Obstructive sleep apnoea syndrome

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Abstract | Obstructive sleep apnoea syndrome (OSAS) is a common clinical condition in which the throat narrows or collapses repeatedly during sleep, causing obstructive sleep apnoea events. The syndrome is particularly prevalent in middle-aged and older adults. The mechanism by which the upper airway collapses is not fully understood but is multifactorial and includes obesity, craniofacial changes, alteration in upper airway muscle function, pharyngeal neuropathy and fluid shift towards the neck. The direct consequences of the collapse are intermittent hypoxia and hypercapnia, recurrent arousals and increase in respiratory efforts, leading to secondary sympathetic activation, oxidative stress and systemic inflammation. Excessive daytime sleepiness is a burden for the majority of patients. OSAS is also associated with cardiovascular co-morbidities, including hypertension, arrhythmias, stroke, coronary heart disease, atherosclerosis and overall increased cardiovascular mortality, as well as metabolic dysfunction. Whether treating sleep apnoea can fully reverse its chronic consequences remains to be established in adequately designed studies. Continuous positive airway pressure (CPAP) is the primary treatment modality in patients with severe OSAS, whereas oral appliances are also widely used in mild to moderate forms. Finally, combining different treatment modalities such as CPAP and weight control is beneficial, but need to be evaluated in randomized controlled trials. For an illustrated summary of this Primer, visit: http://go.nature.com/Lwc6te

Upper airway obstruction during sleep — sleep-disordered breathing — comprises several conditions, of which obstructive sleep apnoea syndrome (OSAS) is the most frequent. Other conditions include central sleep apnoea (an imbalance in the respiratory control owing to enhanced chemosensitivity, which particularly occurs in patients with heart failure), or obesity hypoventilation syndrome, which is an obesity-associated condition associated with hypoventilation owing to a lack of response to carbon dioxide. In this Primer, we focus on OSAS.

OSAS is characterized by recurrent pharyngeal collapses during sleep[1]. The pathophysiology of OSAS is multifactorial and includes a reduction in upper airway dimensions that can result from both anatomical and functional alterations (obesity or maxillofacial structural changes)[2,3] (FIG. 1), and increased pharyngeal collapsibility owing to reduced neuromuscular compensation and lack of the pharyngeal protective reflex during sleep[4]. The decreased upper airway size and increased resistance might result in snoring by vibration of the soft palate, the uvula and/or the lateral walls of the pharynx[1]. The upper airway collapse can be complete, leading to an obstructive apnoea defined as a reduction of air flow of more than 90% associated with persistent respiratory movements. Partial closure corresponds to hypopnoea, which is defined as a reduction in ventilation of more than 30% from baseline and oxygen desaturation of more than 3% from baseline or microarousal[5,6]. Owing to their short duration (3–15 seconds), microarousals are not perceived by the patient but still cause sleep fragmentation. In particular, intermittent hypoxia has a large role in the pathophysiology[7] of apnoeas and hypopnoeas and its consequences, including excessive daytime sleepiness (EDS)[8–10], cardiovascular co-morbidities[11] and an increased risk of death from any cause, at least in severe OSAS[12]. OSAS is now considered a major public health issue affecting 5–15% of the general population, increasing linearly with age up to at least 60–65 years[8,13].

OSAS diagnosis is based on sleep recordings, either a full polysomnography, which includes neurophysiological, cardiac and respiratory signals, or a respiratory polygraphy, which does not include neurophysiological sensors[14]. Patients are only considered to have OSAS when obstructive sleep apnoea (OSA) events result in symptoms (BOX 1). Importantly, sleep apnoea discovered in a sleep recording without any symptoms is usually not considered to be OSAS, except if the apnoea–hypopnoea index (AHI) is >15 (events per hour of sleep)[15].

In this Primer, we review the characteristics of the condition with respect to its epidemiology and mechanisms. We also present the main diagnostic options and the current management. Finally, quality-of-life issues and the main challenges for future OSAS clinical

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management and research are reviewed. It should be noted that we focus on OSAS in adults because there are many differences when comparing OSAS in children and adults (BOX 2).

Epidemiology

OSAS is one of the most prevalent chronic respiratory disorders[16]. The 1993 landmark Wisconsin cohort study, involving employed men and women between 30 years and 60 years of age, demonstrated that 24% of men and 9% of women had an AHI ≥5 (REF. 13). Prevalence estimates for an AHI ≥10 and AHI ≥15 were 15% and 5% in men, and 9% and 4% in women, respectively. The prevalence of OSAS was much lower because additional diagnosis criteria need to be present (BOX 1), and only 4% of men and 2% of women were found to have OSAS with an AHI ≥5 and self-reported EDS[8,13]. However, caution should be exercised in interpreting the prevalence of OSAS because two-thirds as many subjects without sleep apnoea (AHI <5) also report EDS[10].

The prevalence of OSAS is high worldwide (FIG. 2). Moreover, some recent studies even suggest a rise in the prevalence, which probably reflects the growing prevalence of overweight and obese individuals. Indeed, updated population prevalence estimates based on longitudinal data from the Wisconsin cohort study support this notion. In the late 2000s, 13% of men and 6% of women in the 30–70 years age-range had moderate to severe sleep-disordered breathing (AHI ≥15) compared with 5% of men and 4% of women in 1993 (REF. 17). Depending on the age and gender subgroup, the authors concluded that there had been a 14–55% increase in the prevalence of OSAS since the early 1990s.

Although OSAS is typically two times to three times more prevalent in men than women in various general population studies, the ratio is typically even higher in sleep clinic populations[18]. The reason for this discrepancy is unclear but might relate to differences in symptom profile that prompt men to seek medical attention earlier than women. Specific subgroups such as premenopausal women, young and lean individuals, and patients without severe snoring or obvious EDS might also be underdiagnosed by health professionals[19].

Genetic factors have a role in the development of OSAS[20]. Prevalence in first-degree relatives of patients with OSAS is twofold higher compared with first-degree relatives of healthy controls[21]. Susceptibility to OSAS increases with the number of affected relatives[22]. Segregation analysis in the Cleveland Family Study showed that, independent of body mass index (BMI), up to 35% of the variance in the AHI depends on genetic factors[22]. Inherited factors include craniofacial and upper airway morphology, in addition to differences in body fat distribution and control of breathing[20].

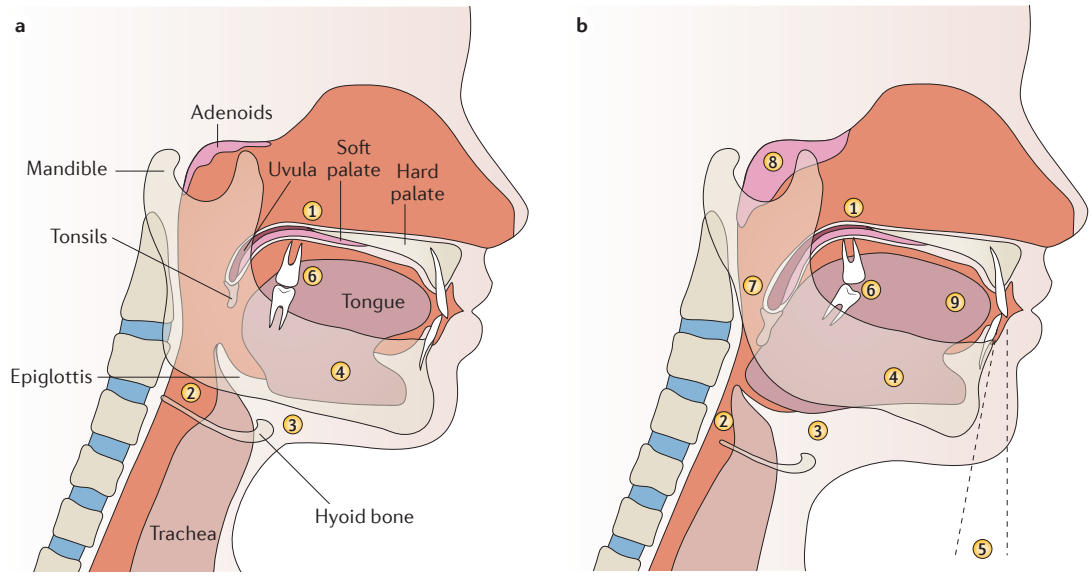


Figure 1 | **Maxillofacial and soft tissue changes occurring in OSAS.** **a** | Normal anatomy. **b** | Typical anatomical changes in obstructive sleep apnoea syndrome (OSAS): a long soft palate and enlarged uvula (1); a reduced retroglossal pharyngeal airway space (2); an increased distance between the hyoid bone and the mandible (3); a shorter and more vertical mandible (4); a retro-position of the mandible, which is measured by the angle (retrognathia) (5); dental overbite or loss of normal dental occlusion (6); tonsillar hypertrophy (7); adenoid hypertrophy (8); and macroglossia (unusual large tongue) (9).

Box 1 | Diagnostic criteria for obstructive sleep apnoea syndrome

The diagnosis of obstructive sleep apnoea syndrome (OSAS)[5,6,15,210] can be made during a sleep study. A diagnosis is made if there are more than five predominantly obstructive respiratory events (obstructive and mixed apnoeas, hypopnoeas or respiratory effort-related arousals) per hour of sleep in a patient with at least one of the following symptoms or clinical signs: excessive daytime sleepiness (EDS), non-restorative sleep, fatigue or insomnia; waking up with choking, breath holding or gasping; witnessed habitual snoring and/or breathing interruptions; and hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation or type 2 diabetes mellitus. Alternatively, the diagnosis of OSAS can also be made if there are ≥15 predominantly obstructive respiratory events per hour of sleep (regardless of the presence of symptoms or clinical signs).

OSAS severity depends on the severity of EDS, the apnoea–hypopnoea index (AHI) and/or oxygen desaturation index range based on overnight monitoring (mild: AHI 5–15; moderate: AHI 15–30; severe: AHI >30). Importantly, sleep apnoea events discovered in a sleep recording in individuals without any symptoms is not considered as OSAS apart from when the AHI is >15.

OSAS is common in the elderly, increasing significantly in those aged above 65 years[16], with a prevalence of up to 80% for an AHI >5 in some studies[8]. However, the clinical significance of sleep apnoea in the elderly is unclear, and most patients are asymptomatic. A recent French study reported an AHI >15 in 53% of normal elderly subjects, 37% of whom had an AHI >30 (REF. 23). However, EDS was less common than that reported previously in middle-aged subjects, with only 9.2% of subjects having an Epworth Sleepiness score[24] >10 and the AHI did not correlate with tests of cognitive function[23].

The prevalence of OSAS in children varies widely in different reports, which partly reflects differences in diagnostic criteria. Studies using laboratory-based polysomnography and involving relatively large general paediatric population samples have reported prevalence rates for OSAS of 1.2–5.7%[25]. Contributing factors to the development of paediatric OSAS include adenotonsillar hypertrophy, obesity and craniofacial dysmorphism[25]. The growing prevalence of childhood obesity is associated with an increasing prevalence of OSAS.

OSAS is commonly associated with co-morbidities; cardiovascular and metabolic abnormalities are observed in up to 50% of patients with OSAS[11]. In fact, OSAS is the most prevalent cause of drug-resistant secondary hypertension[26] and of nocturnal non-dipping blood pressure profiles[27]. The prevalence of OSAS in patients with both type 1 (REFS 28–30) and type 2 diabetes mellitus[31,32] is also high.

Box 2 | OSAS characteristics in children versus adults

- Lower frequency (1–2%)
- Different symptoms: less excessive daytime sleepiness; hyperactivity and behaviour problems; learning difficulties; nocturia; impairment of growth; snoring
- Frequent predisposing factors: adenotonsillar tissue hypertrophy; obesity; subtle or syndromic craniofacial abnormalities
- Lower normal apnoea–hypopnoea index threshold (<1)
- Significant sequelae associated with lower apnoea–hypopnoea index values
- Surgery (adenoids and/or tonsils) are effective in treating 50% of children with obstructive sleep apnoea syndrome

OSAS, obtructive sleep apnoea syndrome.

Mechanisms/pathophysiology

OSAS pathophysiology applies to both upper airway collapse mechanisms and the consequences of OSAS.

Upper airway collapse

The mechanisms of the pharyngeal collapse are complex and multifactorial. Several factors influence the stability of the pharynx and might contribute to its closure during sleep when the activity of the pharyngeal dilating muscles is considerably reduced. When awake, neuronal activity ensures that the dilating muscles of the pharynx are activated, which prevents the pharynx from narrowing and collapsing. When this muscle activation is lost at sleep onset, the airway can narrow and/or collapse, particularly when combined with certain anatomical and functional conditions such as a reduction in upper airway volume, increase in pharyngeal collapsibility, augmentation of upper airway resistance during sleep during both inspiration and expiration, changes in pharyngeal muscle activity and alteration in upper airway protective reflexes[33]. Changes in pharyngeal muscle activity and alterations in upper airway protective reflexes might result from denervation and pharyngeal neuropathy[34].

Upper airway volume reduction due to obesity and/or craniofacial and soft tissues changes is an important cause of the upper airway collapse[2]. In addition, leptin, an important metabolic hormone, is involved in upper airway neuromechanical control[35], and variability in its concentration among obese individuals with equivalent BMI values but different fat distribution might contribute to differences in OSA susceptibility[36]. Also, patients with profound leg oedema as a consequence of cardiac and renal failure or venous insufficiency can experience a leg fluid volume shift from the legs to the neck during the night, which might contribute to upper airway collapse[37].

The inadequate neuromuscular response in OSAS has led to the concept that pharyngeal neuropathy probably plays a part in the upper airway collapse, although the exact mechanisms remain to be fully elucidated. Pharyngeal neuropathy is defined as a sensory impairment, which might reduce the efficacy of the protective pharyngeal reflexes and contribute to upper airway collapse[34]. The neuropathy is presumably caused by structural remodelling of the peripheral branches of the hypoglossal nerve owing to prolonged heavy snoring and associated vibratory lesions of the pharynx[38]. Pharyngeal nerve alterations and even generalized neuropathy are sometimes associated with OSAS[39,40] and are linked with the severity of nocturnal hypoxaemia in patients with severe OSAS.

Non-anatomical features also play an important part in OSAS. Specifically, several mechanisms associated with arousal, the collapsibility of the upper airway and pharyngeal neuromuscular response might be involved in OSAS and might potentially represent therapeutic targets[41]. In particular, the respiratory arousal threshold, critical closing pressure, upper airway muscle responsiveness during sleep and loop gain are important factors involved in OSAS, and might be useful for phenotyping or classifying patients with OSAS[41] (BOX 3). Interestingly, in a study of 17 controls and 58 continuous positive airway pressure

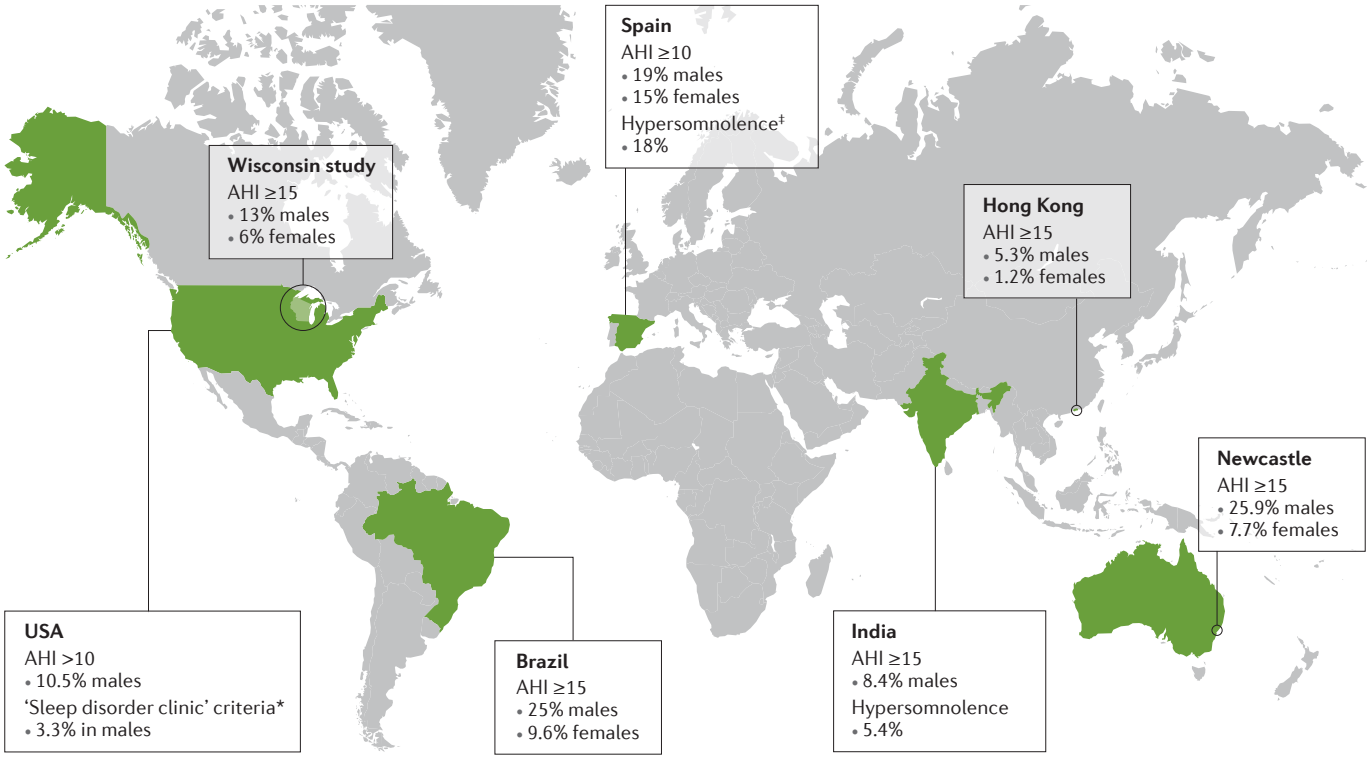


Figure 2 | **Global prevalence of sleep apnoea.** Schematic representation of the apnoea and hypopnoea frequency per hour (apnoea–hypopnoea index; AHI) worldwide. US data are based on the Bixler study in general population cohorts in Pennsylvania[277,278] and the population prevalence estimates obtained from longitudinal data of the Wisconsin cohort study[17]. Obstructive sleep apnoea syndrome (OSAS) is also prevalent in Asian populations[279,280]; a contributing factor might be differences in craniofacial structure compared with white people[281]. The data from Australia were based on one community population report[282,283] and were biased in favour of snorers. The Brazilian data were obtained from a general population study of predominantly middle-aged adults, 60% of whom had a body mass index >25 kg per m^2 (REF. 129). The data in India are based on a cross-sectional prevalence study in healthy urban Indian males aged 35–65 years. Although there are no published data on the prevalence among African populations, OSAS is at least as prevalent in African Americans as in Americans of European descent[284,285]. Care should be taken when attempting to perform inter-study comparisons because of varying definitions of daytime sleepiness, differences in sampling schemes, disparities in techniques used for monitoring sleep and breathing[16]. *'Sleep disorder clinic' criteria include a apnoea–hypopnoea index of ≥10 plus daytime sleepiness, hypertension or another cardiovascular complication. ‡Daytime hypersomnolence (excessive daytime sleepiness) was not related to the severity of OSAS.

(CPAP)-treated patients with OSAS, 36% of patients with OSAS had minimal genioglossus muscle responsiveness during sleep, 37% had a low arousal threshold, 36% had high loop gain and 28% had multiple non-anatomical features. Overall, these non-anatomical features play an important part in 56% of patients with OSAS[41].

Cardiovascular disease

Obstructive apnoeic events incorporate a range of stressors that activate mechanisms contributing to the initiation and progression of cardiac, vascular and metabolic diseases[42]. Obstructed breathing induces markedly negative intrathoracic pressure that stretches intrathoracic structures, in particular the atria of the heart and the large blood vessels. Obstructions to breathing also induce hypoxaemia and hypercapnia[7]. The hypoxaemic stress is further amplified by the subsequent reoxygenation (intermittent hypoxia), resulting in the generation of reactive oxygen species (ROS) and inflammation[43]. Apnoeic events are also accompanied by arousals from sleep, with consequent sleep fragmentation and possibly deprivation, which can activate a broad range of cardiovascular disease mechanisms[44,45]. Outlined below are some of the key mechanisms that are thought to be activated in OSAS, and which might potentiate cardiovascular dysfunction and disease in patients with OSAS either alone or in various combinations.

Sympathetic activation. The autonomic nervous system acts as a motor system undertaking a large number of specialized tasks, both stimulatory and inhibitory, in a wide range of target organs. During sleep, there are major overall autonomic nervous system alterations; for example, there is a decrease in sympathetic activity and increase in parasympathetic activity during non-rapid eye movement sleep and an increase in sympathetic activity during rapid-eye movement sleep[46]. Also, any change in sleep quality or quantity will increase sympathetic activity[45]. Measuring sympathetic activity during sleep is challenging. The reference method consists

of measuring sympathetic traffic to the muscles using microneurography. Hypoxaemia and hypercapnia act through peripheral and central chemoreceptors for oxygen and carbon dioxide to induce an increase in the outflow of the sympathetic nervous system[47,48] (FIG. 3). The increased sympathetic activity during sleep seems to carry over into daytime wakefulness when normoxia is restored. Patients with OSAS, even in the absence of any co-morbidity, have an increased sympathetic drive when awake, evidenced by an increased muscle sympathetic nerve activity and heart rate[49]. When healthy volunteers are exposed to intermittent hypoxia for 1 or 2 weeks, an increase in hypoxic and hypercapnic ventilator responses is observed, which corresponds to an increase in chemoreflexes that contribute to sympathetic overactivity[50]. As a consequence, muscle sympathetic nerve activity is increased, the baroreflex control of sympathetic outflow is reduced and daytime ambulatory blood pressure is elevated[51]. Also, sympathetic outflow to the kidney is elevated and stimulates renin release, which leads to elevated circulating levels of angiotensin II and aldosterone, although observations in OSAS are conflicting[52–54]. These observations strongly suggest that the renin–angiotensin system is involved and might be targeted for treating OSAS-associated hypertension[55]. Furthermore, in rodents exposed to intermittent hypoxia, oxidative stress modulates sympathetic activation and hypertension via the adrenal catecholamine efflux; antioxidants abolish these effects by mitigating oxidative stress [56–58].

Vagal activation. Hypoxaemia also acts via the chemoreflex to induce vagal activation to the heart simultaneously with sympathetic activation to most other vascular beds (the diving reflex)[46]. Profound vagal activation can take place at the beginning of obstructive apnoea in some patients with OSAS, and can result in bradyarrhythmias ranging from sinus bradycardia and atrial ventricular block to asystole lasting 10 seconds or longer[59]. The chemoreflex-induced bradycardia and vagal activation, similar to sympathetic activation, are potentiated in patients with OSAS compared with healthy controls during apnoea[60]. FIGURE 3 summarizes the different effects of intermittent hypoxia on the autonomic nervous system[61].

Oxidative stress. Oxidative stress, sympathetic activation and inflammation are fundamental underlying mechanisms contributing to the development of cardiovascular, cerebrovascular and other morbidities in OSAS[62,63]. Oxidative stress associated with OSAS results from an increased pro-oxidant/antioxidant ratio, which is primarily attributed to the reduced oxygen availability during the apnoeic events and the formation of ROS during reoxygenation when breathing resumes[62]. Oxidative stress initiates a vicious cycle in which it promotes sympathetic activation and inflammation, which in turn potentiates oxidative stress. The combination of oxidative stress, sympathetic activation and inflammation probably leads to endothelial dysfunction, hypertension and atherosclerosis[64,65]. Moreover, oxidative stress also contributes to OSAS-associated co-morbidities such as hyperlipidaemia, insulin resistance and diabetes and is involved in obesity (FIG. 4). However, these ROS-dependent interactions are complex and intertwined (reviewed in REF. 66).

The increase in ROS production associated with hypoxia is attributed to dysfunctional mitochondria, the activation of NADPH oxidase (NOX) and xanthine oxidase and the uncoupling of nitric oxide synthase (NOS), which generates ROS rather than nitric oxide (NO)[62,66], and ultimately poses a cellular threat by directly injuring vital biomolecules such as DNA, proteins, lipids and cellular components, and altering physiological signalling pathways. Mitochondrial distribution and function (impaired oxidative activity) was found to be abnormal in the soft palate muscles of patients with OSAS[67]. Notably, the increased ROS levels in mitochondria of mice subjected to intermittent hypoxia contributed to the development of type 2 diabetes[68] and to neuronal death[69], which may explain part of the neurocognitive morbidity seen in patients who have sleep-disordered breathing[70]. Also, NOX activity is higher in monocyte and granulocytes derived from patients with OSAS[71,72] and from rodents exposed to chronic intermittent hypoxia. The elevated NOX activity and the associated oxidative stress in rats' hearts seem to mediate the deleterious cardiovascular effects of intermittent hypoxia and in particular the increased myocardial susceptibility to infarction[73,74], in addition to causing hypertension[75], cognitive impairment[76] and other organ-specific effects[77]. Recent studies also indicate the importance of certain genetic polymorphisms of *NOX*, which affect oxidative stress levels and concomitant cognitive deficits in patients with OSAS[78]. Allopurinol (a xanthine oxidase inhibitor) not only attenuated oxidative stress markers and improved endothelial function in patients with OSAS[79] and in animal models[80], but also improved myocardial dysfunction[81]. These latter findings suggest that allopurinol might be considered as a treatment modality for mitigating cardiovascular risk in patients with OSAS. Finally, various circulating markers of lipid peroxidation[82–85], DNA[84,86] and protein oxidation are increased

Box 3 | **Key terms in OSAS pathophysiology (pharyngeal collapse)**

- Arousal: each obstructive sleep apnoea (OSA) event is terminated by a short brain activation called arousal or microarousal when between 3 and 15 seconds.
- Upper airway muscle responsiveness: this represents the pharyngeal muscle activation occurring during partial upper airway collapse. It is determined by the slope between the peak genioglossus muscular activity (EMG_{GG}) and nadir epiglottic pressure (P_{epi}) during sleep.
- Loop gain: the loop gain is a dimensionless value of the propensity of a system governed by feedback loops to develop unstable behaviour. The higher the loop gain, the potentially more unstable the respiratory control system becomes. A high loop gain promotes recurrent apnoeas as a response to an initial disturbance because it is over compensated, whereas a low loop gain dampens subsequent oscillations in breathing.
- Critical closing pressure: this is the pressure applied to the upper airway at which the pharynx will close in the absence of muscle activity. It characterizes the mechanical properties or the collapsibility of the pharynx.
- Respiratory arousal threshold: the respiratory arousal threshold is defined as the average nadir epiglottic pressure (P_{epi}) immediately before the cortical arousal terminating an obstructive event.

OSAS, obstructive sleep apnoea syndrome.

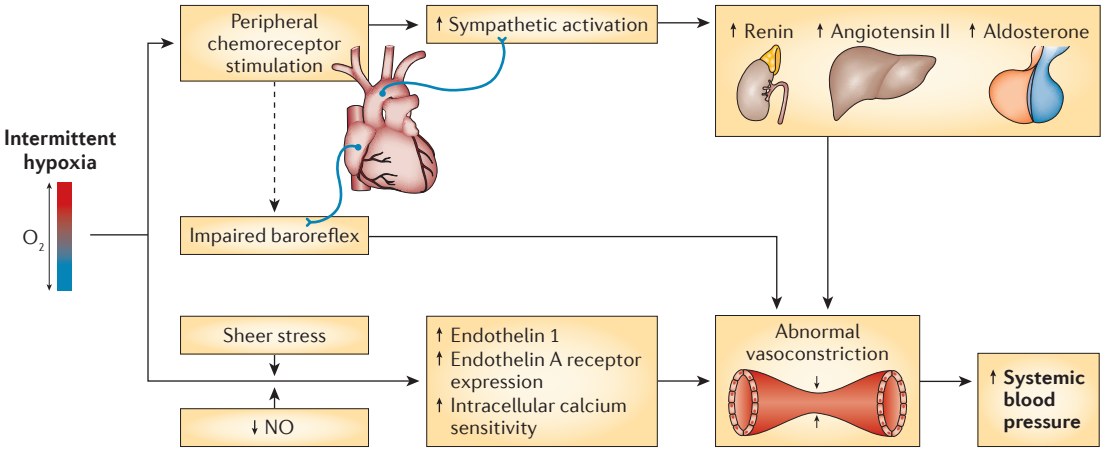


Figure 3 | **Schematic outlining the hypothesized pathways by which intermittent hypoxia activates the autonomic nervous system and leads to hypertension.** Intermittent hypoxia activates the peripheral chemoreceptors (located in the carotid bodies), which partly control the ventilator responses to reductions in blood oxygen content (hypoxic ventilator response) and to increases in blood partial pressure in carbon dioxide (hypercapnic ventilator response). Also, these chemoreflexes increase the outflow of the sympathetic nervous system, activates the renin, angiotensin II and aldosterone system, and enhances vasoconstrictor activity. Impaired baroreflex, reduction in the levels of the vasodilator nitric oxide (NO), increased endothelin production and receptor expression might also alter vasoconstrictor activity and promote an increase in systemic blood pressure. In addition, it has been evidenced that intermittent hypoxia associated with intermittent hypercapnia does not only lead to increased sensitivity to the vasoconstrictor endothelin 1 but also to increased calcium sensitivity in the vessels of exposed animals compared with controls. Broken line; indirect pathway. Figure adapted from REF. 61, Wiley.

in patients with OSAS; their levels correlate with AHI severity[87,88] and are partially normalized by CPAP therapy. Antioxidant levels, which should counteract the increased ROS levels, were decreased in patients with OSAS and increased with CPAP treatment[89,90].

Inflammation. Blood cells of patients with OSAS display a pro-inflammatory and a prothrombotic phenotype, which might facilitate endothelial injury, endothelial dysfunction, atherosclerosis and thrombosis. More profound activation of leukocytes and platelets (hallmarks of inflammation and atherogenic sequelae) was found in patients with OSAS compared with healthy controls[71,91]. Monocytes displayed an inflammatory phenotype characterized by increased production of ROS and adhesion molecules. These adhesion molecules contribute to increased avidity for endothelial cells; their levels depend on the severity of the OSAS (AHI), and are reduced with CPAP treatement[71,92]. Short-lived circulating neutrophils from patients with moderate and severe (but not mild) OSAS showed a prolonged lifespan, which was associated with increased nuclear factor-κB (NF-κB) levels, a higher expression of adhesion molecules and a decreased pro-apoptotic/anti-apoptotic protein balance; CPAP treatment restored neutrophil lifespan and adhesion molecules levels to normal. Similar findings were observed when neutrophils isolated from healthy controls were exposed to intermittent hypoxia *in vitro*[72,93–95].

Some cytotoxic T lymphocyte subpopulations from patients with OSAS also acquire an activated and inflammatory phenotype. $CD8^+$ T cells expressed higher tumour necrosis factor-α (TNFα) levels and their cytotoxic abilities were increased in an AHI severity-dependent manner, whereas $CD4^+$ T cells showed few abnormalities[96,97]. Cytotoxic γδ T cells expressed a stronger adherence and higher cytotoxicity towards endothelial cells, higher levels of pro-inflammatory cytokines such as TNFα and interleukin-8 (IL-8), and lower anti-inflammatory IL-10 levels[98], which might suggest that they are involved in atherogenic processes in patients with OSAS. Platelets derived from patients with OSAS were also activated and displayed a pro-thrombotic phenotype, which was ameliorated by CPAP treatment[99].

In addition, various circulating inflammatory markers also support activation of vascular inflammation in OSAS. C-reactive protein[100], oxidized low-density lipoprotein, soluble adhesion molecules, pro-inflammatory cytokines such as TNFα and IL-6, and coagulability markers[101], are all increased in patients with OSAS, whereas fibrinolytic activity was impaired[63,98,102]. It should be noted, however, that extrapolating from markers derived from the circulation is sometimes contradictory or confusing because it represents a pool derived from many cells[103]. Moreover, in clinical studies in OSAS, co-morbidities such as cardiovascular diseases may explain some of the observed changes[104].

Vascular function. The endothelium plays a key part in vascular homeostasis by regulating vasoconstriction, vasodilation, intravascular coagulation and inflammation. Studies in venous endothelial cells from untreated patients with OSAS compared with age-, sex- and BMI-matched controls, revealed higher endothelial cell oxidative stress and inflammation[105]. Specifically, the expression of endothelial NOS was decreased and the levels of nitrotyrosine were markedly increased,

suggesting potentiation of endothelial cell inflammation and oxidative stress. These abnormalities were attenuated by 4 weeks of CPAP therapy. Also, the repair capacity was impaired and apoptosis was increased in endothelial cells derived from non-obese, co-morbidity-free patients with OSAS compared with healthy controls[106]. In accordance with these observations, patients with OSAS have lower levels of circulating NO compared with healthy controls, which increase after treatment with CPAP[107].

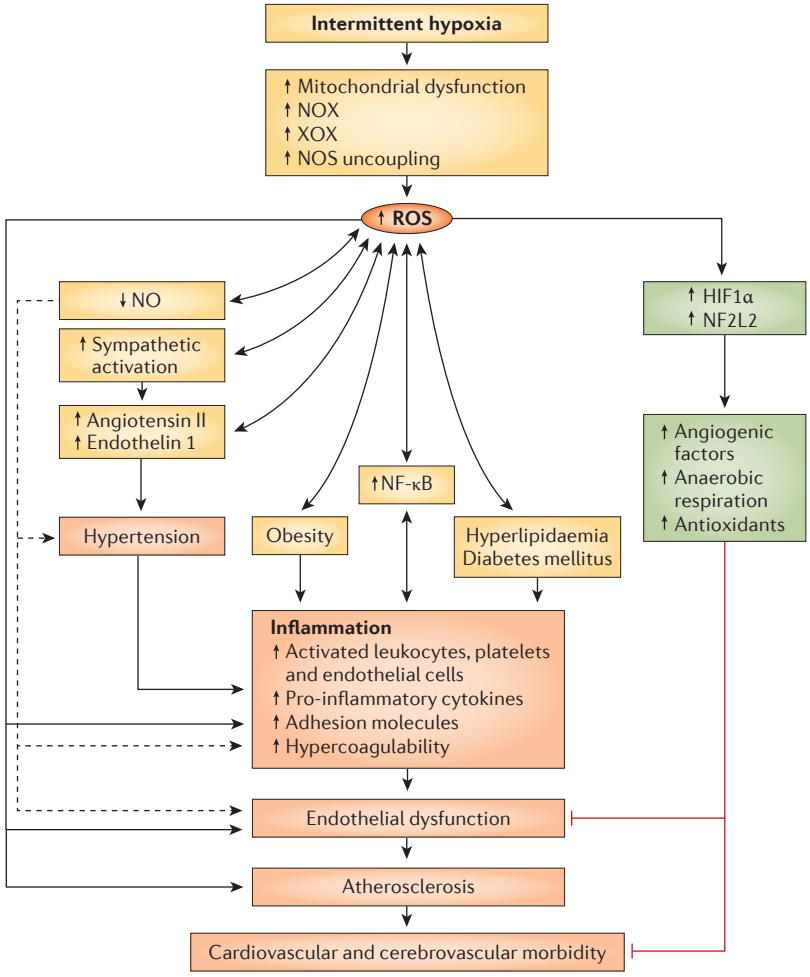


Figure 4 | **Oxidative stress promotes sympathetic activation, cellular and systemic inflammation, and vascular co-morbidities in OSAS.** Intermittent hypoxia induces the production of reactive oxygen species (ROS), resulting in oxidative stress by inducing mitochondrial dysfunction, activating NADPH oxidase (NOX) and xanthine oxidase (XOX), and inducing nitric oxide synthase (NOS) uncoupling. Interaction of ROS with nitric oxide (NO) further promotes oxidative stress while diminishing the bioavailability of NO and thus promoting hypertension, inflammation, endothelial dysfunction, hypercoagulability and atherosclerosis. The ROS-dependent increase in sympathetic activation, and in angiotensin II and endothelin 1 levels contribute to hypertension. Concomitantly, ROS can upregulate numerous redox-sensitive transcription factors, such as nuclear factor-κB (NF-κB), hypoxia inducible factor-1α (HIF1α) and nuclear factor (erythroid-derived 2)-like 2 (NF2L2). NF-κB orchestrates the various inflammatory processes that lead to endothelial dysfunction and atherosclerosis. By contrast, HIF1α and NF2L2, which are also upregulated by ROS levels, are involved in protective mechanisms, which may counteract some of deleterious effects of ROS[66,286–288]. Co-morbidities and conditions associated with obstructive sleep apnoea syndrome (OSAS), such as hypercholesterolaemia, diabetes mellitus and obesity, also have a ROS component and involve NF-κB activation and inflammation. Broken line; indirect pathway. Figure adapted from REF. 66, Elsevier.

Notably, endothelial dysfunction and oxidative stress markers are also improved after treating patients with OSAS with a mandibular dental device owing to an improvement of most sleep-disordered breathing and associated intermittent hypoxia[108].

NO is a key vasodilator released by endothelial cells. NO mediates various protective anti-inflammatory, antioxidant and/or anti-thrombotic functions, which prevent endothelial cell injury and dysfunction, in addition to downregulating the expression of adhesion molecules in leukocytes, platelets and endothelial cells, therefore, limiting their recruitment, aggregation and adhesion to the endothelium and inhibiting vascular smooth cell proliferation[109]. Reduced NO bioavailability is accompanied by elevated endothelial production of endothelin, a potent vasoconstrictor (FIG. 3). Studies have shown elevated levels of circulating endothelin or endothelin precursor in patients with OSAS compared with controls; these elevated levels decrease with acute or chronic CPAP therapy[110,111].

The described cellular and systemic findings have implications for vascular function in patients with OSAS. Hoyos *et al.*[112] concluded that OSAS is accompanied by impairment in endothelial function, at least at the macrovascular level, and that randomized controlled trials (RCTs) show that CPAP improves this endothelial dysfunction. Notably, OSAS and concurrent metabolic syndrome worsen endothelial function synergistically and, as a consequence, individuals with both of these conditions seem to be at a significantly higher risk for cardiovascular complications than patients with either of these conditions alone[113].

Metabolic dysregulation. Increased sympathetic tone is the key mediator of the deteriorated plasma glucose and insulin homeostasis in OSAS[114]. Intermittent hypoxia in rodents reduces glucose uptake in oxidative muscles[115], increases β-cell proliferation and β-cell death; this latter phenomenon is attributed to oxidative stress[116]. In addition, intermittent hypoxia has been shown to induce lipid abnormalities such as increased serum cholesterol and phospholipid levels, upregulation of triglycerides and phospholipids biosynthesis, and inhibition of triglycerides uptake in the liver in humans and animals[117]. Hypoxia is also associated with lipoprotein lipase inhibition in adipose tissue, which leads to an increase in plasma chylomicrons and very-low-density lipoprotein cholesterol, possibly favouring the progression of atherosclerosis[117,118].

Atherosclerosis. Atherosclerosis involves multiple converging processes, such as oxidative stress, vascular inflammation and sympathetic overactivity (FIGS 3,4). OSAS is associated with an increase in intima media thickness and in carotid plaques occurrence (early atherosclerotic lesions), independent of cardiovascular risk factors or cardiovascular and metabolic diseases[119]. Arterial stiffness — a strong predictor of late cardiovascular events — is independently associated with OSAS; a further increase in arterial stiffness is observed when OSAS accompanies either hypertension[120] or

Box 4 | **Risk factors for obstructive sleep apnoea syndrome**

- Advanced age
- Male sex
- Obesity (especially upper body obesity)
- Upper airway narrowing due to craniofacial and soft tissue abnormalities
- Genetic predisposition (family history)
- Smoking
- Nasal congestion
- Menopause, postmenopause
- Medical conditions (such as hypertension, diabetes, Marfan syndrome, acromegaly, hypothyroidism, end-stage renal disease, congestive heart failure, chronic obstructive pulmonary disease, neurological disorders and pregnancy)
- Medications and substances (including alcohol, benzodiazepines and narcotics)

metabolic syndrome[121]. Hypertension in OSAS is primarily diastolic owing to the vasoconstriction, and nocturnal as it is the consequence of night-time hypoxia[122]. The impact of visceral fat versus intermittent hypoxia on atherosclerosis and vascular remodelling in OSAS remains to be determined[7,65,118]. Data in rodents exposed to intermittent hypoxia, however, suggest that visceral fat might be critical because lipectomy prevents most of the vascular lesions formation due to hypoxia[123].

Diagnosis, screening and prevention

Risk factors

Several risk factors for OSAS are summarized in BOX 4, and discussed below.

Age. OSAS can occur at all ages, although the mean age at diagnosis is between 40 and 50 years[13,19,124]. The rates of OSAS seem to increase with age and to plateau after the age of approximately 65 years. However, it needs to be mentioned that otherwise healthy elderly persons commonly have a higher number of apnoea–hypopnoea events during the night than middle-aged adults, which makes it difficult to define a clinically significant cut-off level of apnoea–hypopnoea events in this age group.

Gender. There is a strong predominance of OSAS in men; two times to three times more men are affected than premenopausal age-matched women[125]. The reason for this disparity is not completely understood; however, hormonal influences on breathing control and upper airway muscle activation during sleep and sex-specific fat distribution seem to explain some of this difference. The prevalence of OSAS in women increases after the menopause, possibly because body fat is redistributed to the upper body, including the neck[126–128].

Obesity. The strongest risk factor for OSAS is (upper body) obesity (FIG. 5). The risk of OSAS progressively rises with increases in BMI and even more so with increasing neck circumference[19,124]. This is most probably related to upper airway narrowing as a result of excess fat tissue. In a population-based study of more than 1,000 subjects who underwent a sleep study, OSAS (defined as an AHI ≥15) was present in 11% of men who had a normal BMI, in 21% of those who had a BMI between 25 and 30 kg per m^2, and in 63% of those who were obese (BMI >30 kg per m^2)[129]. The same trend was observed in women: 3% of those who had a normal weight fulfilled the criteria for OSAS, 9% of those who were overweight, and 22% of those who were obese (BMI >30 kg per m^2). As a result of this association, the highest rate of OSAS is found in countries with a high prevalence of obesity and, as the levels of obesity are still increasing, the prevalence of OSAS is also on the increase[17].

Upper airway narrowing. Upper airway narrowing can result from overbite and craniofacial and soft tissue abnormalities, all of which increase the likelihood of having or developing OSAS[19] (FIG. 1). Physical examination-based factors such as a cricomental space less than 1.5 cm, pharyngeal grade (depending on the pharyngeal geometry, this is evaluated by visual inspection of an open mouth) of more than 2 (out of 4) and presence of overbite have been identified as useful predictors of OSAS (positive predictive value of 95%, negative predictive value 49%, sensitivity 40%, specificity 96% if all three features were present)[130]. A simpler approach to assess upper airway narrowing is the Mallampati score, which is assessed by asking the patient to open his or her mouth and protrude the tongue as much as possible while sitting. The score depends on the visibility of the pillars, the soft palate and the uvula. The score also seems to be useful in children, as a recent study found that for every point increase in the Mallampati score, the odds ratio of having OSAS increased by more than sixfold[131].

Diagnosis

A detailed medical history and clinical examination are important in the evaluation of patients suspected of having OSAS. However, clinical features alone are insufficient to diagnose the disorder with sufficient certainty. Additionally, abnormal respiratory events during a sleep study without any clinical symptoms do not necessarily establish a diagnosis of OSAS. Therefore, the diagnosis of OSAS relies on matching clinical features and objective findings from a sleep study[132] (BOX 1). Some predictive information can be obtained from self-reported questionnaires (for example, the Berlin Questionnaire or Stop-Bang Questionnaire)[133], which are used in some sleep centres to simplify the assessment of patients with suspected OSAS. However, to date, there is no sufficiently reliable test in patients to diagnose OSAS during daytime. The medical history should include the patient's partner as he or she can provide important information about what occurs during the night.

Nocturnal symptoms. Snoring and witnessed apnoeas are the hallmark symptoms of OSAS as they reflect the critical narrowing of the upper airway. Nocturnal choking or gasping also seem to be useful for identifying patients with OSAS; a recent systematic review reported a sensitivity and specificity of 52% and 84%, respectively, for this symptom[134]. Some patients also report frequent nocturia and restless sleep, the latter possibly reflects the disturbing effects of arousals on sleep.

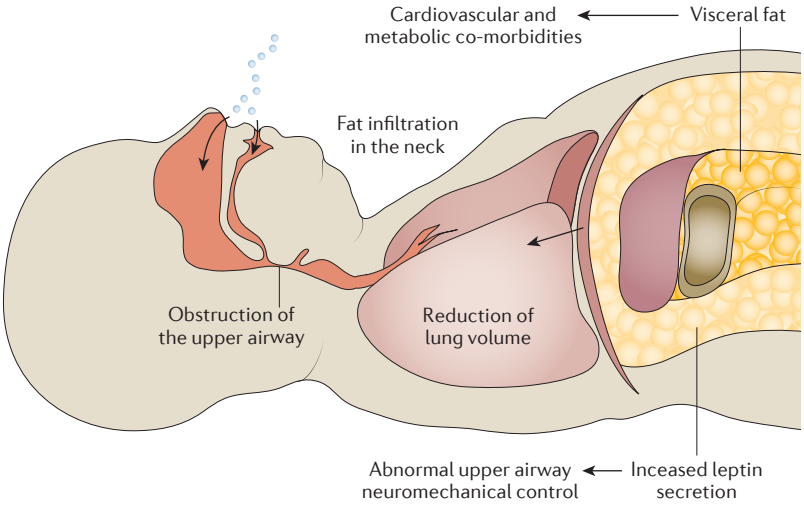


Figure 5 | **Role of obesity in OSAS.** Obesity predisposes to obstructive sleep apnoea syndrome (OSAS) due to fat infiltration at the neck level, leading to upper airway collapse, and increased abdominal pressure, leading to lung volume reduction. Adipose tissue accumulation might also alter the neuromechanical control of the upper airway via the specific effects of leptin. Visceral fat is involved in cardiovascular and metabolic OSAS co-morbidities[123]. 'Bubbles' represent inhaled or exhaled gases. Figure adapted from REF. 289, Elsevier.

Daytime symptoms. The most common complaint of patients with OSAS is EDS and a tendency to fall asleep during the daytime. This symptom shows substantial intersubject variability and the definition of an abnormal degree of sleepiness can be challenging. Furthermore, the severity of EDS does not seem to correlate with the severity of OSAS[135]. The most widely used questionnaire to assess the patient's subjective sleepiness is the Epworth Sleepiness Scale[24], which asks the patients to rate their tendency to fall asleep in eight different situations: sitting and reading; watching television; sitting inactive in a public place, a theatre or a meeting; as a passenger in a car for 1 hour; lying down to rest in the afternoon; sitting and talking to someone; sitting quietly after a lunch without alcohol; and in a car while stopped for a few minutes in traffic. Other objective tests to assess sleepiness include the Multiple Sleep Latency Test, the Maintenance of Wakefulness Test and the Osler Test[136–138]. However, such tests are time-consuming and expensive and, accordingly, are rarely used in everyday clinical practice. Other daytime symptoms reported by patients with OSAS include fatigue, difficulty concentrating, personality changes and depression. There is also a wide range of cognitive and attentional deficits that have been described in OSAS (for reviews see REFS 139,140).

Specific phenotypes. OSAS can be associated with chronic obstructive pulmonary disease (COPD), which, when co-occurring with OSAS, is described as 'overlap syndrome'[141]. During sleep, patients with both COPD and OSAS experience more frequent episodes of oxygen desaturation and more total sleep time with hypoxaemia and hypercapnia than patients with OSAS but without COPD or patients with COPD alone. The apnoeic events are also associated with more profound hypoxaemia and more frequent and severe cardiac arrhythmias. Finally, patients with overlap syndrome are more likely to develop daytime pulmonary hypertension and right heart failure and have a poorer prognosis compared with patients with OSAS alone[141]. A cohort study of patients with overlap syndrome showed an increased risk of death from any cause compared with patients with only COPD and hospitalization owing to COPD exacerbation. Effective treatment with CPAP was associated with improved survival and decreased hospitalizations[142].

Finally, OSAS can be accompanied by atrial fibrillation. In general population cohorts, compared with those without OSAS and adjusting for age, sex, BMI and prevalent coronary heart disease, individuals with OSAS had four times the likelihood of also having atrial fibrillation[143]. In clinical populations, OSAS is strikingly more prevalent in patients with atrial fibrillation than in high-risk patients with multiple other cardiovascular diseases[144]. Also, the risk of atrial fibrillation recurrence after cardioversion (a procedure in which an abnormal heart rate is converted to a normal heart rate using electricity or medical intervention) is increased in patients with OSAS[145]. There is both an increased risk for atrial fibrillation and sudden cardiac death related to OSAS[146]. Currently, however, few data exist to support the efficacy of OSAS treatment as an adjunct for arrhythmia prevention or management.

Clinical prediction models. Several clinical prediction models for OSAS have been developed[147]. Usually, such models include anthropometric characteristics (for example, neck circumference or BMI) and witnessed breathing abnormalities during sleep (such as snoring, apnoea or choking episodes). However, the sensitivity (76–96%) of these models is generally much higher than their specificity (13–54%) and, therefore, they might be used to exclude OSAS rather than diagnose the disorder without a sleep study[147].

Sleep studies. The sleep study is the most important investigation in the process of making the diagnosis of OSAS. Typically, there are three major types of sleep studies: full polysomnography, respiratory polygraphy and overnight oximetry. Polysomnography is regarded as the diagnostic gold standard and usually includes assessment of oximetry, snoring, body and leg movements, oronasal airflow, excursion of the chest and abdomen, as well as an electrocardiogram, electroencephalogram, electro-oculogram and electromyogram to identify sleep stages (FIG. 6). Respiratory polygraphy usually includes all these assessments but without an electroencephalogram, electro-oculogram and electromyogram. The equipment for respiratory polygraphy and oximetry is suitable for home sleep studies, which allows the patients to sleep in their own environment and potentially reflect normal ambient conditions better than a sleep laboratory. By contrast, polysomnography generally requires a sleep laboratory and a trained technician to set up and supervise the sleep study during the entire night and, accordingly, is resource-intensive. However, there are some limitations in the interpretation of results obtained

from home sleep studies, such as a higher rate of technically unsatisfactory studies compared with polysomnography, the limitation of not knowing whether the patient was awake or asleep, and other diagnoses such as periodic limb movement syndrome might be missed. Nonetheless, limited sleep studies, such as respiratory polygraphy, have become the routine investigation in many sleep centres in cases where OSAS is suspected. Although oximetry alone can identify OSAS in most patients with a high clinical likelihood, false-positive oximetry occurs with Cheyne–Stokes breathing[148] and when there is a low baseline oxygen saturation (for example, in patients with COPD). False-negative results can occur in non-obese patients and those with primarily hypopnoeas; thus, oximetry is of limited value in milder cases of OSAS.

Screening

To date, there are no data available from RCTs on the effect of screening for OSAS on mortality. Thus, a general screening of a population at high risk for OSAS (middle-aged, obese subjects) cannot be recommended at this time. However, as there are concerns that OSAS might increase the risk of perioperative morbidity and mortality because of potential difficulty in maintaining a patent upper airway, the American Society of Anesthesiologists, among others, has reported practice guidelines for the perioperative management of patients with OSAS[149]. These guidelines recommend a systematic evaluation of patients who are to undergo surgery to identify the presence of OSAS[149].

Prevention

As obesity is the most important risk factor for the development of OSAS, the single most effective way to reduce the rates of OSAS in a population is to prevent or reduce overweight and obesity. Several RCTs have shown a substantial reduction of OSAS after substantial weight reduction and this seems to be true for both dietary and surgical approaches[150–152]. However, there is a paucity of data showing that weight reduction strategies are effective in reducing the frequency of OSAS in the long term.

Management

The treatment of OSAS aims to alleviate symptoms and to improve quality of life, to reduce the burden of

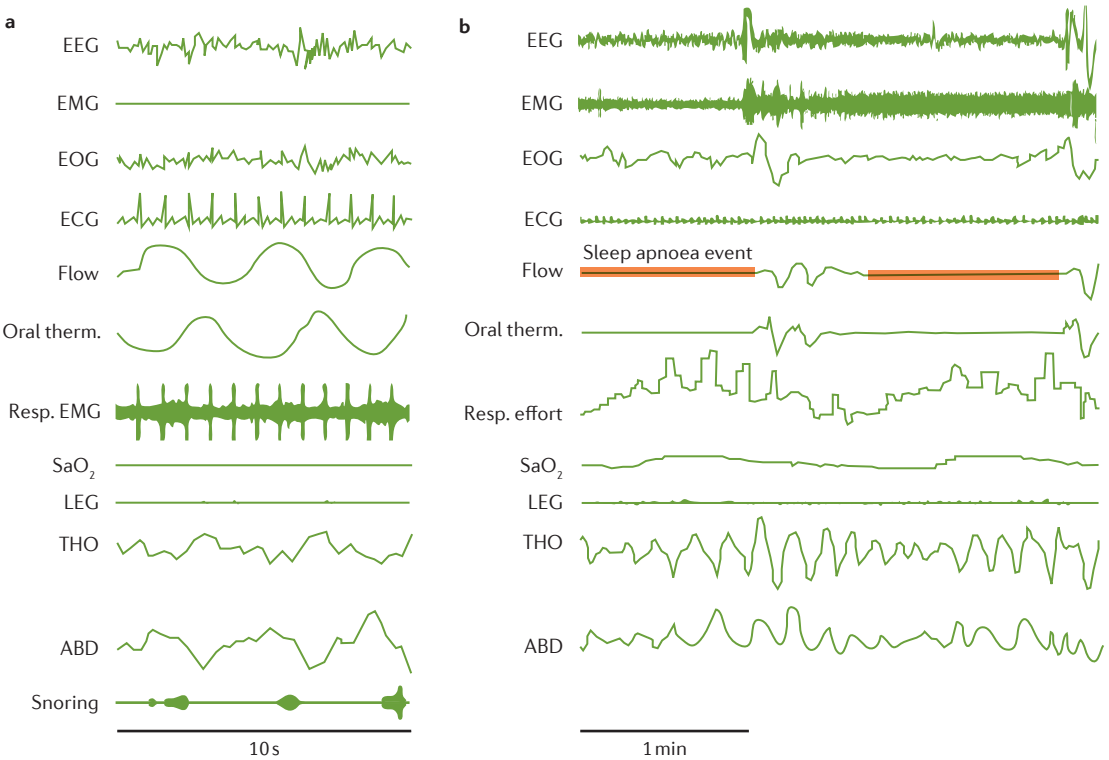


Figure 6 | **Polysomnography.** **a** | Polysomnography in a normal individual. This 10 second tracing displays all the signals needed for a polysomnography. Note that there is no apnoea or hypopnoea. Only snoring is present. **b** | Polysomnography in a patient with obstructive sleep apnoea syndrome (OSAS). In this patient, two episodes of obstructive apnoeas occur (orange boxes). Each event is associated with a cessation of flow, a progressive increase in respiratory effort and a reduction in oxygen saturation, which is delayed due to circulation time. Note the opposition phase between the thoracic and abdominal movements, which corresponds to persistent respiratory efforts despite the closure of the pharynx and subsequent cessation of flow. Also each of obstructive apnoea event is associated with an arousal visible on the electroencephalogram (EEG), electromyogram (EMG) and electro-oculogram (EOG). This arousal terminates the obstructive apnoea in increasing the activity of pharyngeal dilating muscles. ABD, abdominal movements; ECG, electrocardiogram; Flow, nasal flow; Leg, detection of leg movement; Oral therm., mouth breathing; Resp., respiratory; SaO_2, transcutaneous oxygen saturation; THO, thoracic movements.

co-morbidities and to decrease mortality. Consequently, the treatment strategy for a given patient should be tailored according to OSAS severity and related co-morbidities.

Severe OSAS

In cases of severe OSAS, treatment is necessary and CPAP is the first-line option. When there are neither symptoms nor co-morbidities, CPAP use should be evaluated as it is not considered a cardiovascular primary prevention measure. However, it should be considered particularly in professional drivers because a significant improvement has been reported even in apparently asymptomatic subjects[153]. Maxillofacial surgery can be considered as a potential alternative in a limited number of young, non-obese and well-motivated subjects presenting with craniofacial abnormalities. Regardless, weight loss is mandatory when overweight or obesity is present.

CPAP. CPAP[154] is primarily intended to suppress EDS and improve daytime functioning[155,156] (BOX 5). The beneficial effect of CPAP on symptoms and quality of life is obtained after only a few days of treatment[157,158] and depends on adherence[159,160].

Regarding cardiovascular outcomes, meta-analyses have demonstrated that CPAP reduces the 24-hour mean blood pressure by approximately 2 mmHg (pooled estimated effect)[161–163]; the range of improvement being larger in the subgroup with resistant hypertension[164]. The extent of blood pressure reduction seen in meta-analyses is probably underestimating the true effect of CPAP in adherent patients[165,166]. Uncontrolled studies and prospective clinical cohorts suggest that CPAP is able to reduce the number of fatal and non-fatal cardiovascular events, including arrhythmias, myocardial infarction and stroke[167,168]. This remains to be established in large RCTs (for example, SAVE[169] and ISAACC[170]). CPAP effects on incident hypertension and cardiovascular events were not significant in the intention-to-treat analysis of the largest RCT conducted to date, but became significant in the subgroup analysis of patients with OSAS who used CPAP for more than 4 hours per night[153]. However, not all studies showed a positive impact of CPAP alone on cardiovascular outcome, and point to the need of a multimodal treatment strategy (BOX 6).

Compliance to CPAP is a crucial issue. Many studies based in the United States[171–174] have reported a low compliance and an irregular use of CPAP compared with a higher rate adherence (ranging from 65% to 80%)[158,175,176] and acceptance (approximately 15% of patients refusing this treatment after a single night's use)[175] in Europe. The observed differences in compliance might reflect the respective efficacy of follow-up in different healthcare systems. A spectrum of minor adverse effects affecting most of the CPAP-treated patients but can be easily addressed by appropriate technical follow-up[174,177].

CPAP has limitations and combination therapies (CPAP plus weight loss or CPAP plus specific antihypertensive treatments) might be required to reverse the chronic consequences of OSAS (BOX 6). In a recent study, weight loss provided an incremental reduction in insulin resistance and serum triglyceride levels when combined with CPAP, whereas adherence to a regimen of weight loss plus CPAP resulted in incremental reductions in blood pressure compared with either intervention alone[178]. Recently, a meta-analysis has confirmed a beneficial effect of weight loss combined with CPAP[179].

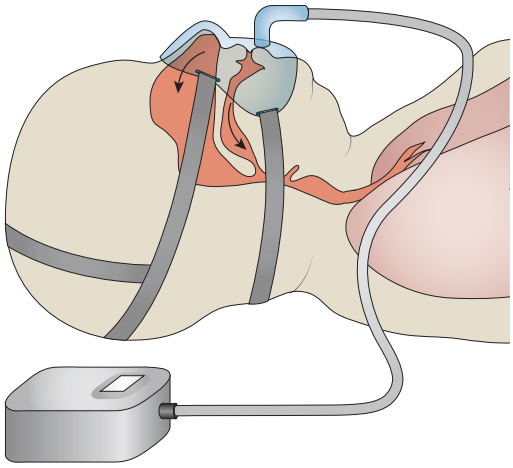
Upper airway surgery. Palatal surgeries such as uvulopalatopharyngoplasty (UPPP) address soft tissue issues at the pharyngeal level (uvula, soft palate, adenoids and tonsils). The aim of UPPP is to enlarge the oropharyngeal airway and to reduce the collapsibility of the pharynx[180]. However, the impact on the AHI is limited in severe OSAS and long-term deterioration has been reported[181,182]. Thus, UPPP should be restricted to patients presenting with a retropalatal collapse, although this is difficult to firmly diagnose[182]. Also, in mild OSAS, no actual evidence of a clear long-term benefit of UPPP exists, nor for other techniques such as laser or radiofrequency[181]. Finally, UPPP might even reduce the efficacy of further CPAP treatment by increasing oral breathing and subsequently generating mouth leaks, which might reduce the maximal level of pressure that can be tolerated[183].

Maxillofacial surgery is the only surgical procedure with high success rates, although only for a minority of patients with OSAS who have craniofacial dysmorphy.

Box 5 | Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is a treatment that uses mild air pressure to keep the airways open. CPAP treatment involves a CPAP machine, which has three main parts: a mask or other device that fits over the nose or the nose and mouth, with straps that keeps the mask in place; a tube that connects the mask to the machine's motor; and a motor that blows air into the tube.

Some CPAP devices have other features, such as heated humidifiers. CPAP machines are small, lightweight and relatively quiet. The noise that they make is soft and rhythmic.



Box 6 | **Limitations of continuous positive airway pressure treatment**

Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) in patients correctly treated with continuous positive airway pressure (CPAP) remains in 10–40% of patients[159,262,263]. The postulated causes include prior irreversible hypoxic damage, sleepiness due to reduced sleep duration and poor sleep hygiene, or co-morbidities such as depression, diabetes and obesity[264]. Physicians treating patients with obstructive sleep apnoea syndrome (OSAS) should, therefore, be aware of coexisting sleep disorders or medical and psychiatric conditions that might require further management. Wake stimulant medications are commonly prescribed in the United States to reduce EDS in CPAP-treated OSAS[265,266] but should be restricted to patients in whom other causes of residual sleepiness have been excluded.

CPAP has a limited impact on cardiovascular and metabolic outcomes

Metabolic abnormalities do often not improve in obese patients with OSAS after CPAP treatment whether diabetic or not[251,267–270]. CPAP efficacy should be put in a realistic perspective compared to the rigorous effects of medications, weight loss or exercise to reduce cardiovascular and metabolic risk[250]. Antihypertensive drugs are far more effective than CPAP in controlling blood pressure, although there is a beneficial effect when combining both treatments[55]. A study involving 181 randomly assigned patients with OSAS to treatment with CPAP, a weight-loss intervention, or CPAP plus a weight-loss intervention for 24 weeks showed a massive reduction in systolic blood pressure in the combined intervention group (14.1 mm Hg; $P < 0.001$) compared to CPAP alone (3.0 mm Hg; $P < 0.001$). CPAP alone had no effect on lipid profile, C-reactive protein or insulin sensitivity[178]. Although most respiratory physicians limit their intervention to prescribing CPAP, a multiple modalities approach to treatment might be beneficial to improve cardiovascular and metabolic abnormalities in patients with OSAS. Exercise[271], antioxidant and anti-inflammatory drugs[272,273] are currently being evaluated in comparison or in addition to CPAP.

A recent study reported 89% of patients[184] were considered a surgical success (AHI <20 and a ≥50% reduction in the AHI) with the percentage of subjects with an AHI <15, <10 and <5 after maxillofacial surgery of 77.6%, 63.4% and 43.2%, respectively) with no difference between the short-term and long-term results. Younger age, lower preoperative weight and AHI, and a greater degree of maxillary advancement were predictive of increased surgical success. This surgery is complex but safe in expert hands and requires well-motivated patients who are well informed of the risks, including that of persistent partial facial aesthesia. The surgery is, therefore, only recommended for young, non-obese patients with craniofacial anomalies.

Weight loss and bariatric surgery. A recent systematic review showed that weight loss through lifestyle and dietary interventions results in improvements in OSAS parameters, but is generally insufficient to normalize them[152]. The effect of weight loss induced by a very low energy diet has been evaluated in a RCT[185]. A greater improvement was demonstrated in patients with severe OSAS at baseline compared with those with moderate OSAS, despite similar weight loss. Thus, it seems that those with severe OSAS are better candidates for such caloric restriction[185]. Interestingly, a meta-analysis revealed that CPAP was associated with a significant increase in the BMI, with high baseline weight as a predictor. Additional therapies for body weight reduction must be recommended for overweight or obese patients with OSAS who initiate CPAP therapy[186]. A RCT comparing CPAP and weight loss with combined interventions over each one alone confirmed these results[178].

Bariatric surgery demonstrated positive results not only for OSAS but also for OSAS metabolic consequences and co-morbidities[187,188]. A meta-analysis showed that a reduction in the mean BMI by 17.9 kg per m^2 from 55.3 kg per m^2 to 37.7 kg per m^2 through bariatric surgery reduced the baseline AHI from 55 to 16. However, a significant proportion of patients with OSAS needed to continue CPAP despite this major improvement because the mean AHI after surgery was consistent with moderately severe residual disease that still required specific treatment[189]. Bariatric surgery in patients with OSAS did not lead to a greater improvement in the AHI compared to a conventional weight loss programme, although the reduction in weight was considerably more pronounced with surgery[151,189]. In addition, care should be taken in the perioperative and postoperative period of bariatric surgery because OSAS is a major risk factor for subsequent adverse events such as death, venous thromboembolism, percutaneous, endoscopic or operative reintervention, and failure to be discharged from the hospital[190].

Mild to moderate OSAS

In mild to moderate OSAS, symptoms determine treatment. As the benefit on cardiovascular outcomes remains uncertain, treating asymptomatic patients is controversial[165]. Oral appliances are preferred as primary treatment if feasible from a dental point of view. However, the presence of considerable co-morbidities (high cardiovascular risk) might favour the use of CPAP instead.

Oral appliances. Oral appliances, such as the mandibular advancement device (BOX 7), aim to widen the upper airway during sleep to reduce the risk of upper airway collapse in patients with OSAS (for reviews see REFS 191,192). The use of oral appliances during sleep improves the AHI and EDS[193]. Head-to-head trials confirm that CPAP is superior in reducing OSAS parameters on polysomnography, including AHI, oxygen desaturation indices and sleep fragmentation[194]; however, this greater efficacy does not necessarily translate into better health outcomes in clinical practice. Comparable effectiveness of oral appliances and CPAP with regard to EDS and daytime functioning suggests that inferiority in reducing the AHI is probably counteracted by greater treatment adherence to oral appliances[191]. Successfully titrated oral appliances are highly effective at reducing the AHI and are associated with a higher reported compliance than CPAP, with >70% of patients preferring this treatment[195].

Data regarding cardiovascular outcomes are scarce. However, a RCT comparing the effects of 1 month of CPAP versus oral appliances on the 24-hour blood pressure profile showed no difference between the two treatments, although it should be noted that neither treatment improved blood pressure[194]. A recent meta-analysis suggested favourable effect of oral appliances on systolic blood pressure, mean arterial pressure and diastolic blood pressure[196]. However, most of the

studies were observational. Thus, more RCTs involving a larger number of patients and longer treatment periods are warranted to confirm the effects of oral appliances on cardiovascular parameters[196].

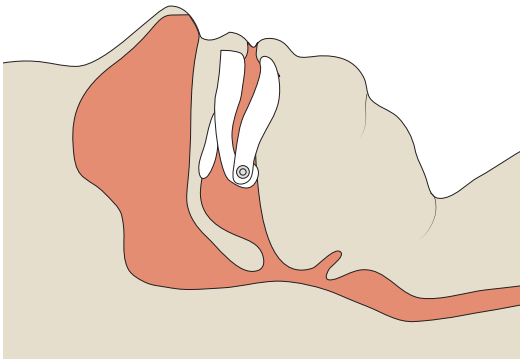
CPAP treatment. The main concerns for CPAP use in patients with mild to moderate OSAS, who often have few symptoms, are compliance and benefits on cardiovascular outcomes. A meta-analysis reported a mean CPAP treatment duration of 3.6 hours[156] per night in moderate OSAS, which is less than in more severe OSAS and less than what is usually considered as needed to reverse the chronic consequences of OSAS (4–5 hours per night). The MOSAIC study[197], conducted in patients with mild and minimally symptomatic OSAS, showed that CPAP could reduce subjective and objective symptoms but did not improve calculated cardiovascular risk. Also, a recent meta-analysis[165,166] did not find any beneficial impact of CPAP on blood pressure in minimally symptomatic OSAS, except in those patients who used CPAP for >4 hours per night. This target seems difficult to achieve as the mean CPAP compliance in the MOSAIC study was only 3.2 hours per night. Ultimately, in mild OSAS, CPAP elicits small improvements in sleepiness, which is probably of limited clinical significance and only provides a fringe benefit on cardiovascular outcomes, making its use controversial.

Weight loss and bariatric surgery. In patients with mild to moderate OSAS, there is evidence to indicate that weight loss might have more impact on the AHI than in severe OSA[179]. Also, weight loss by caloric restriction has been advocated over bariatric surgery owing to adverse effects of the surgery. More recently, anorexigens and other drugs for weight control have been used[198,199]. However, these drugs should be used with caution, especially in co-morbid conditions, because the use is often restricted by national and international health agencies.

Sleep posture. Positional sleep apnoea syndrome is defined as an AHI of more than two times higher when sleeping in the supine position (lying face up) than in the lateral position[200] (lying on one's side) and is mainly found in the mild to moderate OSAS population, the prevalence is approximately 50% in mild, 20% in moderate and 7% with severe OSAS[201]. Indeed, sleeping in the supine position might be detrimental in some patients as it can lead to the fall of the base of tongue, which further reduces the size of the pharynx. Also, changes in pharyngeal shape can aggravate the upper airway collapse. The upper airway changes from a more transversely oriented elliptical shape when supine to a more circular shape when in the lateral recumbent posture. Increased circularity decreases the propensity to pharyngeal collapse and may account for the postural dependency of OSAS[202]. Thus, sleeping in the lateral position might be a therapeutic option in these patients[203]. A RCT comparing CPAP and positional treatment showed a significant difference regarding the AHI in favour of CPAP, but no difference regarding symptoms, sleep structure, objective vigilance, cognitive tests and quality of life[203]. Long-term adherence to traditional supine avoidance techniques is, however, poor[204] and requires innovative approaches.

Box 7 | **Mandibular advancement device**

By repositioning the lower jaw forwards, the mandibular advancement device (MAD) helps to prevent the collapse of the tongue and soft tissues at the pharyngeal level, although the mechanisms are not fully understood. In patients who respond to treatment, MADs elevate the lateral parts of the upper airway at the velopharyngeal level, relocate the pharyngeal fat pads laterally from the airway and move the tongue base muscles anteriorly. MADs also change the dilator muscle activity, with genioglossus activation during wakefulness. During sleep, this muscle has been observed to reduce its activity during incremental mandibular advancement, whereas the masseter and submental muscles increase their activity[192]. Differences between devices include adjustable versus non-adjustable, self-moulded, and semi- or fully bespoke[274]. Recent technological developments enable assessment of objective compliance using an embedded microsensor thermometer with on-chip integrated readout[275]. Contraindications to the use of oral appliances include poor dental status, which is required to support the device, periodontal problems inducing tooth mobility and active temporomandibular joint disorders[276].



Quality of life

Quality of life can be defined as the overall state of well-being that individuals experience, as assessed by subjective measures of functioning, health and satisfaction with the important dimensions of their lives[205]. Impaired quality of life has been identified by the American Academy of Sleep Medicine as one of the characteristics associated with OSAS[206]. The repetitive obstructive events associated with OSAS lead to cortical arousal, intermittent hypoxaemia and increased sympathetic flow. All of these consequences dramatically affect the quality of sleep, which is intrinsically linked to quality of life. In fact, certain authors have described all aspects of quality of life (including physical and emotional health and social functioning) as markedly impaired in OSAS[207]. CPAP treatment improves EDS and quality of life in most patients with OSAS[173,203,208]. The magnitude of the improvement is related to the degree of quality-of-life impairment before treatment, rather than to the severity of the disease[207]. Additionally, several RCTs have shown impairment in quality of life and improvement with CPAP using both nonspecific and specific questionnaires regarding quality of life[159,209].

One of the major consequences of OSAS is driving impairment. The EDS and attentional deficits associated with OSAS increase the risk of traffic accidents: compared with those without sleep apnoea, OSAS patients with an AHI ≥10 have an odds ratio of approximately 6 (REF. 210).The driving impairment might occur without perceived EDS[211]. Also, CPAP treatment has been repeatedly evidenced as reducing traffic accidents in OSAS[212,213].

However, OSAS might be asymptomatic and might not have any effect on quality of life, particularly in patients with mild to moderate OSAS[214]. Some authors have reported only limited alterations in quality of life detected by some scales at baseline, hence, limiting the range of responsiveness after CPAP[215]. Similarly, other authors have reported that associations between OSAS severity and neurocognitive function were weak and inconsistent[216]. These discrepancies in the effects of OSAS on quality of life might be related to both the lack of sensitivity of the questionnaires in detecting small changes in this population and the presence of a ceiling effect in a relatively healthy population. However, several authors have administered quality-of-life questionnaires specifically designed for patients with OSAS[217,218] and have demonstrated that these questionnaires are a valid measure of health-related quality of life in these patients and are sensitive to treatment-induced changes[217–220] (TABLE 1).

Table 1 | **QOL questionnaires specifically designed for patients with OSAS**

Questionnaire name (acronym)	No. of items	Domains or factors (no. of items)	Refs
Quebec Sleep Questionnaire (QSQ)	32	Domain 1: hypersomnolence (6 items) Domain 2: diurnal symptoms (10 items) Domain 3: nocturnal symptoms (7 items) Domain 4: emotions (5 items) Domain 5: social interactions (4 items)	217
Calgary Sleep Apnea Quality of Life Index (SAQLI)	40 + 5	Domain 1: daily functioning (11 items) Domain 2: social interactions (13 items) Domain 3: emotional functioning (11 items) Domain 4: symptoms (5 items) Domain 5 (optional): treatment-related symptoms (5 items)	218
Functional Outcomes of Sleep Questionnaire (FOSQ)	30	Factor 1: activity level (9 items) Factor 2: vigilance (7 items) Factor 3: intimacy and sexual relationships (4 items) Factor 4: general productivity (8 items) Factor 5: social outcome (9 items)	219
Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10)	10	Factor 1: activity level (3 items) Factor 2: vigilance (3 items) Factor 3: intimacy and sexual relationships (1 item) Factor 4: general productivity (2 items) Factor 5: social outcome (1 item)	220

OSAS, obstructive sleep apnoea syndrome; QOL, quality-of-life.

Outlook

Mechanisms of upper airway collapse

OSAS has become a highly active research field. As previously described, pharyngeal collapse is multifactorial. A combination of anatomical and functional changes at the upper airway level[2,33], obesity and fat infiltration at the neck level[221], fluid changes from the legs during the night and pharyngeal neuropathy all have a role in variable proportions. Obesity not only reduces thoracic volume but excess fat tissue might also alter upper airway function. Indeed, leptin is also involved in the neuromechanical control of the upper airways[35]. Leptin is therefore one potential factor that accounts for the different phenotypes of OSAS because variability in leptin concentration among obese individuals with the same BMI might favour the occurrence and severity of OSAS[36]. However, the upper airway response is not only linked to the degree of neuromuscular activation. Glucose uptake in the genioglossus (the main muscle in the tongue) is reduced, which is probably secondary to alterations in tongue muscle fibre-type or secondary to chronic denervation[222]. Also, fluid shift from the legs might play a part, whereby fluid that accumulates in the intravascular and interstitial spaces of the legs during the day redistributes rostrally when lying down — all due to gravity. If this fluid accumulates in the neck, tissue pressure increases, which causes the upper airway to narrow and predisposes to OSAS[37] (FIG. 7). Risk factors for fluid shift are heart failure and end-stage renal disease. Upper airway mucosal water content and internal jugular vein volume were the only independent correlates of the AHI in patients with end-stage renal disease, together explaining 72% of AHI variance[223]. Whether prevention of fluid retention in the legs by exercising, use of compression stockings, dialysis or diuretic treatment is of therapeutic value in OSAS, needs large and long-term RCTs[37].

Protective mechanisms

Another field of complexity and uncertainty is the presence of potential protective mechanisms of intermittent hypoxia and OSAS. Indeed, not all subjects exposed to apnoeas and intermittent hypoxia will develop cardiovascular sequelae and epidemiological[97,224], clinical[225,226] and experimental data[227] suggest that intermittent hypoxia may exert some beneficial effects through various mechanisms, including an increase in angiogenic capacities. ROS are intricate and multifaceted molecules; depending on their concentrations, ROS signalling and damage can vary considerably[66] because of the activation of multiple as well as opposing pathways. For example, evidence obtained from animal models confirms that moderate ROS levels as a consequence of moderate intermittent hypoxia trigger activation of cardiac and cerebral protective mechanisms, whereas severe intermittent hypoxia and high ROS levels inflict detrimental effects[228–230]. ROS levels might depend on OSAS severity and duration, as well as the intracellular localization of ROS production and local antioxidant systems[58]. Additional factors such as nutrition, drug consumption, physical activity and genetic variability affecting the oxidant/antioxidant milieu might also alter the

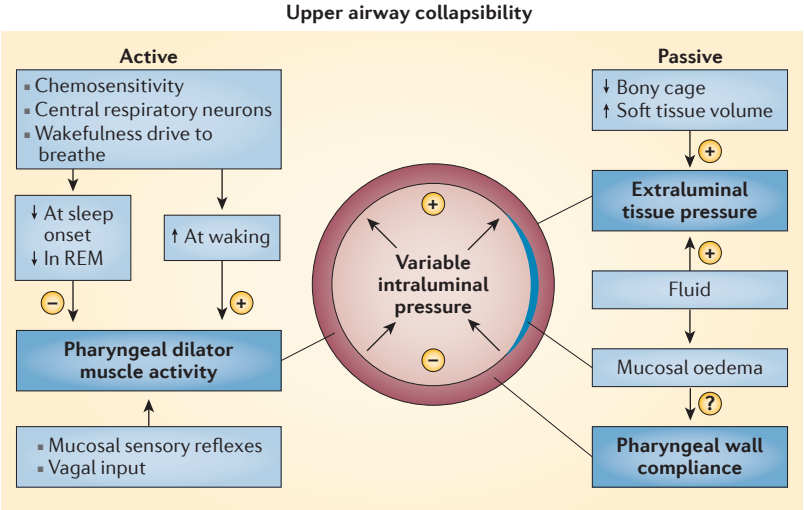


Figure 7 | **Contribution of fluid shift to upper airway collapsibility in the pathogenesis of OSAS.** Several dynamic factors, including fluid shift to the neck, determine the active (pharyngeal dilator muscle activity) and passive (intra- and extraluminal pressure and pharyngeal wall compliance) properties of the upper airway, which can increase collapsibility and lead to obstruction and obstructive sleep apnoea syndrome (OSAS). Figure reproduced from REF. 37, Wiley. REM, rapid eye movement sleep.

redox balance and might at the same time also promote ROS-dependent upregulation of adaptive mechanisms, as illustrated in FIG. 4.

Epidemiological studies suggest a possible activation of protective mechanisms in OSAS. There is evidence of a decline in mortality of patients with OSAS with age, particularly in the elderly[224,231,232], and a lack of association between OSAS and cardiovascular outcomes in some cardiovascular settings, such as acute coronary syndrome[226,233]. In addition, increases in endothelial progenitor cell numbers and functions[227] and increased collateralization of blood vessels[234] in coronary heart disease with concomitant OSAS support the activation of such protective mechanisms[225]. Collectively, these findings support the feasibility of activating protective mechanisms in some instances in OSAS and possibly harnessing the beneficial effects of intermittent hypoxia[225,234,235]. However, the specific patterns of activation have yet to be delineated[66,236].

Novel therapeutic approaches

Drugs have been tested in OSAS with minimal success, and the feasibility of an effective drug for preventing upper airway collapse has been questioned. One study reported that the AHI was lower following treatment with intranasal fluticasone (a glucocorticoid) compared with placebo (23.3 versus 30.3; $P<0.05$) in 24 patients with OSAS and rhinitis[237]. Physostigmine (a cholinesterase inhibitor) reduced the AHI to 41 compared with 54 on placebo ($P=0.045$) with a more pronounced effect on rapid-eye movement sleep (30 versus 54 on placebo; $P=0.017$)[238], and mirtazapine (a noradrenergic and specific serotonergic antidepressant with anxiolytic, hypnotic and antiemetic properties) produced a 46% improvement in the AHI ($P=0.04$)[239], but this effect was not reproduced in a larger RCT[240].

Activation of the upper airway might be another therapeutic approach. Potassium conductance is a common mechanism by which state-dependent neuromodulators reduce motor neuron excitability. Recent animal experiments have shown that blocking certain potassium channels at the hypoglossal motor pool substantially enhance genioglossus muscle activity in sleep, suggesting a new direction for research into drug therapies for OSAS. Moreover, a potassium channel blocker increased upper airway reflex activity after topical administration to animals and prevented negative pressure-induced collapse of the upper airway[241]. The role of potassium channel blockers in the treatment of OSAS remains to be adequately tested in humans.

Direct stimulation of the twelfth (hypoglossal) nerve, which innervates muscles of the tongue, is now considered to prevent upper airway collapse during sleep. The rate of response is variable when using unilateral stimulation[242,243]. However, accumulating evidence suggests that it might represent a valid therapeutic option[244–247]. Major issues are safety, long-term efficacy, cost-effectiveness and how to identify predictive factors of response to select suitable candidates for this procedure[248,249].

Finally, OSAS management might change with new technologies. Diagnosis has to be simplified owing to high prevalence and limited resources. Also, monitoring at home may promote stronger adherence to OSAS treatment and better management of systemic consequences. In this field, telemedicine is certainly a promising field. However, various management modalities should be evaluated in terms of outcome measures and not only in comparing technologies[14].

Chronic consequences

A major issue is whether treating OSAS can reverse its chronic consequences and sequelae. Uncontrolled studies and prospective clinical cohorts suggest that CPAP is able to reduce the number of fatal and non-fatal cardiovascular events, including arrhythmias, myocardial infarction and stroke[167,168]. However, this effect has not been established in large RCTs; nevertheless, several ongoing studies may provide some answers in the future[169]. In fact, CPAP effects on incident hypertension and cardiovascular events were not significant in the intention-to-treat analysis of the largest RCT conducted to date and only became significant in the subgroup of patients using CPAP more than 4 hours a day[153]. Another burning question is how CPAP or any other treatment of OSAS compares with the specific treatment of the associated co-morbidities with, for example, antihypertensive drugs[55] and weight loss[178]. These treatments seem far more effective on these associated co-morbidities than treating OSAS alone. Combining CPAP plus antihypertensive drugs or CPAP plus weight control, for example, for further implementation in clinical practices is therefore very interesting. Although OSAS is associated with metabolic disorders[118], it remains uncertain whether treating OSAS will improve blood glucose control[178], lipid metabolism[178,250] or adipose tissue distribution[251]. Additionally, more studies on the effects oral appliances have on

chronic consequences of OSAS should be performed, particularly in those with mild to moderate OSAS in which CPAP is much more difficult to use.

OSAS and cancer

Two large observational studies have found an association between OSAS and cancer[252–254]; gastrointestinal, respiratory tract, breast, and skin cancers have been reported thus far. The relationship between OSAS and cancer has been studied in animal[255–257] and clinical studies, suggesting that OSAS — mainly through intermittent hypoxia — is associated with an increase in growth rate[255], incidence[253] and mortality[254] of cancer. Recently, OSAS has been associated with the aggressiveness of cutaneous melanoma[252,258]. Intermittent hypoxia is a particular condition with relatively specific cellular effects[259], including changes in host immune responses that could favour cancer progression[260]. Intermittent hypoxia in animals leads to carcinogenesis and acceleration of tumour growth[255]. In addition, sleep fragmentation has also been demonstrated to promote tumour progression in animal models through the recruitment of tumour-associated macrophages and activation of Toll-like receptor 4 signalling pathways[261]. However, the data supporting the relationship between OSAS and cancer are preliminary and need confirmation[252].

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Competing interests
The authors declare no competing interests.

CORRECTION

Obstructive sleep apnoea syndrome

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