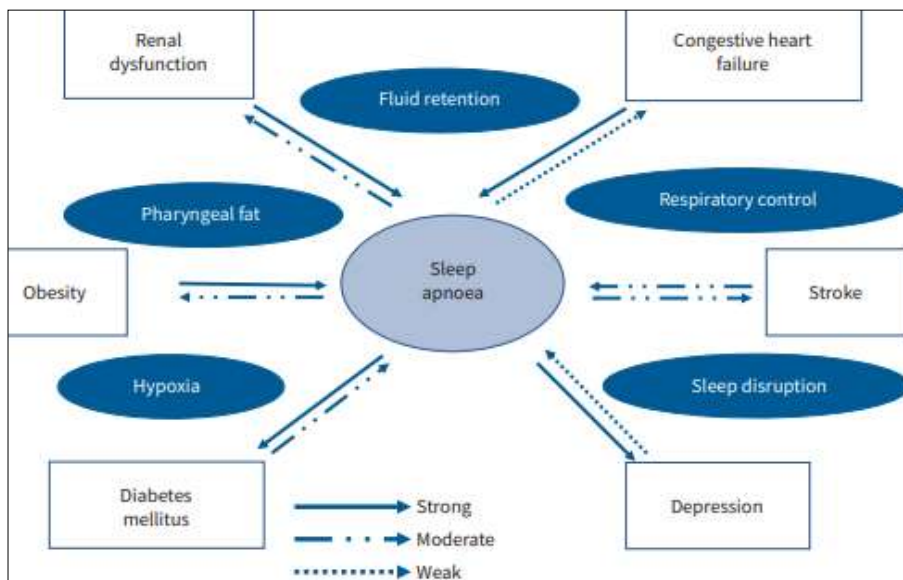
A prospective study conducted in Taiwan found that those suffering from OSA had a greater likelihood of afterwards physician-diagnosed depression [57], and that patients with depression at baseline had a boosted risk of incident OSA at follow-up, and this was true regardless of socioeconomic status or the presence of other co-morbidities.

**Link between OSA and sadness**

There is a correlation between the severity of SDB and an elevated risk of depression, and clinical cohorts have found an average incidence of depression in OSA between 20% and 40%. Other, smaller studies, however, found that OSA itself was not a predictor of either depression ratings or hospitalization rates [58].

**Effects of treatment**

Small but significant improvements in depressed symptomatology were found using validated depression measures in a meta-analysis of 22 RCTs on CPAP plus mandibular advancement device (MAD) treatment for OSA [59]. Analysis showed that individuals with more severe depression symptoms at the start of treatment responded best. Independent of medications, treating OSA with CPAP for a minimum of five hours nightly for a minimum of 3 months alleviated depressed symptoms, including suicidal thoughts.



**Fig 4:** Proposed bidirectional relationships between obstructive sleep apnoea and comorbidity. The levels of evidence favoring inter-relationships ranging from strong to weak are the author’s opinions based on the available evidence

**Link between depression and OSA**

There has not been a lot of research on whether or not depression is a cause of OSA. Patients with MDD are more likely to develop sleep apnea (OSA), and prevalence data show that 15% of mental health inpatients with MDD have elevated AHI on overnight polysomnography. Another research revealed a greater frequency of 39% and hypothesised that sleeplessness had a role in this finding [56]. The results of this study are bolstered by the fact that diagnosed and likely OSA patients were not included.

**Therapeutic Effects**

A meta-analysis of prospective trials including five different antidepressants indicated that only two were effective at lowering AHI without influencing daytime drowsiness or nighttime performance [60]. Some antidepressant medications, especially if they cause weight gain, may exacerbate OSA in those who haven't yet been diagnosed with the condition. Benzodiazepines impact upper airway tone as well as modify the arousal threshold, which can lead to an increase in both the length and frequency of apnoeic occurrences.

## Conclusion

Many different comorbidities have been linked to OSA, and some of them may really be indicators of risk for OSA through various pathways. While the significance of OSA as a separate risk factor for comorbidity has been researched extensively, the inverse link is less well explored but nevertheless offers an essential topic for further investigation. Figure 4 displays the authors' evaluation of the potential reciprocal associations between OSA and comorbidities.

## Conflict of Interest

Not available

## Financial Support

Not available

## References

- Lévy P, Kohler M, McNicholas WT. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers*. 2015;1:1-20.
- McNicholas WT. Obstructive sleep apnoea and comorbidity – an overview of the association and impact of continuous positive airway pressure therapy. *Expert Rev Respir Med*. 2019;13:251-261.
- McNicholas WT, Bonsignore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J*. 2007;29:156-178.
- Castro-Grattoni AL, Alvarez-Buvé R, Torres M. Intermittent hypoxia-induced cardiovascular remodeling is reversed by normoxia in a mouse model of sleep apnea. *Chest*. 2016;149:1400-1408.
- Murphy AM, Thomas A, Crinion SJ. Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. *Eur Respir J*. 2017;49:1601731.
- Schiza S, Lévy P, Martínez-García MA. The search for realistic evidence on the outcomes of obstructive sleep apnoea. *Eur. Respir. J*. 2021;58:2101963.
- Drager LF, Togeiro SM, Polotsky VY. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol*. 2013;62:569-576.
- Phillips CL, Hoyos CM, Yee BJ. CrossTalk opposing view: sleep apnoea causes metabolic syndrome. *J Physiol*. 2016;594:4691-4694.
- Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. *Eur Respir J*. 1995;8:1161-1178.
- Tuomilehto H, Seppä J, Uusitupa M. Obesity and obstructive sleep apnea – Clinical significance of weight loss. *Sleep Med Rev*. 2013;17:321-329.
- Kuna ST, Reboussin DM, Strotmeyer ES. Effects of weight loss on obstructive sleep apnea severity. ten-year results of the sleep AHEAD study. *Am J Respir Crit Care Med*. 2021;203:221-229.
- Sutherland K, Phillips CL, Yee BJ. Maxillomandibular volume influences the relationship between weight loss and improvement in obstructive sleep apnea. *Sleep*. 2016;39:43-49.
- Borel AL, Leblanc X, Almeras N. Sleep apnoea attenuates the effects of a lifestyle intervention programme in men with visceral obesity. *Thorax*. 2012;67:735-741. 24
- Redenius R, Murphy C, O'Neill E. Does CPAP lead to change in BMI? *J Clin Sleep Med*. 2008;4:205-209.
- Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: A state of the art review. *Chest*. 2017;152:1070-1086.
- Kent BD, Grote L, Ryan S. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) Study. *Chest*. 2014;146:982-990.
- Lindberg E, Theorell-Haglöw J, Svensson M. Sleep apnea and glucose metabolism: A long-term follow-up in a community-based sample. *Chest*. 2012;142:935-942.
- Kendzerska T, Gershon AS, Hawker G. Obstructive sleep apnea and incident diabetes. A historical cohort study. *Am J Respir Crit Care Med*. 2014;190:218-225.
- Chirinos JA, Gurubhagavatula I, Teff K. CPAP, weight loss or both for obstructive sleep apnea. *N Engl J Med*. 2014;370:2265-2275.
- Subramanian A, Adderley NJ, Tracy A. Risk of incident obstructive sleep apnea among patients with type 2 diabetes. *Diabetes Care*. 2019;42:954-963.
- Huang T, Lin BM, Stampfer MJ. A Population-based study of the bidirectional association between obstructive sleep apnea and type 2 diabetes in three prospective U.S. cohorts. *Diabetes Care*. 2018;41:2111-2119.
- Nieto FJ, Young TB, Lind BK. Association of sleep-disordered breathing, sleep apnea and hypertension in a large community-based study. *Sleep Heart Health Study*. *JAMA*. 2000;283:1829-1836.
- Peppard PE, Young T, Palta M. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378-1384.
- Xia W, Huang Y, Peng B. Relationship between obstructive sleep apnoea syndrome and essential hypertension: a dose-response meta-analysis. *Sleep Med*. 2018;47:11-18.
- Bouloukaki I, Grote L, McNicholas WT. Mild obstructive sleep apnea increases hypertension risk, challenging traditional severity classification. *J Clin Sleep Med*. 2020;16:889-898.
- Vgontzas AN, Li Y, He F. Mild-to-moderate sleep apnea is associated with incident hypertension: age effect. *Sleep*. 2019;42:zsy265.
- Pengo MF, Soranna D, Giontella A. Obstructive sleep apnoea treatment and blood pressure: which phenotypes predict a response? A systematic review and meta-analysis. *Eur Respir J*. 2020;55:1901945.
- Khurshid K, Yabes J, Weiss PM. Effect of antihypertensive medications on the severity of obstructive sleep apnea: a systematic review and meta-analysis. *J Clin Sleep Med*. 2016;12:1143-1151.
- Lyons OD, Bradley TD. Heart failure and sleep apnea. *Can J Cardiol*. 2015;31:898-908.
- Gottlieb DJ, Yenokyan G, Newman AB. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation*. 2010;122:352-360.
- Wang H, Parker JD, Newton GE. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol*. 2007;49:1625-1631.
- Kaneko Y, Floras JS, Usui K. Cardiovascular effects of continuous positive airway pressure in patients with



- heart failure and obstructive sleep apnea. *N Engl. J Med.* 2003;348:1233-1241.
33. Lévy P, Ryan S, Oldenburg O. Sleep apnoea and the heart. *Eur Respir Rev.* 2013;22:333-352.
  34. Marin JM, Carrizo SJ, Vicente E. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005;365:1046-1053.
  35. Schulz R, Blau A, Börgel J. Sleep apnoea in heart failure. *Eur Respir J.* 2007;29:1201-1205.
  36. Revol B, Jullian-Desayes I, Bailly S. Who may benefit from diuretics in OSA? A propensity score-match observational study. *Chest.* 2020;158:359-364.
  37. Abuyassin B, Sharma K, Ayas NT. Obstructive sleep apnea and kidney disease: a potential bidirectional relationship? *J Clin Sleep Med.* 2015;11:915-924.
  38. Lyons OD, Inami T, Perger E. The effect of fluid overload on sleep apnoea severity in haemodialysis patients. *Eur Respir J.* 2017;49:1601789.
  39. Santos RS, Motwani SS, Elias RM. Chronic kidney disease and sleeping disordered breathing (SDB). *Curr Hypertens Rev.* 2016;12:43-47.
  40. Beecroft JM, Zaltzman J, Prasad R. Impact of kidney transplantation on sleep apnoea in patients with end-stage renal disease. *Nephrol Dial Transplant.* 2007;22:3028-3033.
  41. Chu H, Shih CJ, Ou SM. Association of sleep apnoea with chronic kidney disease in a large cohort from Taiwan. *Respirology.* 2016;21:754-760.
  42. Loffler KA, Heeley E, Freed R. Effect of obstructive sleep apnea treatment on renal function in patients with cardiovascular disease. *Am J Respir. Crit. Care Med.* 2017;196:1456-1462.
  43. Bassetti CLA, Randerath W, Vignatelli L. EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke. *Eur J Neurol.* 2020;27:1117-1136.
  44. Li M, Hou WS, Zhang XW. Obstructive sleep apnea and risk of stroke: A meta-analysis of prospective studies. *Int. J Cardiol.* 2014;172:466-469.
  45. Redline S, Yenokyan G, Gottlieb DJ. Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. *Am J Respir. Crit. Care Med.* 2010;182:269-277.
  46. Young T. Rationale, design and findings from the Wisconsin Sleep Cohort study: Toward understanding the total societal burden of sleep disordered breathing. *Sleep Med Clin.* 2009;4:37-46.
  47. Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: A meta-analysis. *J Clin. Sleep Med.* 2010;6:131-137.
  48. Haba-Rubio J, Vujica J, Franc Y. Effect of CPAP treatment of sleep apnea on clinical prognosis after ischemic stroke: An observational study. *J Clin. Sleep Med.* 2019;15:839-847.
  49. Bravata DM, Sico J, Vaz Fragoso CA. Diagnosing and treating sleep apnea in patients with acute cerebrovascular disease. *J Am Heart Assoc.* 2018;7:e008841.
  50. Menon D, Sukumaran S, Varma R. Impact of obstructive sleep apnea on neurological recovery after ischemic stroke: A prospective study. *Acta Neurol Scand.* 2017;136:419-426.
  51. Sahlin C, Sandberg O, Gustafson Y. Obstructive sleep apnea is a risk factor for death in patients with stroke: A 10-year follow-up. *Arch Intern Med.* 2008;168:297-301.
  52. Sanders MH, Newman AB, Haggerty CL. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *Am J Respir Crit Care Med.* 2003;167:7-14.
  53. Soler X, Gaio E, Powell FL. High prevalence of obstructive sleep apnea in patients with moderate to severe chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* 2015;12:1219-1225.
  54. Zhao YY, Blackwell T, Ensrud KE. Sleep apnea and obstructive airway disease in older men: Outcomes of sleep disorders in older men study. *Sleep.* 2016;39:1343-1351.
  55. Wang Y, Hu K, Liu K. Obstructive sleep apnea exacerbates airway inflammation in patients with chronic obstructive pulmonary disease. *Sleep Med.* 2015;16:1123-1130.
  56. Ong JC, Gress JL, San Pedro-Salcedo MG. Frequency and predictors of obstructive sleep apnea among individuals with major depressive disorder and insomnia. *J Psychosom Res.* 2009;67:135-141.
  57. Pan ML, Tsao HM, Hsu CC. Bidirectional association between obstructive sleep apnea and depression: a population-based longitudinal study. *Medicine (Baltimore).* 2016;95:e4833.
  58. Kendzerska T, Gershon AS, Hawker GA. Obstructive sleep apnoea is not a risk factor for incident hospitalised depression: A historical cohort study. *Eur Respir J.* 2017;49:1601361.
  59. Povitz M, Bolo CE, Heitman SJ. Effect of treatment of obstructive sleep apnea on depressive symptoms: Systematic review and meta-analysis. *PLoS Med.* 2014;11:e1001762.
  60. AbdelFattah MR, Jung SW, Greenspan MA. Efficacy of antidepressants in the treatment of obstructive sleep apnea compared to placebo. A systematic review with meta-analyses. *Sleep Breath.* 2020;24:443-453.

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