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REVIEW

Obstructive Sleep Apnea and Cardiometabolic Disease: Obesity, Hypertension, and Diabetes

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ABSTRACT: Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder, characterized by recurrent upper airway obstruction during sleep, resulting in intermittent hypoxia, increased sympathetic activation, and sleep deficiency. Over the past 2 decades, there has been a robust body of evidence to support a strong link between OSA and cardiometabolic diseases. Obesity is an important risk factor for OSA. Observational studies indicate that OSA is a strong risk factor for the development of hypertension and diabetes. Moreover, clinical and experimental studies support a causal role of OSA in hypertension and impairments in glucose metabolism, beyond excess weight. Notably, OSA is particularly underdiagnosed and undertreated in women, which may heighten the cardiometabolic risk. OSA is often overlooked during pregnancy and has been linked to adverse cardiometabolic outcomes in observational studies. In randomized clinical trials, treatment of OSA with continuous positive airway pressure reduces blood pressure in individuals with hypertension, but the beneficial effects of continuous positive airway pressure on glycemic outcomes are less convincing. Inconsistent cardiometabolic response to OSA treatment can be partly explained by failure to consider heterogeneity in OSA and variable continuous positive airway pressure adherence among diverse populations. In this review, we summarize the relationships between OSA and cardiometabolic conditions with a particular focus on obesity, hypertension, and diabetes. We review the current knowledge on the heterogeneity in OSA and discuss potential underlying mechanisms for impairments in blood pressure and glucose metabolism in OSA. We also provide a clinical perspective for OSA management considering current research gaps and emerging approaches for the prevention and treatment of cardiometabolic disease.

Key Words: hypertension ■ obesity ■ pregnancy ■ sleep apnea ■ sleep duration

Obstructive sleep apnea (OSA) is a highly common sleep disorder leading to sleep deficiency.[1,2] OSA is recognized as a heterogeneous condition with varying causes, pathophysiology, and clinical symptomatology and presentation.[3–5] Cardiometabolic disease broadly refers to a cluster of interrelated conditions that negatively impact cardiovascular and metabolic health. Over the past 2 decades, there has been a robust body of evidence linking OSA to cardiometabolic disease states including obesity, diabetes, hypertension, ischemic heart disease, arrhythmia, heart failure, renal disease, cerebrovascular disease, dyslipidemia, and fatty liver disease (Figure 1). Moreover, OSA is associated with increased all-cause and cardiovascular mortality.[4] While nearly 1 billion adults worldwide are affected by OSA, ≈80% remain undiagnosed and untreated, highlighting a serious public health concern.[6,7] In this article, we will focus on current knowledge on how OSA heterogeneity relates to obesity, hypertension, and diabetes. We will specifically review the underlying mechanisms by which OSA may impair glucose metabolism and blood pressure (BP) control. We will also provide a clinical perspective on OSA management for the prevention and treatment of cardiometabolic diseases.

NORMAL SLEEP AND CARDIOMETABOLIC FUNCTION

Normal sleep occurs in alternating cycles of nonrapid eye movement and rapid eye movement (REM) sleep with distinct brain activity and physiological functions (Figure 2A). Deep nonrapid eye movement sleep (N3 sleep) or slow wave sleep (SWS) accounts for 10% to 25% of total sleep time depending on age and sex. REM sleep, first discovered by Aserinsky and Kleitman[8] in 1953, typically

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Nonstandard Abbreviations and Acronyms

AHI	apnea-hypopnea index
BMI	body mass index
BP	blood pressure
CPAP	continuous positive airway pressure
OSA	obstructive sleep apnea
REM	rapid eye movement
SWS	slow wave sleep

involves dreaming, marked by rapid eye movements and loss of muscle tone. While SWS occurs predominantly during the early sleep period, REM sleep predominates the later part of the night. Sleep stage changes are accompanied by modulation of autonomic cardiovascular control (Figure 2B). Heart rate and BP decrease during sleep accompanied by a decrease in minute ventilation primarily due to reduced tidal volume.[9] The physiological drop in BP during sleep, commonly referred to as normal dipping, typically ranges from 10% to 20% compared with daytime levels. SWS is characterized by high-amplitude, low-frequency (0.5–4 Hz) brain waves, the so-called delta waves.[10] SWS involves regular breathing and predominantly vagal activation, and reduced sympathetic activity, BP, and heart rate. During REM sleep, brain activity resembles wakefulness, and breathing may become irregular. Intermittent increases in sympathetic activation may result in BP surges and bursts of cardiac autonomic activation. Sleep also plays a role in neuroendocrine regulation of glucose homeostasis and energy metabolism. Glucose utilization is highest during wake, lowest in nonrapid eye movement sleep, and intermediate in REM sleep.[11–14] The initiation of SWS is temporally associated with transient metabolic, hormonal, and neurophysiological changes, including decreased brain glucose utilization, stimulation of growth hormone release, inhibition of corticotropic activity, and increased vagal activity, all of which can influence glucose homeostasis and BP control.[15] During the early sleep period, circulating levels of appetite-stimulating hormone ghrelin (produced by the stomach) and satiety hormone leptin (produced by adipose tissue) both increase, and they decline in the later part of the night.[15] Normal sleep induces a decrease in energy expenditure, which is absent when wakefulness is maintained.[16] Taken together, sleep plays a fundamental role in maintaining physiological homeostasis including cardiovascular, respiratory, metabolic, and endocrine functions.

OSA PATHOGENESIS AND CLINICAL PRESENTATION

OSA is characterized by recurrent complete (apnea) and partial (hypopnea) upper airway obstructions during sleep, resulting in intermittent hypoxia, sleep fragmentation, increased sympathetic activity, and poor sleep quality. OSA is defined as an apnea-hypopnea index (AHI) of ≥5 events/h accompanied by symptoms such as sleepiness, fatigue, insomnia, or reduced quality of life or an AHI ≥15 without symptoms.[17] OSA can be diagnosed by standard polysomnography or home sleep apnea testing in patients with a high pretest probability without complex

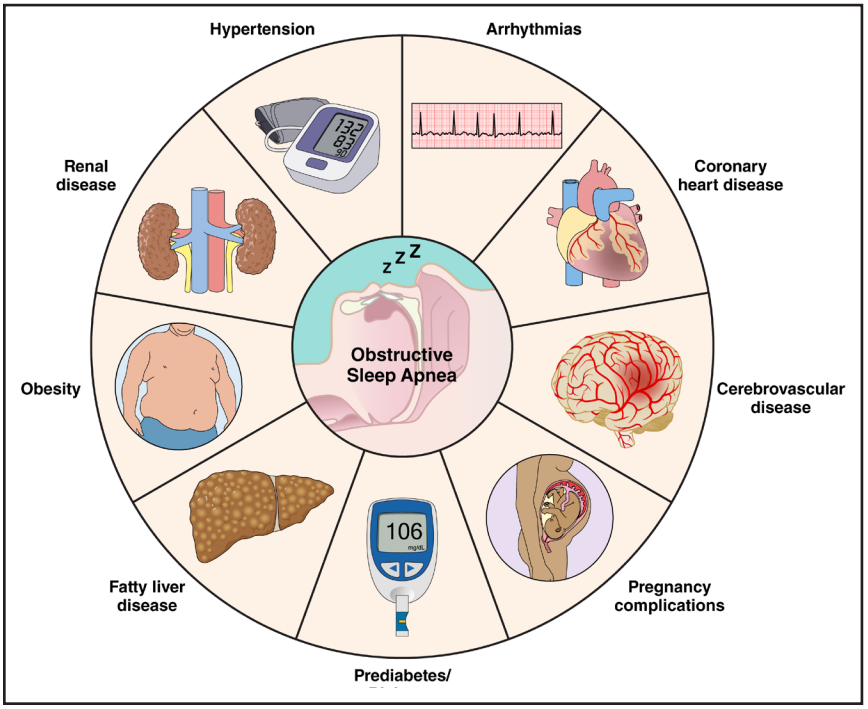

Figure 1. Obstructive sleep apnea (OSA) and associated cardiometabolic conditions.
OSA is associated with cardiometabolic disease states including obesity, diabetes, hypertension, ischemic heart disease, arrhythmia, heart failure, renal disease, cerebrovascular disease, dyslipidemia, and fatty liver disease. It is noteworthy that a bidirectional association exists between OSA and these cardiometabolic conditions. Illustration credit: Sceyence Studios.

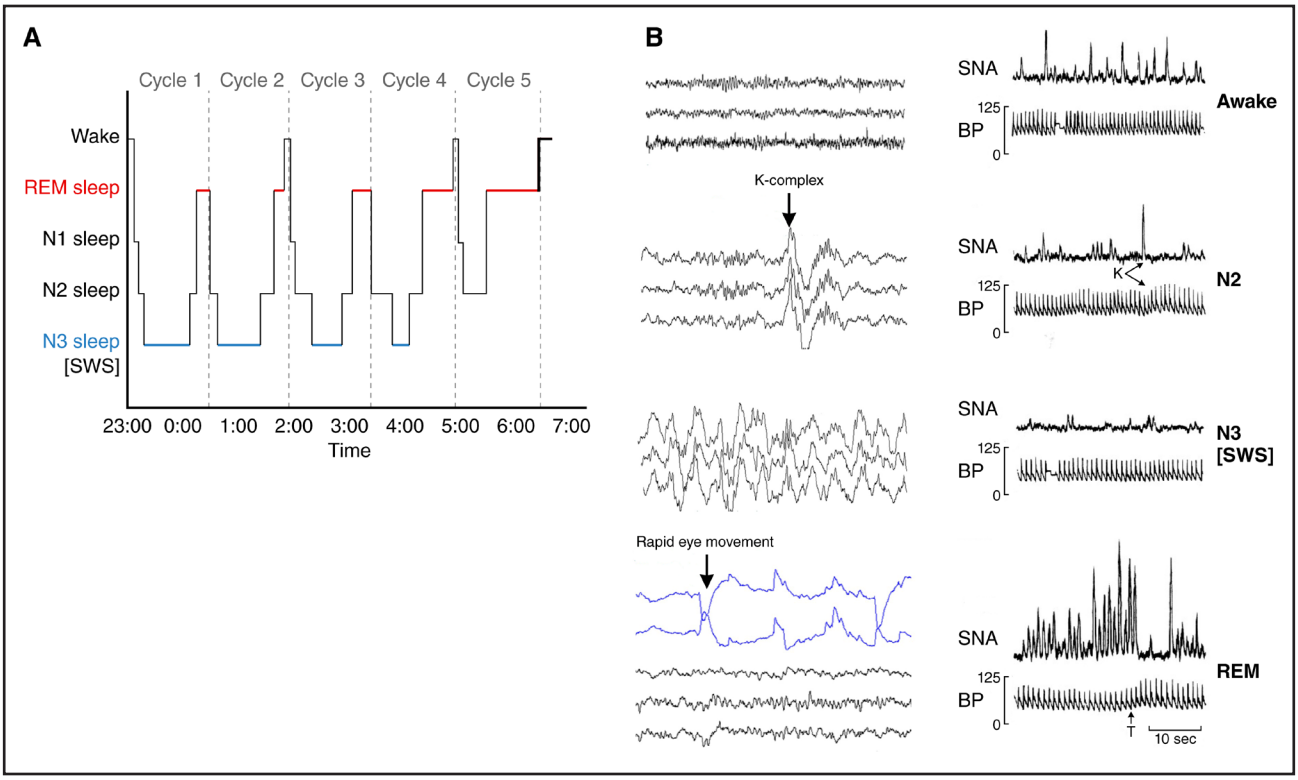

Figure 2. Normal sleep and autonomic cardiovascular control.
A, Hypnogram representing alternating cycles of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. These cycles typically last about 90 minutes and recur roughly 4× to 6 times per night. Approximately 75% of sleep time is spent in NREM sleep, which is further divided into 3 stages: N1 sleep, a brief transitional stage from wake to sleep; N2 sleep, that is, light NREM sleep accounting for the majority of NREM; and N3 sleep, that is, deep NREM sleep or slow wave sleep (SWS), accounting for 10% to 25% of total sleep time depending on age and sex. REM sleep, typically involves dreaming and is marked by rapid eye movements and loss of muscle tone. While SWS occurs predominantly during the early sleep period, REM sleep predominates the later part of the night. **B**, Recordings of the electroencephalogram (EEG) on the **left** and of muscle sympathetic nerve activity (SNA) and beat-by-beat blood pressure (BP) on the **right** during wakefulness (awake), during N2 sleep, during N3 or slow wave sleep, and during REM sleep. The high-frequency EEG during wakefulness transitions gradually to the high-amplitude, low-frequency slow waves seen during N3 or slow wave sleep and low-amplitude, high-frequency brain activity is evident during REM sleep. Rapid eye movements on the electrooculogram are indicated in blue during REM sleep. During N2 sleep, sympathetic activity, heart rate, and BP decrease from wakefulness with abrupt increases during K-complexes (indicated on the EEG, as well as the BP and sympathetic response indicated by K on the adjacent tracing). The EEG slow waves during N3 sleep are accompanied by marked reductions in sympathetic outflow, BP, and heart rate. During REM, sympathetic activity is elevated even higher than during wakefulness with abrupt fluctuations in BP and heart rate. The T symbol during the REM sympathetic and BP recording indicates the onset of tonic REM when sympathetic activity is lower than during phasic REM that precedes it. Illustration credit: Sceyence Studios.

comorbidities.[17,18] Because home testing can underestimate the AHI, patients at high risk for OSA and a negative home sleep apnea test should be further evaluated. It is noteworthy that home testing typically does not include an electroencephalogram signal to accurately capture sleep architecture. Thus, underestimation of OSA may occur partly due to undetected hypopneas that are associated with cortical arousals or sleep fragmentation on the electroencephalogram signal. Underestimated OSA by home testing may be especially higher in women or older adults who may have sleep fragmentation-predominant OSA. In the general population, OSA prevalence is estimated to be 9% to 38%.[5,19,20] Excess weight is the strongest risk factor for OSA.[21] Other traditional risk factors include male sex, postmenopausal status, older age, craniofacial or upper airway abnormalities, and family history of OSA.[22] Although male sex is a traditional risk factor, the sex gap narrows around the age of menopause when vulnerability to OSA markedly increases also in women. OSA negatively impacts quality of life and is associated with neurocognitive impairments and an elevated risk of motor vehicle accidents due to excessive daytime sleepiness.[23] Continuous positive airway pressure (CPAP) therapy remains the mainstay of OSA treatment. It is highly efficacious in reducing AHI and improving quality of life and daytime sleepiness.[23] However, adherence to CPAP treatment is highly variable among patients; using a cutoff of 4-hour nightly usage, the nonadherence rate is ≈40% to 80% across studies.[24] Alternative treatment options for OSA include mandibular advancement devices, positional therapy, hypoglossal nerve stimulation, and upper airway surgery. Weight loss interventions are an integral

component of OSA management in individuals with overweight or obesity.[25] In addition to lifestyle interventions (diet and exercise), bariatric surgery or pharmacotherapy may be considered for weight loss.[25,26]

While the AHI remains the standard metric for defining OSA severity, it fails to capture OSA heterogeneity and its consequences.[27–30] Notably, CPAP trials assessing the effect of OSA treatment on cardiovascular outcomes have yielded neutral findings, partly due to failure to consider OSA heterogeneity.[4] OSA arises from diverse pathophysiological mechanisms, referred to as endotypes. While impaired pharyngeal anatomy and upper airway collapsibility are nearly universal contributors, the severity of anatomic compromise varies considerably between individuals. Importantly, ≈70% of individuals exhibit impairments in >1 nonanatomic endotype, such as low arousal threshold, high loop gain (ie, unstable control of breathing), and poor upper airway muscle compensation.[31] Unique clusters of endotypes with distinct polysomnographic and clinical symptom characteristics have also been identified.[32] For example, those with high collapsibility and loop gain are more likely to have obesity and experience severe oxygen desaturation. Hypoxic burden, a metric that quantifies the duration and depth of respiratory event–related oxygen desaturations, may be a more robust predictor of cardiovascular risk than AHI alone.[33] Elevated heart rate response appears to predict improved cardiovascular risk reduction with CPAP treatment.[34] Symptom-based phenotypes (eg, excessive daytime sleepiness and insomnia) may better identify those at greater cardiovascular risk, beyond AHI.[35,36]

OSA AND OBESITY

Obesity is classically defined using body mass index (BMI) ≥30 kg/m^2. However, this definition does not provide adequate information about the degree and distribution of adiposity or cardiometabolic health status at an individual level.[37] Recent consensus recommendations highlight the importance of incorporating either direct measurement of body fat, if available, or at least 1 anthropometric criterion (eg, waist-height ratio) in addition to BMI, using validated thresholds for age, sex, and ethnicity.[37] About two-thirds of US adults are overweight or obese.[38] Obesity and related cardiometabolic risks are major public health concerns.[39,40] Excess weight strongly increases OSA risk,[19,21] primarily due to its impact on upper airway structure and collapsibility (Figure 3). In particular, fat accumulation around the neck leads to a mechanical load on the pharyngeal structures, narrowing the upper airway.[41,42] Moreover, fat deposition in the lateral pharyngeal structures contributes to airway collapse, and increased AHI is correlated with worsening retroglossal dimensions.[42,43] Importantly, classification of obesity relying on BMI does not inform about visceral adiposity or subcutaneous neck fat, which are more

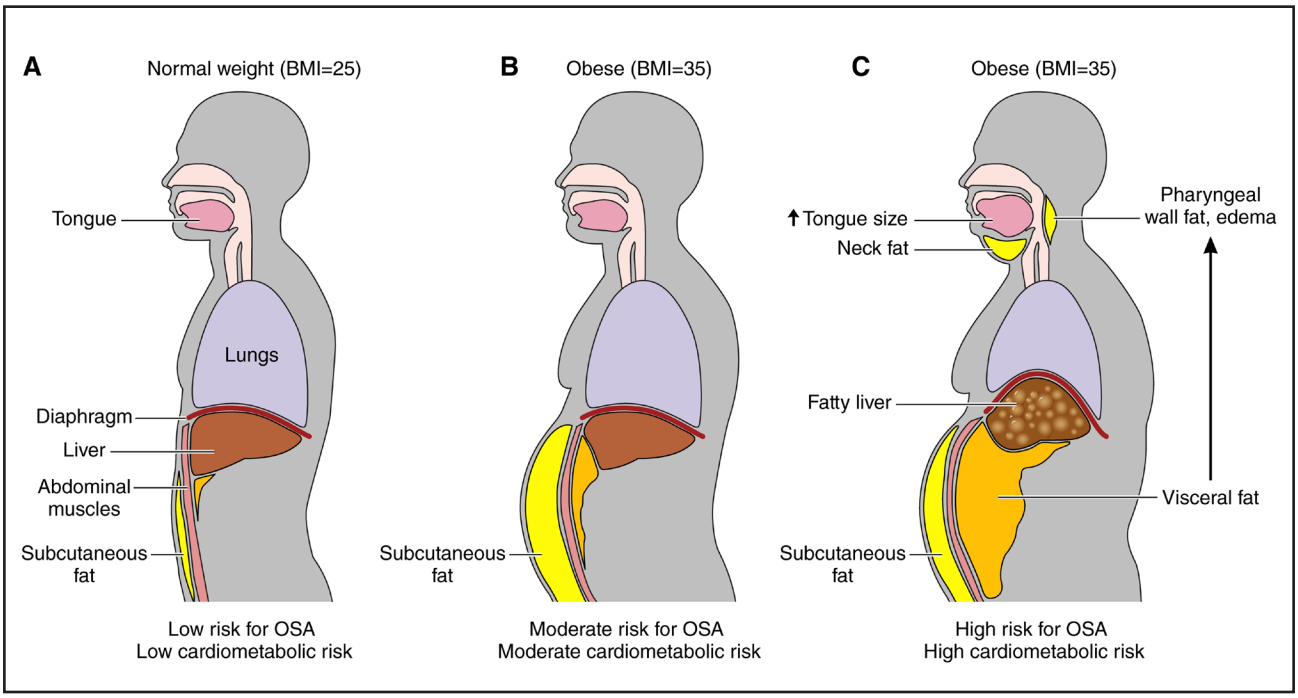

Figure 3. Relationship between obstructive sleep apnea (OSA) and obesity.
A, A normal-weight individual. **B** and **C**, Both depict individuals classified as obese based on body mass index (BMI) but with different body fat distributions. Two individuals with the same BMI can have markedly different levels of visceral and ectopic (eg, liver) fat. Upper airway fat deposition, visceral adiposity, and liver fat are more strongly associated with OSA and cardiometabolic risk than subcutaneous fat. Illustration credit: Sceyence Studios.

strongly correlated with OSA severity.[44] Ectopic fat accumulation, in particular in the liver, has also been associated with OSA severity.[45] However, not all patients with OSA are obese.[26] Indeed, a meta-analysis of >12 000 adults indicated that only one-third of those with OSA had obesity, with 44% having overweight and 24% having normal weight or underweight.[46] Women with OSA and those who were younger (ie, <65 years) were more likely to have obesity. A bidirectional relationship between OSA and obesity has been increasingly recognized.[41] In a large prospective population–based cohort, a 10% increase in body weight was associated with a 32% increase in AHI, while a 10% weight loss corresponded to a 26% decrease in AHI.[21] A recent meta-analysis found a dose-response relationship in which weight reduction was associated with clinically relevant improvements in OSA severity as assessed by AHI, while a proportionally smaller effect on AHI was observed with a weight reduction beyond 20%.[47] Whether OSA contributes to weight gain, putatively through sleep deficiency[2] and dysregulation of appetite-regulating hormones, increased caloric intake, and reduced energy expenditure[48–51] remains to be further investigated. Individuals with OSA and short sleep duration appear to have a greater risk for visceral adiposity.[52] Decreased physical activity in OSA may further contribute to weight gain.[53] Interestingly, CPAP use is associated with modest weight gain, particularly in patients who use CPAP ≤5 h/night and those without cardiovascular disease,[54] but the underlying mechanisms remain unclear.

OSA AND HYPERTENSION

OSA and hypertension are highly comorbid, with ≥50% of patients with OSA having hypertension[55–57] and 38% to 56% of patients with hypertension having OSA.[58–60] It is estimated that 71% to 83%[62,63] of patients with resistant hypertension have OSA, and OSA prevalence exceeds 95% in those with refractory hypertension.[63] Nocturnal (asleep) hypertension is highly prevalent in OSA.[64,65] Individuals with OSA are more likely to exhibit a nondipping BP pattern (a fall of BP <10% during sleep) compared with those without OSA.[66] Reverse dipping (an increase in BP during sleep) is also more frequent in OSA.[67] Those with abnormal dipping profiles manifest a markedly higher cardiovascular risk than individuals with similar overall BP and a normal nocturnal BP profile.[68]

Observational Evidence

In prospective studies, OSA is a predictor of incident hypertension. A landmark study of longitudinal data from the Wisconsin Sleep Cohort showed that worsening AHI increases the likelihood of hypertension at follow-up[69] with AHI ≥15 portending nearly 3× higher risk. Moreover, the odds of developing a nondipping BP profile were >3- and 4-fold higher in those with mild and moderate-to-severe OSA than in individuals without OSA, respectively.[70] Some,[71,72] but not all,[73,74] observations suggested an independent association between OSA and new-onset hypertension.[71,72] OSA severity during REM sleep may be especially prognostic for hypertension, possibly due to longer event duration coupled with more profound hypoxemia and greater sympathetic activation. Studies have found that REM AHI predicts prevalent and incident hypertension,[75,76] and incident nondipping,[77] independently of confounders. Hypoxic burden has been linked to commensurate increases in BP.[78] Studies of clinical subtypes of OSA based on different clusters of patient characteristics, symptoms, and disease severity reported distinct associations between OSA clusters and hypertension. For example, in one study, hypertension was more prevalent in the disturbed sleep cluster than the minimally symptomatic or excessively sleepy clusters, despite similar average AHI across clusters.[79]

Interventional Evidence

In a meta-analysis of 68 randomized controlled trials, OSA treatment by CPAP or mandibular advancement devices resulted in a pooled estimate of overall ≈2-mm Hg reduction in office or ambulatory BP, with heterogeneity in treatment response.[80] Albeit modest, this degree of BP reduction is considered beneficial, being associated with a 7% and 10% reduced risk of coronary artery disease and stroke, respectively.[81] It is well recognized that patients with OSA with resistant hypertension have the most pronounced BP falls following CPAP, with 6- and 4-mm Hg decreases in 24-hour systolic BP and diastolic BP during both daytime and nighttime.[82] Nocturnal hypoxemia also predicts BP response to CPAP, with greater BP reductions in patients with OSA experiencing more severe hypoxemia.[80] In patients with nonsleepy OSA with hypertension, CPAP does not change[83] or marginally decreases 24-hour BP.[84] In addition, CPAP treatment does not protect against new-onset hypertension in patients without daytime sleepiness.[85] Recently, loop gain has been found to be associated with favorable BP changes after CPAP, with patients with OSA exhibiting higher loop gain showing greater decreases in BP.[86] It is noteworthy that variable CPAP adherence in OSA likely contributes to the heterogeneity in BP response to treatment. Although per-protocol analyses reported greater benefit on BP in OSA with adherent CPAP usage,[84,85] meta-analysis does not support treatment adherence as an effect modifier.[80] In a recent randomized controlled trial, OSA treatment by hypoglossal nerve stimulation did not improve BP compared with sham therapy.[87] Mandibular advancement devices minimally improve BP (averaging 1 mm Hg), while supplemental oxygen does not provide benefits.[80,88] Behavioral

weight loss interventions potentiate BP-lowering effects of CPAP.[89] Emerging evidence from new incretin-based drugs for weight loss suggests improvements in both OSA severity and BP.[90] There is considerable heterogeneity in the effects of antihypertensive drugs in OSA,[91] with beneficial effects from diuretics and renin-angiotensin-aldosterone system inhibitors.[92] In patients with resistant hypertension on multiple antihypertensives, CPAP may have an additive benefit on BP control. Robust evidence from randomized controlled trials is needed to guide optimal antihypertensive regimens in OSA.

Mechanisms Linking OSA to Hypertension: Experimental Evidence

OSA-induced hypoxia, hypercapnia, arousals, and sleep disruption can lead to hypertension through several interconnected pathophysiological mechanisms (Figure 4). Repetitive apneas and hypopneas with oxygen desaturations activate carotid body chemoreceptors. This chemoreflex response consists of bradycardia due to cardiac vagal activation and increased central sympathetic outflow to peripheral blood vessels.[93] At obstructive respiratory event termination, abrupt lung inflation and thoracic afferent stretch inhibit cardiac vagal activation and increase sympathetic activity, resulting in tachycardia.[94] The increased cardiac output then enters a vasoconstricted circulation, eliciting marked increases in BP.[94] Baroreflex impairment can exacerbate established hypertension.[95] OSA can result in free radical formation due to oxidative stress[96,97] and systemic inflammation,[98] further contributing to hypertension. Because of repetitive hypoxemia, OSA may also increase renin-angiotensin-aldosterone activation, especially in resistant hypertension, possibly explaining the high co-occurrence of these conditions.[99] Collectively, endothelial dysfunction,[100] baroreflex impairment,[95] and atherosclerotic changes in the peripheral[101] and coronary vasculature[102] likely result in hypertension, often with a nondipping or reverse dipping profile. In experimental animal models, exposure to intermittent hypoxia raises BP[103–105] through augmented chemoreceptor sensitivity in the carotid body and consequent increases in sympathoadrenal outflow, promoting hypertension.[106–108] In addition, baroreflex impairment, renin-angiotensin-aldosterone system activation,[109,110] endothelial dysfunction, increases in endothelin-1 mediated vasoconstriction, and vascular remodeling[105,111] can manifest following hypoxia exposure. In healthy humans, acute hypoxia potentiates sympathetic activity, vasoconstriction, and BP surges during voluntary apneas.[112–114] Prolonged exposure of healthy individuals to intermittent hypoxia during sleep augments peripheral chemosensitivity,[115] blunts baroreceptor sensitivity,[116] exacerbates sympathetic activity,[116,117] and increases vascular resistance.[117] Interestingly, daytime BP elevation is evident event after a single night of intermittent hypoxia and continues to increase after 2 to 4 weeks of exposure.[115–117] In sleep fragmentation models, mice exposed to 20 weeks of sleep fragmentation developed systemic hypertension along with endothelial dysfunction and vascular remodeling.[118] In a canine OSA model of intermittent airway occlusion, arousals following apnea termination resulted in BP surges.[119,120] An earlier animal model comparing experimentally induced apneas by tracheal balloon versus sleep fragmentation has shown that sympathetic overactivity to chemoreceptor stimulation was a consequence of arousal from sleep.[121] In humans, experimentally induced arousals raise BP to a similar magnitude that occurs at apnea termination,[122,123] and the hypertensive effects of arousals are comparable during normoxia and hypercapnic hypoxia.[124] Collectively, these findings suggest that sleep fragmentation also plays an important role in OSA-related hypertension.

OSA AND DIABETES

Overall, current evidence supports a causal and bidirectional association between OSA and diabetes.[125–128]

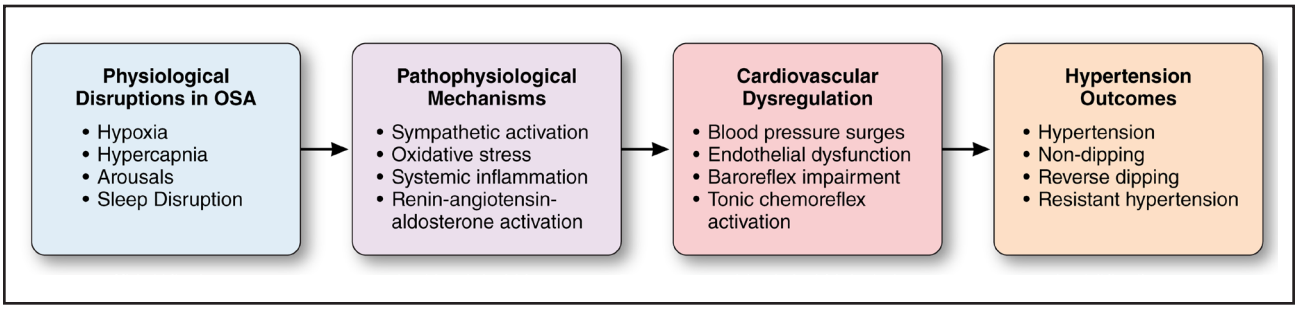

Figure 4. Potential mechanisms linking obstructive sleep apnea (OSA) to the development of hypertension.
OSA can trigger hypoxia, hypercapnia arousals, and sleep disruption that elicit increases in sympathetic activity, oxidative stress, systemic inflammation, and renin-angiotensin-aldosterone activation. These pathways lead to surges in blood pressure, endothelial dysfunction, baroreflex impairment, and tonic chemoreflex activation even during normoxic daytime wakefulness, with consequences for established hypertension often with a nondipping or even a reverse dipping profile, as well as resistant hypertension. Illustration credit: Sceyence Studios.

Diabetes is a heterogeneous condition with regard to pathophysiological factors contributing to disease risk and progression, and response to treatment.[129] Type 2 diabetes, the most common type, is strongly associated with overweight and obesity, and OSA is exceedingly common among these patients.[125,126,128] In addition, OSA is prevalent in type 1 diabetes, which is characterized by insulin deficiency, particularly in patients with moderate-to-severe OSA having worse glycemic control.[125,130–132] OSA has been reported in adults with maturity-onset diabetes of the young,[133] a unique form of diabetes caused by genetic mutations that classically presents without obesity or insulin resistance, which warrants further investigation.

Observational Evidence

In community-based cohorts, OSA was associated with a 37% increased risk of developing type 2 diabetes after adjustment for several confounders.[134] In one study with a median follow-up of 13 years, OSA was associated with a greater risk of developing diabetes after adjustment for BMI and waist circumference.[135] In a meta-analysis of prospective cohort studies involving 64 101 patients, OSA was associated with an adjusted pooled relative risk of type 2 diabetes of 1.35, comparable to that of traditional risk factors (eg, physical inactivity).[136] A modest increased risk of OSA in patients with diabetes has also been reported, possibly through diabetes-related inflammation and autonomic neuropathy disrupting upper airway stability and breathing.[134] Numerous studies found associations between OSA severity and insulin resistance and glucose intolerance in individuals with and without diabetes after controlling for multiple confounders including obesity.[126,128,137–141] For example, in a clinical cohort of adults without diabetes, OSA was associated with impairments in insulin sensitivity and pancreatic β-cell function after controlling for adiposity.[137] Notably, even in young lean men without other cardiometabolic risk factors, the presence of OSA has been associated with reduced insulin sensitivity.[142] Studies have also found strong associations between OSA during REM sleep and insulin resistance and glucose intolerance.[143] In one cohort, distinct OSA phenotypes (eg, hypopnea and hypoxia) improved the prediction of type 2 diabetes risk beyond AHI.[144] In a recent study, OSA severity (oxygen desaturation index quartiles) was associated with greater postprandial glucose levels in adults with type 2 diabetes.[145] Glycemic variability, independent of glycemic control, has emerged as a prognostic marker in individuals with and without type 2 diabetes.[146,147] In adults with type 2 diabetes, moderate-to-severe OSA was associated with greater glycemic variability than mild OSA.[148] Poor sleep quality was associated with greater overnight glycemic variability assessed by continuous glucose monitoring in a real-life setting in adults with type 1 diabetes.[149]

Interventional Evidence

Randomized controlled trials have not been convincing for a clear benefit of CPAP treatment on glucose-related outcomes. In one meta-analysis, CPAP did not improve glycemic control as assessed by hemoglobin A1c levels in individuals with type 2 diabetes,[150] while 2 other meta-analyses reported improvements after CPAP.[151,152] In individuals without diabetes, data from a meta-analysis showed that CPAP improves insulin sensitivity.[153] In a recent meta-analysis, CPAP modestly improved insulin sensitivity, with greater benefits in sleepy patients.[154] In a proof-of-concept randomized controlled study,[155] 8-hour nightly supervised CPAP use in the laboratory for 2 weeks improved insulin sensitivity and glucose tolerance in individuals with prediabetes, an early stage characterized by elevated glucose levels, not sufficient to meet the diagnostic criteria for diabetes. In addition, the optimal CPAP use reduced norepinephrine levels, a marker of sympathetic activity, 24-hour BP, and resting heart rate, which is a strong predictor of adverse cardiovascular outcomes, both at night and during the day.[156] Notably, the magnitude of reduction in daytime resting heart rate after treatment correlated with the magnitude of decrease in norepinephrine levels and OSA severity indices.[156] Post hoc analyses of a randomized crossover study in individuals with prediabetes found that CPAP improves insulin sensitivity among those with severe OSA.[157] In a nonrandomized intervention in patients with type 2 diabetes and OSA, 1 week of optimal in-laboratory CPAP treatment for 8 hours per night improved early morning glycemic control.[158] In another study, a single night of CPAP withdrawal resulted in increased glucose levels and free fatty acids during sleep.[159] In secondary analyses from the SAVE (Sleep Apnea cardio-Vascular Endpoints) study among 888 participants with established cardiovascular disease and OSA, there was no evidence (median follow-up of 4.3 years) that CPAP improves glycemic control over usual care[160] though mean CPAP usage was low at 3.5 hours. Interestingly, there was a signal for a possible protective role of CPAP in women with type 2 diabetes. In another randomized clinical trial, CPAP therapy did not improve glycemic control or variability in patients with moderate-to-severe OSA and type 2 diabetes, but exploratory analyses suggested that CPAP may improve glucose variability in women.[161]

Specifically, the lack of a clear benefit of CPAP treatment on glycemic outcomes may be due to several factors. It is possible that metabolic impairments at an advanced disease stage are unresponsive to treatment. In support of this hypothesis, CPAP trials have shown improvements in glucose tolerance and insulin resistance in prediabetes. Future interventions can investigate

whether OSA treatment is beneficial for early markers of diabetes risk, for example, 1-hour glucose levels post-oral glucose challenge that predicts progression to diabetes and cardiovascular disease even in individuals with normal glucose tolerance.[162] Varying CPAP adherence may also explain the inconsistent findings.[24] It is noteworthy that the current CPAP adherence tracking systems do not capture night-to-night variability in sleep patterns within and between individuals, which may contribute to the heterogeneity in cardiometabolic response to treatment. Indeed, a dose-response relationship has been shown between hours of CPAP usage and health care utilization, with measurable benefits even at low usage of 1 to 3 hours per night.[163] To address this variability in sleep patterns, a novel CPAP adherence metric, that is, the percentage of CPAP adherence that measures CPAP use relative to the time spent in bed, has been developed.[164] Long-term randomized controlled trials with rigorous measures of glycemic control, larger sample sizes, and more accurate CPAP adherence metrics are needed to identify subgroups of patients who are most likely to benefit from OSA treatment. More broadly, clinical trials have not provided consistent evidence that CPAP treatment improves cardiovascular outcomes, which may be partly explained by low levels of adherence to CPAP and the failure to consider OSA heterogeneity.[4]

Mechanisms Linking OSA to Impairment in Glucose Metabolism: Experimental Evidence

Glucose intolerance and type 2 diabetes develop when pancreatic β cells cannot upregulate insulin secretion relative to the degree of insulin resistance as occurs in obesity, aging, or pregnancy. Excess weight can cause insulin resistance, β-cell dysfunction, and the development of type 2 diabetes.[165] Research over the past 2 decades supports a strong link between untreated OSA and impairments in glucose metabolism, beyond excess weight.[128,140,166] A direct link between OSA and insulin resistance and glucose intolerance can occur through multiple interrelated mechanisms including sympathetic overactivity and catecholamine release, defects in fatty acid metabolism and ectopic lipid deposition in the skeletal muscle and liver, oxidative stress and mitochondrial dysfunction, hypothalamic-pituitary-adrenal axis activation and cortisol release, systemic inflammation, and endothelial dysfunction (Figure 5). Sympathetic activation is a potent stimulator of lipolysis, that is, increased release of fatty acids into the circulation.[165] Clinical and experimental data indicate that OSA stimulates lipolysis.[159,167–170] It is conceivable that OSA-triggered sympathetic overactivity can stimulate excess fatty acid delivery to skeletal muscle and cause defects in mitochondrial metabolism with subsequent

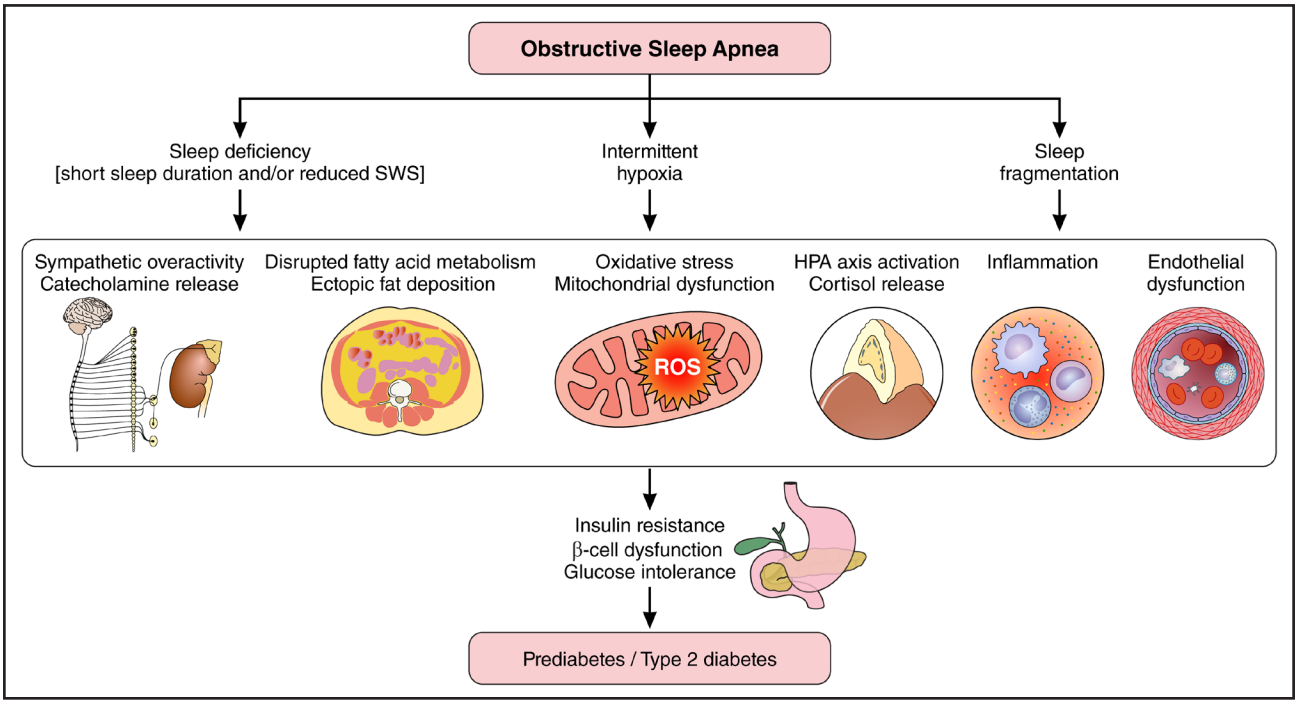

Figure 5. Potential mechanisms linking obstructive sleep apnea (OSA) to the development of prediabetes and type 2 diabetes. OSA is characterized by intermittent hypoxia, sleep fragmentation, and sleep deficiency. Collectively, these may lead to insulin resistance, pancreatic β-cell dysfunction and glucose intolerance, and progression to prediabetes and type 2 diabetes through multiple interrelated biological mechanisms: sympathetic overactivity, catecholamine release, disrupted fatty acid metabolism and ectopic fat deposition in liver and skeletal muscle, oxidative stress and mitochondrial dysfunction, hypothalamic-pituitary-adrenal (HPA) axis activation and cortisol release, systemic inflammation, and endothelial function. SWS indicates slow wave sleep. Illustration credit: Sceyence Studios.

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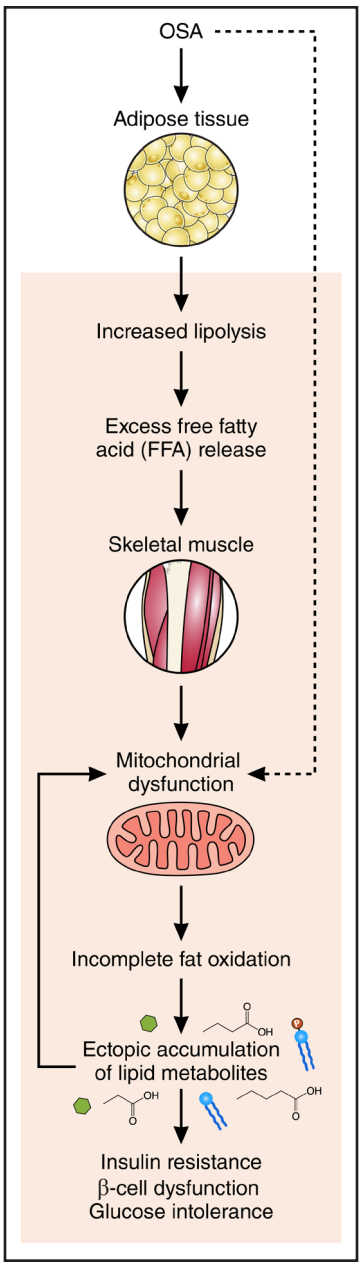

Figure 6. Hypothetical mechanisms by which mitochondrial dysfunction in obstructive sleep apnea (OSA) can lead to insulin resistance and glucose intolerance.
OSA can increase adipose tissue lipolysis, likely through sympathetic activation, resulting in excess fatty acid delivery to skeletal muscle, which, in turn, might cause mitochondrial dysfunction, incomplete fat oxidation, and subsequent ectopic lipid accumulation, which, in turn, might further impair mitochondrial function, ultimately leading to insulin resistance and glucose intolerance. OSA can also directly impair mitochondrial function through the accumulation of reactive oxygen species. Illustration credit: Sceyence Studios.

ectopic fat accumulation of lipid metabolites, leading to insulin resistance and glucose intolerance[165] (Figure 6). In support of this hypothesis, pharmacological suppression of lipolysis in animals prevented intermittent hypoxia-induced impairments in glucose tolerance and insulin sensitivity.[167] OSA can also directly impair mitochondrial function (eg, accumulation of reactive oxygen species). Future studies can explore these cellular bioenergetic pathways to elucidate how OSA contributes to peripheral insulin resistance. In a clinical study using isotope-tracer–based methods to assess glucose metabolism, OSA was a key determinant of peripheral insulin resistance in individuals with obesity.[171] Experimental evidence also strongly supports biological plausibility for impairments and glucose metabolism in OSA. Exposure to intermittent hypoxia or sleep fragmentation in animals or healthy humans results in insulin resistance and glucose intolerance.[172–176] In animal models, intermittent hypoxia (few hours to several weeks) has led to impaired glucose tolerance, insulin resistance, increased hepatic glucose production, and decreased muscle glucose uptake.[177–186] Animal models of sleep fragmentation have produced glucose intolerance and insulin resistance.[187–189] In healthy humans, short-term exposure to intermittent hypoxia (3–6 hours) caused higher glucose levels and insulin resistance.[190–192] Similarly, healthy human studies have shown that short-term (2–3 days) exposure to sleep fragmentation results in glucose intolerance and insulin resistance.[175,176] In a recent study, healthy humans exposed to 2 weeks of chronic intermittent hypoxia showed high sympathetic activity along with increased lipolysis and free fatty acid levels.[193] In addition, sleep deficiency with insufficient sleep duration and reduced SWS in the context of OSA may further compound perturbations in glucose metabolism and increase cardiometabolic risk.

OSA IN WOMEN

Prevalence and Clinical Presentation

OSA diagnosis is higher in men than in women with a male-to-female ratio of 8:1 in sleep clinics and 2:1 in community-based cohorts,[194] but this gap narrows with aging, particularly after menopause.[195,196] OSA prevalence is high (≈40%) among women with polycystic ovary syndrome,[197] the most common endocrine disorder in premenopausal women, characterized by hyperandrogenemia, insulin resistance, and a substantially increased risk for cardiometabolic disease. Observational evidence suggests that OSA may worsen insulin resistance and glucose intolerance in this high-risk population.[197] While men with OSA often present with classic symptoms of snoring and excessive daytime sleepiness, women are more likely to present with insomnia and nonspecific symptoms such as fatigue and depression.[194] Although OSA tends to manifest with shorter event duration and lower overall AHI in women, they frequently report poorer sleep quality than men.[198] The differences in prevalence estimates and clinical presentation of OSA in women may stem from a combination of biological and hormonal

factors or differences in upper airway anatomy or how OSA symptoms (eg, snoring) are reported by individuals or their bed partners. Common screening tools (eg, STOP-BANG [Snoring, Tiredness, Observed apnea, high blood Pressure, BMI, Age, Neck circumference, and Gender] survey) developed with male-centric symptomatology may contribute to underdiagnosis in women.[199] With regard to endotypes, women tend to exhibit lower loop gain, less airway collapsibility, and a lower arousal threshold.[200] OSA definitions relying on 4% desaturation criteria may underestimate OSA in women, who generally show greater propensity for sleep fragmentation rather than desaturation.[200] OSA severity is greater during REM sleep in women, while men seem to have more severe OSA in nonrapid eye movement sleep.[201] REM-predominant OSA may be a subtype especially vulnerable to hypertension.

Sex Differences in OSA and Cardiometabolic Disease

Higher prevalence of REM-predominant OSA in women[202,203] may partially account for the findings that women with OSA are at higher risk of hypertension than men with OSA[202,204] despite lower AHI and milder hypoxemia. Severe OSA was independently associated with incident hypertension in women but not in men in the Sleep Heart Health Study,[73] while contrasting associations were found in the Vitoria Sleep Cohort.[205]

Similarly, OSA severity predicted refractory hypertension in men but not in women.[206] Sex differences also reveal that insulin resistance and metabolic syndrome are more prevalent among women compared with men. In a prospective cohort with a 16-year follow-up, OSA was strongly associated with incident diabetes in women but not in men.[207] In a large population–based study with a 25-year follow-up, OSA was associated with type 2 diabetes, even after adjusting for multiple confounders, with an effect more pronounced in women.[208] A clinical study indicated that the negative impact of OSA on glucose metabolism was larger in men than in women.[209] While there was no overall benefit of CPAP on glycemic indices in secondary analysis of data from the SAVE study, women with type 2 diabetes assigned to CPAP showed improved glucose.[160] A randomized controlled trial among patients with moderate-to-severe OSA and type 2 diabetes suggested that CPAP may improve postprandial glycemic variability in women.[161] Given these mixed observations, future research is needed to investigate whether and how sex modifies cardiometabolic outcomes in OSA. Notably, women are underrepresented in OSA research, particularly in interventional studies.[210] A multicenter randomized controlled trial in women with OSA found marginal BP reduction following CPAP.[211] Despite comparable BP decreases with CPAP treatment in randomized controlled trials that included <80% versus >80% male participants,[80] it remains uncertain whether sex-specific effects of CPAP on BP are adequately captured in these trials. Overall, OSA is underdiagnosed and undertreated in women[212] likely due to multiple factors, and thus, they may face a greater cardiometabolic risk.[213] The current data highlight the need for future research to identify sex-specific vulnerabilities in OSA-related cardiometabolic outcomes.[214]

OSA in Pregnancy

During pregnancy, OSA prevalence generally exceeds that of premenopausal women,[20] with estimates ranging from ≈17% to 45% using in-laboratory polysomnography.[215] This wide range reflects variations in the timing of assessment and comorbid risk factors (eg, obesity, hypertension, and diabetes). Notably, OSA in pregnancy is much more common in women who are obese and older. Increased maternal age and first-trimester BMI are predictive of OSA later in pregnancy.[216] The prevalence is lower (≈4%–8%)[217] by home sleep apnea testing likely due to its reduced sensitivity in pregnancy, where OSA often manifests as milder respiratory events such as flow limitation that is a subtle form of partial upper airway obstruction not meeting criteria for apneas or hypopneas,[218] snoring, and hypopneas with arousals.[216,219]

Pregnancy is a state of heightened vulnerability to cardiometabolic risk and physiological changes including weight gain and hormonal fluctuations. The latter may amplify upper airway collapsibility and risk for OSA, which may further exacerbate cardiometabolic-related complications in pregnancy. During normal pregnancy, insulin sensitivity is reduced to ensure an adequate glucose supply to the fetus. However, an inability to compensate for this physiological state with upregulation of insulin secretion can lead to hyperglycemia and gestational diabetes.[220–222] OSA during pregnancy is associated with an increased risk of gestational diabetes.[217,223] Greater severity of OSA was associated with worse nocturnal glucose levels[217] as measured by continuous glucose monitoring.[224] Similarly, observational evidence indicates that OSA is associated with hypertensive disorders of pregnancy.[225] In the largest pregnancy cohort study with objective testing for OSA, exposure-response was demonstrated with increasing severity of OSA (ie, AHI) and hypertensive disorders of pregnancy.[217] Mechanisms linking OSA during pregnancy to gestational hypertension or diabetes have primarily been based on studies in animal models, indicating that oxidative stress and inflammation, increased sympathetic activity, and endothelial dysfunction could be implicated.

There are fewer studies examining the link between OSA during pregnancy and adverse fetal outcomes.[219] A few studies have shown associations with low birth weight or small for gestational age infants and premature

birth.[218,219,226] Unlike in other adult populations, subtle forms of upper airway obstruction have been associated with adverse cardiometabolic outcomes in pregnancy. Recent findings highlight that flow limitation is linked with a higher risk of preeclampsia, hypertensive disorders of pregnancy, and infants with low birthweight.[218,219,227] As such, flow limitation may represent an early intervention target to reduce the adverse health outcomes associated with OSA during pregnancy. In postpartum, over half of women have persistent OSA, but its overall severity generally improves.[228] In a large prospective study, persistent elevations in AHI and oxygen desaturation index in the years following delivery were associated with a significantly higher risk of hypertension and metabolic syndrome later in life.[229] The impact of treatment of OSA on cardiometabolic outcomes in pregnancy is largely limited to small, nonrandomized pilot studies.[215] While some studies suggested that CPAP may reduce nocturnal BP and cardiac output, others have been neutral.[215] Notably, poor CPAP treatment adherence during pregnancy is an important limitation.[230–232] Evidence is scarce on the effects of CPAP on glucose regulation in pregnancy,[232,233] with one randomized controlled trial showing improvements in nocturnal glucose levels among women with gestational diabetes.[233] One pilot study reported that mandibular advancement devices are well-tolerated in pregnancy but seem less efficacious in reducing the AHI compared with CPAP.[234] Larger, rigorous, and well-designed trials are needed to evaluate the impact of OSA treatment during pregnancy on maternal and fetal cardiometabolic health. In sum, OSA is often underdiagnosed in pregnancy due to a lack of awareness and variable symptom presentation.[235] Emerging evidence suggests that OSA during pregnancy may pose risks to both maternal and fetal health, underscoring the need for further research and evidence-based guidelines for diagnosis and management.[215]

RACIAL/ETHNIC DIFFERENCES IN OSA AND CARDIOMETABOLIC DISEASE

Racial and ethnic minorities are disproportionately burdened by OSA and cardiometabolic diseases including obesity, hypertension, and diabetes.[214,236–238] Moreover, minority groups experience significant disparities in sleep health because optimal sleep is strongly influenced by social determinants of health.[239] More specifically, several factors including home and environmental social and physical conditions, cultural and low socioeconomic status–related stress, and work status (eg, shift work) can all influence sleep patterns. In minority groups, OSA is disproportionately underdiagnosed (only <10% with clinically significant OSA reporting an OSA diagnosis) and undertreated.[240,241] The prevalence and severity of OSA are higher in Black populations than in White populations, particularly for symptomatic OSA.[241,242] Asians have a higher susceptibility to upper airway collapse with increasing adiposity compared with other minority groups.[241] Black adults with OSA are twice more likely to have resistant hypertension than those without OSA.[243] The Hispanic/Latino background modifies the association between OSA and hypertension.[244] Evidence from CPAP trials in diverse populations is lacking, and it is unknown whether race/ethnicity modifies BP response to treatment. Minority groups also have an increased prevalence of diabetes and cardiometabolic disease related to OSA.[245,246] These disparities could be explained by several societal and institutional factors that constrain access to health care and timely management of OSA (eg, limited availability of sleep specialists and preventive care), which may exacerbate cardiometabolic diseases. Also, CPAP adherence is lower in minorities and low socioeconomic status groups,[247] which may partially explain the higher rates of hypertension and diabetes. Multiple social stressors (eg, housing instability and lack of access to behavioral support for optimizing CPAP use) can influence CPAP adherence. It is also noteworthy that currently used fixed CPAP adherence targets may not adequately capture the known racial/ethnic and socioeconomic differences in sleep patterns, particularly sleep duration.[164,248] Revisions to current CPAP adherence metrics and policies for insurance coverage can reduce inequalities in OSA care. Future research using interventions to treat OSA can further examine how racial/ethnic differences modify cardiometabolic outcomes including obesity, diabetes, and hypertension.[249]

OTHER SLEEP CONDITIONS AND CARDIOMETABOLIC DISEASE IN OSA

Insomnia and Narcolepsy

Insomnia symptoms including difficulty initiating, maintaining sleep, or early morning awakenings have been reported in OSA. Comorbid insomnia and sleep apnea, commonly referred to as comorbid insomnia and sleep apnea, are highly prevalent with 30% to 50% of patients with OSA reporting insomnia symptoms and 30% to 40% of those with insomnia having OSA.[250,251] Female sex, advanced age, and poor mental health are potential risk factors for comorbid insomnia and sleep apnea.[252,253] Compared with OSA or insomnia alone, comorbid insomnia and sleep apnea are generally associated with greater morbidity[252,254] including a higher risk of cardiometabolic disease.[253,255,256] Cognitive-behavioral therapy for insomnia improves sleep in patients with co-morbid insomnia and sleep apnea,[257] but its potential effect on BP control is yet to be determined. A bidirectionality between OSA and insomnia has also been postulated.[258] Patients with OSA with a low arousal threshold may exhibit more frequent OSA-induced sleep fragmentation

and awakenings, promoting insomnia.[259] OSA may also perpetuate the hyperarousal state of insomnia through cortical arousals and sympathetic activation elicited by respiratory events.[260] On the other hand, sleep instability from insomnia may alter the respiratory arousal threshold and exacerbate OSA. Insomnia-related sleep loss may also worsen OSA severity, possibly by increasing upper airway collapsibility.[261] OSA can also co-occur with narcolepsy, a sleep disorder characterized by hypocretin deficiency, cataplexy (sudden loss of muscle tone triggered by strong emotions), disrupted nighttime sleep, and severe daytime sleepiness. Patients with narcolepsy consistently show increased prevalence of obesity, hypertension, hyperlipidemia, and diabetes.[262] The prevalence of undiagnosed narcolepsy in patients with OSA remains uncertain. Longitudinal large population–based data indicated that narcolepsy is associated with increased cardiovascular disease risk,[263,264] which can exacerbate the cardiovascular morbidity and mortality in individuals with comorbid OSA.

Sleep Depth: Role of SWS

SWS, a key marker of sleep depth, is temporally associated with transient autonomic and neuroendocrine changes that can affect BP and glucose regulation.[10,265,266] SWS declines with aging, and women generally have more SWS.[266] In OSA, transient improvement in respiratory events occurs during SWS, likely due to a less collapsible upper airway and higher arousal threshold.[259,267–269] Low levels of SWS and slow wave activity are reported in OSA, which can be restored with effective treatment.[270,271] Observational data from large population cohorts indicate that reduced SWS is prospectively associated with increased hypertension and type 2 diabetes risk in individuals with or without OSA.[272–276] A clinic-based study found an inverse relationship between OSA severity and slow wave activity in men but not in women,[277] whereas a population-based study reported an association between reduced SWS and elevated BP only in women.[278] In experimental studies in healthy young adults (93% men), on average, a ≥50% reduction in SWS (selective or nonspecific acoustic sleep fragmentation) over the course of 1 to 3 nights resulted in impairments in insulin sensitivity and glucose tolerance, increased sympathetic activity and cortisol levels, and attenuation of BP dipping.[175,176,279–283] Recent mechanistic data support a reciprocal interaction between SWS and heart health through immune pathways.[284] Emerging data on SWS enhancement using different approaches (eg, acoustic, hypnotic, and pharmacological) combined with recent advances in technology are encouraging for a potential cardiometabolic benefit.[285–290] Interestingly, exercise interventions in individuals with or without OSA may increase SWS and reduce OSA severity markers.[291–294] In sum, sleep depth or SWS is emerging as a potential modifiable factor in diabetes and hypertension risk. Future research could explore underlying mechanisms and sex-specific effects linking SWS to diabetes and hypertension and pave the way for novel clinical interventions for cardiometabolic disease prevention and treatment.[295]

Sleep Duration

Sleep deficiency or short sleep duration has been reported in individuals with OSA, which can potentially exacerbate cardiometabolic risk such as obesity, diabetes, and hypertension.[52,296–298] According to the recent national surveys, about one-third of the US general population reported not getting the recommended 7 to 9 hours of sleep.[299,300] Over the past several decades, substantial evidence has demonstrated that short sleep duration is strongly associated with increased cardiovascular and metabolic risk.[301–305] Experimental sleep restriction in healthy individuals has consistently demonstrated perturbations in glucose metabolism,[306] increased energy intake with minimal change in energy expenditure,[301,307,308] weight gain, and preferential fat accumulation.[309–311] In a meta-analysis of prospective cohorts, short sleep duration was associated with a 38% likelihood of obesity[312] and increased risk of developing diabetes and hypertension.[313,314] Potential mechanisms for overeating and weight gain with sleep loss include alterations in appetite-regulating hormones (eg, increased ghrelin) and changes in brain regions related to reward-seeking behavior, that is, increased hedonic eating.[301,315] Experimental sleep restriction has also shown increased sympathetic activity and BP,[316–318] impaired endothelial function,[317] and inflammation.[319] Given the strong link between short sleep and cardiometabolic risk, optimizing sleep duration, that is, sleep extension, has emerged as a potential intervention for cardiometabolic risk reduction.[320–326] A recent randomized controlled study has found that short-term sleep extension reduced objectively measured energy intake by a clinically meaningful amount (on average 270 kcal/d) in real-life settings in adults with overweight who habitually curtail their sleep duration.[327] Overall, the current evidence supports the notion that adequate sleep duration could be a public health target for preventing obesity and associated cardiometabolic dieases.[301,328] Future research can explore whether optimizing sleep duration added to standard OSA treatments could be an effective strategy for the management of cardiometabolic disease in this population.

CLINICAL PERSPECTIVES

Screening and Diagnosis of OSA in Hypertension and Diabetes Management

Current guidelines recommend testing for OSA in patients with hypertension, especially those with uncontrolled or

resistant hypertension, and for secondary causes of hypertension.[329,330] In a meta-analysis of 48 randomized trials with a total of 344 716 patients, a 5-mm Hg reduction of systolic BP reduced the risk of major cardiovascular events by about 10%, irrespective of preexisting cardiovascular disease or baseline BP.[331] These findings highlight the importance of broader screening and treatment of OSA to improve cardiovascular risk reduction.[331] Given the large evidence linking insufficient sleep to impairments in glucose control, the Precision Medicine in Diabetes Initiative included screening for sleep health,[332] but these recommendations are yet to be widely implemented in clinical practice.[333] Similarly, the high prevalence of OSA in cardiovascular disease strongly highlights the need for careful screening for OSA in clinical cardiology practices. This can be accomplished by screening questionnaires (eg, STOP-BANG) and home sleep apnea testing. Further guidance can be obtained from an outline on whom to screen and how to screen for OSA in a cardiology practice.[334] Sleep evaluation in a cardiology practice can be further facilitated by an innovative cardiology-based American Academy of Sleep Medicine specialty accreditation pathway, whereby cardiologists in certified clinics are able to order home sleep apnea tests, provide relevant kits and instructions, and review study results with their patients.[334] Nevertheless, specialized sleep medicine services are limited, especially among underserved populations, contributing to underdiagnosis and inadequate treatment of OSA, and unfavorable cardiometabolic outcomes. Advances in health care technology including wearable technology with the capability of long-term monitoring, telehealth platforms, and artificial intelligence-powered data analytics may expand OSA care and potentially mitigate associated cardiometabolic disease burden.[335] As night-to-night OSA variability may lead to misclassification of disease severity and missed diagnosis,[336] multinight evaluation leveraging new technology has the premise of better capturing OSA. Multimodal telemonitoring can promote continuity of care and facilitate treatment adherence tracking and troubleshooting, ultimately improving the patient-centered care and cardiometabolic outcomes.[337]

Prevention and Treatment of Cardiometabolic Disease in OSA

Strategies focused on cardiometabolic disease prevention using proven traditional dietary interventions (eg, Mediterranean-style or DASH [Dietary Approaches to Stop Hypertension] diets) and exercise regimens (eg, resistance training) are often neglected in OSA management.[338,339] A meta-analysis of controlled interventional studies indicated that exercise training in individuals with OSA reduces disease severity along with body fat and neck circumference.[294] Specific interventions to reduce cardiometabolic risk can also be guided by following the American Heart Associations' Life's Essential 8, which recently added sleep health as its eighth essential metric for promoting cardiovascular health alongside other metrics including maintaining a healthy weight through diet and exercise, quitting tobacco, managing cholesterol, and glucose and BP control.[340] Improved psychological well-being with stress management (eg, meditation and mindfulness) may contribute to improvements in sleep and BP.[341] CPAP therapy is underscored for lowering BP in patients with comorbid OSA and hypertension, especially those with resistant hypertension. Mineralocorticoid receptor antagonists such as spironolactone are recommended for comorbid OSA and resistant hypertension.

Weight loss is an essential component of OSA management in people with overweight and obesity.[47,51] Meta-analyses indicate that lifestyle interventions aimed at weight loss (ie, diet and exercise) reduce OSA severity (eg, 10% weight loss predicting a decrease in AHI by 26%) and improve daytime sleepiness and cardiometabolic outcomes.[47,342,343] In a randomized trial in individuals with OSA and obesity, weight loss through lifestyle intervention provided an incremental improvement in insulin sensitivity when combined with CPAP.[344] Importantly, sustained weight loss and long-term cardiometabolic benefits remain a challenge.[51,345,346] Bariatric surgery for weight loss can successfully improve OSA severity with a potential for long-term benefit.[347,348] Patients who attain OSA remission after bariatric surgery (65% in meta-analysis) are more likely to improve their cardiometabolic profile and reduce the risk for major adverse cardiovascular events and all-cause mortality.[347] In a recent retrospective study of patients undergoing metabolic surgery for obesity, those with moderate-to-severe OSA had marked improvements in OSA severity and a lower risk of incident major adverse cardiovascular outcomes and death compared with usual nonsurgical care.[349]

Recently, incretin-based therapies (eg, glucagon-like peptide 1 receptor agonists), originally approved for the treatment of type 2 diabetes in 2005, have emerged as a new alternative for weight management and cardiometabolic risk reduction in OSA.[90,350–352] A meta-analysis of 6 studies in individuals with OSA who have been on incretin-based therapy with a follow-up duration ranging from 4 to 52 weeks indicated that these drugs reduce OSA severity, particularly in those with severe OSA and obesity, promote weight loss, and reduce BP.[90] The primary effect of these drugs is attributed to weight loss, mainly through appetite suppression. Notably, weight regain occurs when patients stop taking these drugs. Tirzepatide, a combined agonist for glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide receptors, was recently approved for use in individuals with moderate-to-severe OSA and obesity.[351] One proof-of-concept randomized controlled study of patients with moderate-to-severe OSA and obesity suggested that CPAP therapy improves vascular inflammation independent of glucagon-like peptide 1 receptor agonist (liraglutide)–mediated weight loss[353]; however, the degree of weight loss was considerably low compared with the SURMOUNT-OSA trial.[351] that showed reductions in AHI

and systolic BP across both CPAP users and nonusers. In a recent study, tirzepatide, compared with liraglutide and semaglutide, was associated with a lower incidence of major adverse cardiovascular events in patients with OSA and type 2 diabetes.[354] Other than weight loss, the putative mechanisms underlying the cardiometabolic benefits of glucagon-like peptide 1 receptor agonists may involve improved insulin sensitivity,[355] reduced inflammation, and direct cardioprotective effects.[356] Taken together, recent advances in incretin-based pharmacotherapies added a new avenue to the cardiometabolic disease prevention and treatment in OSA.[350,357] How these novel agents fit in with other therapeutic options in OSA is an ongoing area of research, and the precise guidelines for their use in the management of OSA remain to be determined.[350] It is also noteworthy that there is still a lot of uncertainty about the long-term biological effects of these medications, and how they will ultimately change people's eating habits and lifestyle behaviors remains an open question. For example, whether individuals will develop a tolerance to their appetite-suppressing effects over the long term is unclear. Further rigorous research is needed in various patient populations to determine the role of incretin-based pharmacotherapies in OSA management[350] to address specific research gaps on long-term adherence, patient-reported outcomes, cost and accessibility, and use of CPAP or other therapies (eg, mandibular advancement devices and hypoglossal nerve stimulation) in combination with these drugs.

SUMMARY AND FUTURE RESEARCH AGENDA

Current evidence supports a strong association between OSA and cardiometabolic disease. Mechanistic evidence provides biological plausibility and supports OSA as a modifiable risk factor for the development of hypertension and type 2 diabetes. Randomized controlled trials have been less convincing for the benefit of CPAP treatment of OSA on glycemic outcomes, but they demonstrated a BP-lowering effect, especially in patients with severe OSA, those with excessive daytime sleepiness, and those with resistant hypertension. Notably, current CPAP adherence tracking systems do not capture night-to-night variability in sleep patterns, which may contribute to variable cardiometabolic response to treatment. In addition, evidence suggests an important role of reduced SWS in the development of diabetes and hypertension, which warrants further research in OSA. Several open questions related to the interplay between OSA and cardiometabolic disease remain to be answered (Table). A better understanding of how distinct OSA endophenotypic traits influence cardiometabolic disease risk, particularly identification of subgroups of patients with OSA who are at greatest risk for hypertension and diabetes, can help to develop more personalized treatment approaches. Most research on cardiometabolic disease in OSA was conducted in men, and thus, further investigation is needed in women. Elucidating systemic and cellular pathways that contribute to disruptions in BP and glucose control in OSA may ultimately help develop novel approaches to prevent and treat cardiometabolic disease. Long-term rigorous randomized controlled trials are needed to identify subgroups of patients who are most likely to benefit from OSA treatment for the prevention and treatment of cardiometabolic disease. For example, pathway-specific polygenic risk scores suggest an interaction between OSA and genetic risk, highlighting a premise for personalization of OSA treatment to reduce cardiometabolic risk guided by genetic risk profiles.[358] Future research can leverage new technology, telehealth, and advanced analytical approaches using multilevel data to improve the diagnostic and prognostic information. In summary, the future of clinical management for OSA may involve personalized approaches, technology-supported remote monitoring of treatment, and incorporation of novel therapies while emphasizing the key importance of risk factor modification and multidisciplinary care.

Table. Research Agenda of Key Open Questions and Considerations for Future Research.

Whether and how OSA endophenotypes modify the association between OSA and cardiometabolic diseases?
What are the key OSA metrics (eg, hypoxic burden) driving each specific hypertensive and metabolic condition?
Elucidate novel mechanistic pathways linking OSA to hypertension and diabetes to inform the development of novel treatments.
Are there biomarkers predictive of blood pressure and metabolic benefit from OSA treatment?
Conduct randomized controlled trials investigating the effects of OSA treatment on cardiometabolic outcomes in diverse populations, particularly women.
Who are the subgroups of patients most likely to benefit from OSA treatment to improve cardiometabolic outcomes, particularly glucose control?
Identify optimal timing of OSA screening during pregnancy and effective treatment approaches to improve cardiometabolic outcomes.
Does optimizing sleep duration as a behavioral strategy improve cardiometabolic outcomes in individuals with and without OSA?
Investigate whether enhancement of SWS can be protective against the development of hypertension and diabetes in individuals with and without OSA?
How to better leverage sleep technologies (eg, wearables) and advanced data algorithms for improved OSA diagnosis and long-term monitoring of treatment effects on cardiometabolic outcomes.

OSA indicates obstructive sleep apnea; and SWS, slow wave sleep.

ARTICLE INFORMATION

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REVIEW

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