Chapter 11
The Role of Sleep Apnea in Diabetes Mellitus and Cardiovascular Disease

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Introduction

Sleep-disordered breathing (SDB), which encompasses both obstructive sleep apnea (OSA) and central sleep apnea (CSA), is highly prevalent in patients with cardiometabolic disease. A growing body of evidence supports a causal association between SDB and incidence and morbidity of hypertension (HTN), coronary heart disease (CAD), arrhythmia, heart failure (HF), stroke, and type 2 diabetes (T2DM) [1]. While the subgroups of SDB are attributed to different pathophysiologies, they often coexist in the same patient, especially in patients with co-morbid cardiometabolic disease, such as HF or atrial fibrillation (AF). Recognition and treatment of SDB may impact cardiovascular disease morbidity. This chapter will discuss current understanding of the pathophysiology and mechanisms of SDB, links between SDB and cardiovascular disease, and the impact of SDB treatment on cardiovascular outcomes.

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Definitions

OSA is a type of sleep-related breathing disorder characterized by recurrent episodes of total (apnea) or partial (hypopnea) upper airway collapse during sleep, despite ongoing respiratory effort, which results in intermittent hypoxia and hypercapnia and terminates in arousal from sleep with reopening of the airway [2].

CSA is a sleep breathing disorder characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. The condition can be primary (i.e., idiopathic CSA) or secondary. Secondary CSA can occur with Cheyne-Stokes breathing (CSB), a medical condition, a drug or substance (such as with narcotics), or high-altitude periodic breathing [3]. CSA is defined as ≥5 central apneas and hypopneas per hour of sleep (central apnea hypopnea index, CAHI ≥ 5) with CAHI accounting for >50% of all respiratory events [4].

The diagnostic and scoring criteria used for SDB are biased toward obstruction, in part due to difficulty reliably differentiating central verses obstructive hypopneas [5]. Central and obstructive physiologies may coexist, the central component often unrecognized clinically, impacting treatment tolerance and efficacy.

The severity of sleep apnea is determined by the number of respiratory events (apneas and hypopneas) per hour of sleep during a sleep study, referred to as the apnea–hypopnea index (AHI). The AHI 4% index requires that hypopneas are associated with at least a 4% decrease in oxygen saturation. The AHI 3% or arousal index, the alternative Academy of Sleep Medicine (AASM) definition, includes hypopneas that are associated with at least 3% decrease in oxygen saturation or an arousal from sleep. The higher the AHI, the more severe the sleep apnea (mild SDB = AHI ≥ 5 and < 15 events/h of sleep; moderate = AHI = 15–30 events and severe = AHI ≥ 30 events) [6]. The respiratory disturbance index (RDI), a marker of sleep fragmentation, includes apneas, hypopneas, and respiratory effort-related arousals (RERAs) per hour of sleep on a sleep study. These different definitions are often used interchangeable in the literature and it is important to know which definition was used (or is recognized by various insurers for treatment coverage) (Figs. 11.1, 11.2, and 11.3).

Prevalence and Risk Factors

SDB is a common disorder. Population-based studies suggest that OSA of all severities affects up to 34% of middle-aged men and 17% of middle-aged women [8]. The prevalence is considerably higher in patients with cardiometabolic disease and continues to rise as the population grows more obese [9–11]. Accurate phenotyping of the different types of sleep apnea is limited using conventional polysomnography such that the true prevalence of CSA remains uncertain.

While OSA is attributable to upper airway anatomy, it is also affected by control of breathing and arousal threshold. CSA (in states of hyperventilation) is primarily due to unstable control of breathing or chemoreflex instability, though upper airway features also contribute. In some patients with SDB, increased arousability or low

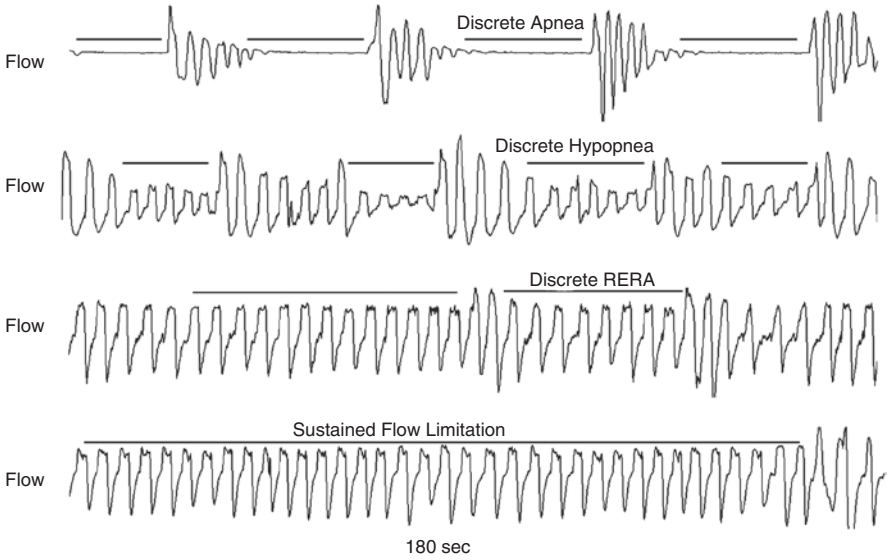


Fig. 11.1 Ventilatory events in sleep-disordered breathing detected in sleep studies. RERA: respiratory effort-related arousal [7]

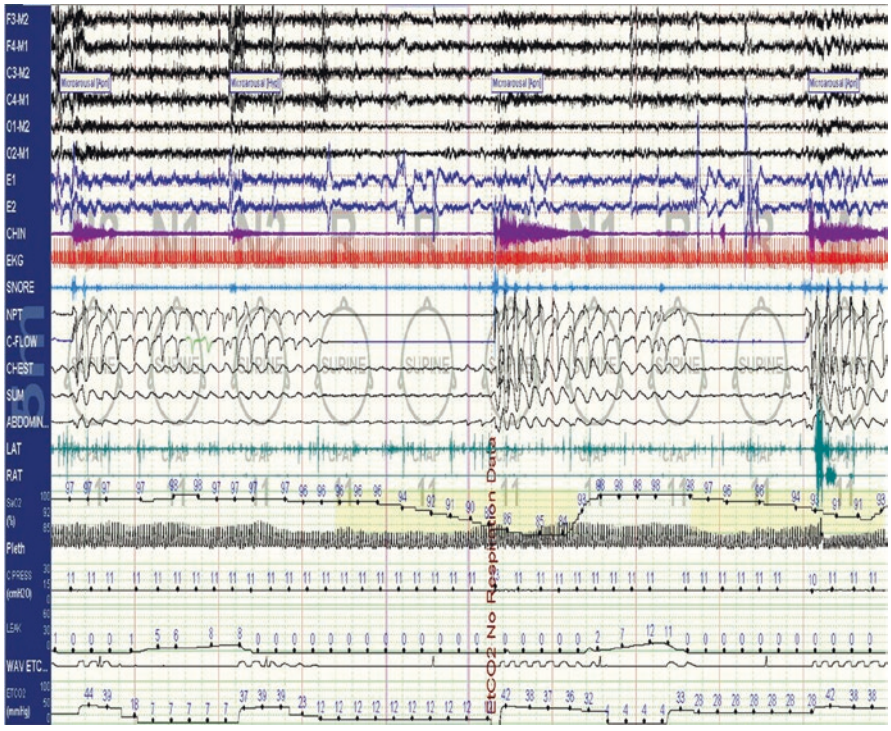


Fig. 11.2 Polysomnogram snapshot from a patient with obstructive sleep apnea with REM-dominant obstructive events. Ten-minute compression, each vertical line is 30 s

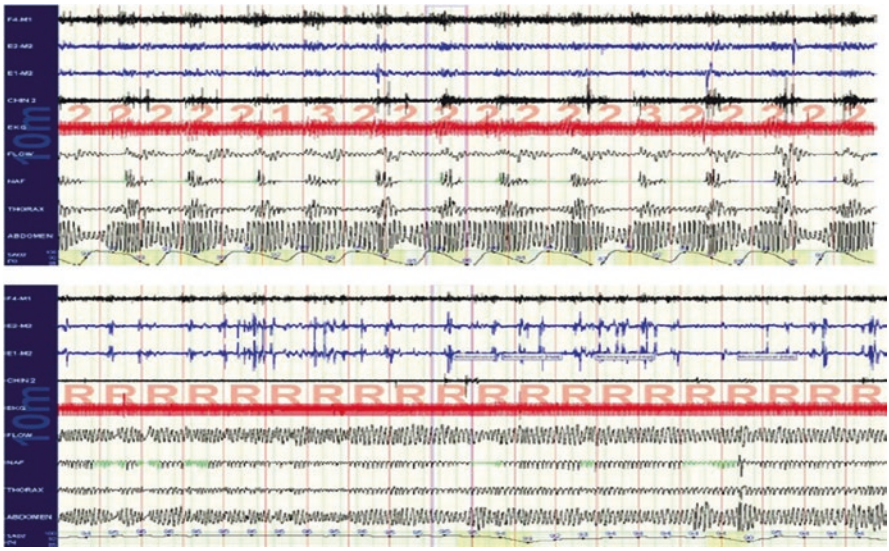


Fig. 11.3 Central sleep apnea with long cycle periodic breathing. Polysomnogram snapshot from a patient with congestive HF. Ten-minute compression, each vertical line is 30 s. In the top portion, depicting non-REM sleep, there is self-similar waxing and waning flow and effort with 45–50 s cycle duration. Breathing stabilizes during the bottom portion, depicting REM sleep

arousal threshold amplifies the abnormalities of upper airway anatomy or breathing control. Obesity is the primary risk factor for OSA. However, 20–40% of patients with OSA are not obese. Certain craniofacial features, such as retrognathia or narrowed nares also contribute. HF is the main cause of CSA.

Pathophysiology

Obstructive Sleep Apnea

There have been significant advances in the understanding of OSA over recent decades. The pathogenesis of OSA is attributed to complex interactions between upper airway anatomy, arousal threshold, and breathing control that alter the balance between forces promoting airway patency and those promoting airway collapsibility. There are four main physiological traits or OSA phenotypes that are recognized: (1) upper airway anatomy that is narrow and/or collapsible; (2) inadequate responsiveness of the upper airway dilator muscles during sleep; (3) low respiratory arousal threshold; and (4) unstable or overly sensitive respiratory control, a concept referred to as high loop gain (defined as a large ventilatory response to a change in ventilation) [12–15].

Anatomic contributions from adipose deposition, soft tissue (i.e., tonsillar hypertrophy, enlarged uvula), craniofacial features (such as small mandible or maxilla and/or narrowed or obstructed nares), large base of tongue, and elongated palate contribute to a reduced cross-sectional area of the upper airway during sleep The impact of body and neck position on the airway lumen, recumbent fluid shifts from the lower extremities and trunk, and snoring-related vibratory damage to intramucosal nerve endings may also contribute to airway collapsibility in OSA. During wakefulness, the pharyngeal dilator muscles (which include the genioglossus) have increased tone known as the "wakefulness drive." These dilator muscles relax during sleep, most pronounced in rapid eye movement (REM) sleep, contributing to upper airways resistance [16, 17]. Other factors that promote upper airways resistance during sleep include negative intrathoracic pressure during apneic events and decreased tracheal tug from reduced lung volumes (especially during supine body position) [18, 19]. Repeated arousals lead to fragmented sleep and result in chronic partial sleep deprivation and possible symptoms of insomnia, excessive daytime sleepiness, decreased quality of life (QOL), mood disturbance, impaired vigilance and attention, and increased risk of motor vehicle and workplace accidents [20]. High loop gain is an exaggerated response of the respiratory system to slight increases in the CO_2 level. An event of OSA causes hypoxia and hypercapnia, leading to an increase in neuronal activity and ventilatory drive and arousal. The increased ventilatory drive in turn results in negative luminal pressure, further increasing the likelihood of airway collapse [21].

Chronic exposure to SDB events is associated with a profile of systemic disturbances that include increased inflammation, oxidative stress, sympathetic activation, fatty acid lipolysis, alterations of the hypothalamic–pituitary axis, endothelial dysfunction, and coagulopathy. These pathophysiologic disturbances are the intermediaries linking OSA to cardiac and metabolic disease.

Central Sleep Apnea

CSA is attributed to heightened peripheral and central chemo-responsiveness. In CSA there is a tendency toward hyperventilation during both sleep and wake, resulting in relative hypocapnia. As a result, one's CO_2 level during sleep (most notably during non-REM) falls below their apnea threshold (hypocapnic apnea threshold, HAT), the level of PaCO2 below which a central apnea occurs. Pulmonary congestion which may occur in HF also contributes to a state of relative hyperventilation [22, 23]. The cycle length (the cycle duration of the periodic breathing pattern) in CSA is proportional to the lung to chemoreceptor circulation time, and inversely proportional to cardiac output. In systolic HF, periodic breathing cycle length is longer (>45 s cycles), while short cycle periodic breathing (<45 s cycles) is seen in idiopathic CSA, high altitude, and complex apnea (when LVEF is preserved) (Fig. 11.4, Table 11.1).

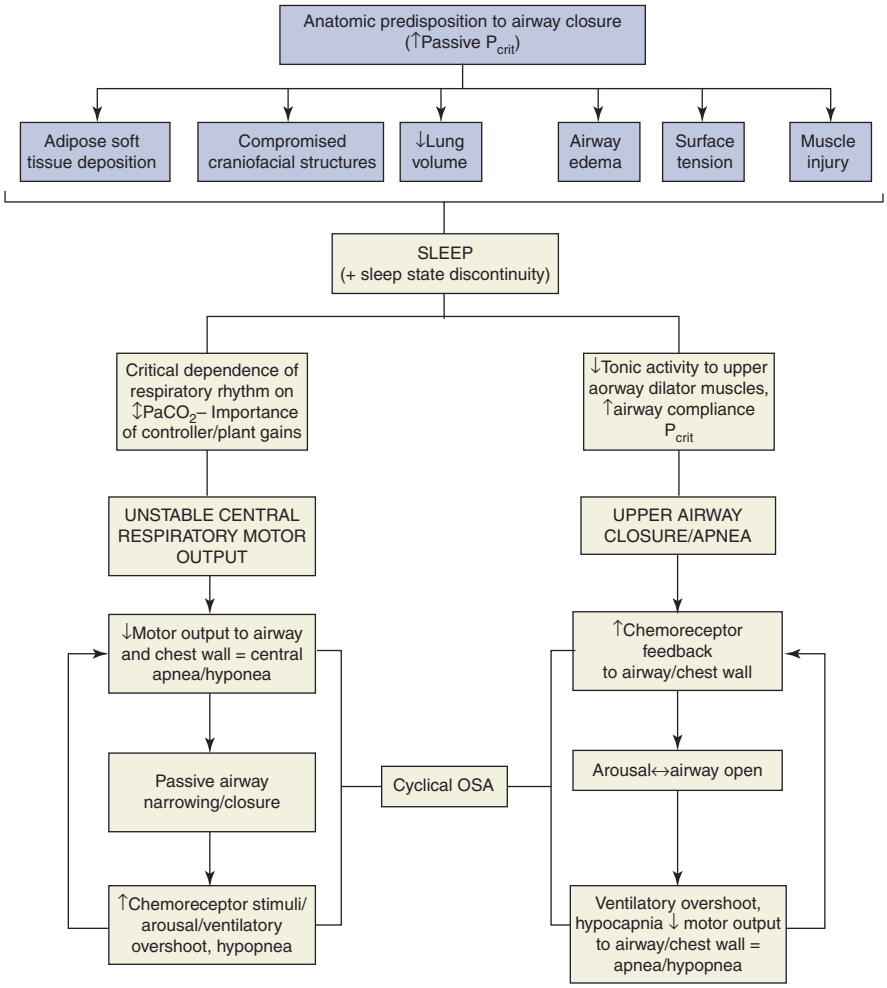


Fig. 11.4 Schematic demonstrating proposed pathogenetic mechanisms leading to obstructive apneas [24]

Table 11.1 OSA and CSA features [25]

Sleep apnea types and characteristics		
Feature	Obstructive sleep apnea	Central sleep apnea, periodic breathing
Fundamental mechanism	Upper airway collapsibility	Decreased (hypercapnic CSA) or increased sensitivity (hypocapnic CSA and PB) of the respiratory chemoreflex
Dominant presentation	Excessive sleepiness/fatigue	Insomnia/fragmented sleep
Sleep stage of expression	REM > NREM (can be nearly exclusively REM)	NREM (can be exclusively NREM)
Visual morphology	Absent or reduced flow during ongoing or increasing effort	Absent of reduced flow with absent effort, or concordant reduction in flow and effort
	Deep "V" shaped oxygen desaturations Individual respiratory event durations tend to vary	PB has metronomic waxing-waning appearance and regular cycle time from one peak or one event to the next (clone/mirror image-like)
	Can cause long periods (tens of seconds) of partially obstructed flow	"Band" oxygen desaturations (consecutive dips are identical over a several minutes)
		Opiates induced NREM-dominant mixtures of obstructive and central apnea, with an ataxic pattern
Associated conditions	Obesity, anatomical narrowing, male gender, and race effects	Heart failure (systolic or diastolic), high altitude. Race effects not known at sea level.
		Hypertrophic cardiomyopathy-typically mixed obstructive and central
		Opiates have unique features—slightly hypercapnic
		COPD, neuromuscular disorders, neurological disorders for hypercapnic CSA
		Craniovertebral junction anomalies including Arnold-Chiari malformation

(continued)

Table 12.1 (continued)

Sleep apnea types and characteristics		
Feature	Obstructive sleep apnea	Central sleep apnea, periodic breathing
Treatments	CPAP, BPAP for pressure intolerance, surgery, treatment of upper airway allergies, oral appliance, Provent (nasal EPAP), and weight loss	Adaptive ventilation, O_2 minimizing hypocapnia, acetazolamide, sedatives
	Surgical approaches include tonsillectomy, nasal turbinate reduction or septoplasty, advancing the tongue base, maxillomandibular advancement	
	Soft tissue reduction uses various techniques, each with relative advantages and disadvantages, including the "standard knife", laser, coblation, somnoplasty.	
Complications	Hypertension, congestive heart failure, stroke, depression, metabolic syndrome and hyperglycemia—these are relatively well established	Atrial fibrillation—possible. This arrhythmia is common (40%) even in young individuals with idiopathic central sleep apnea
	Triggering of cardiac arrhythmias including atrial fibrillation	Progression of heart failure remains unresolved Oxygen desaturations usually not severe enough to cause pulmonary hypertension
	Possibly cancers, via hypoxia induced increases in vascular endothelial growth factor (VGEF) increases; supportive data in humans and rodents is very preliminary but biological plausible	
	Pulmonary hypertension	

SDB evaluation, Screening, and Diagnosis

Despite growing awareness about SDB from health professionals and the public, upwards of 80% of clinically relevant sleep apnea remains undiagnosed, disproportionally impacting women, ethnic and minority groups, and the elderly [26, 27], and routine screening for SDB in the general primary care practice has not been established due to insufficient supporting evidence [28]. However, in subgroups of patients for whom there is a known high prevalence of SDB (as shown in Table 11.2), including those encountered in cardiology practices, screening and evaluation for SDB are strongly advised [31].

Questionnaires and clinical tools can inform screening for sleep apnea and provide insight regarding risk stratification, but no questionnaire or tool is able to definitively rule in or out SDB. Validated questionnaires (shown in Figs. 11.5, 11.6, and 11.7 and Table 11.3) include the following: (1) The Epworth Sleepiness Scale, an eight-question scale used to measure the degree of daytime sleepiness; (2) The Berlin Questionnaire, a ten-question test (divided into three categories) used to

Table 11.2 High-risk conditions for SDB

Severe obesity (BMI > 35 kg/m^2)
Preoperative screening for gastric bypass surgery
Congestive heart failure
Hypertrophic cardiomyopathy
Recurrent atrial fibrillation
Nocturnal dysrhythmias
Treatment-resistant hypertension
Polycystic ovarian syndrome
Congestive heart failure
Type 2 diabetes
Stroke
Pulmonary hypertension
Commercial drivers
Adults with chromosomal abnormalities, such as Down's Syndrome [29, 30]

How likely are you to doze off in the following situations?	No Chance	Slight Chance	Moderate Chance	High Chance
Sitting and reading	❍ 0	❍ 1	❍ 2	❍ 3
Watching television	❍ 0	❍ 1	❍ 2	❍ 3
Sitting inactive, in a public space	❍ 0	❍ 1	❍ 2	❍ 3
Lying down to rest in the afternoon when circumstances permit	❍ 0	❍ 1	❍ 2	❍ 3
Sitting and talking to someone	❍ 0	❍ 1	❍ 2	❍ 3
Sitting quietly after a lunch without alcohol	❍ 0	❍ 1	❍ 2	❍ 3
As a passenger in a car for an hour without a break	❍ 0	❍ 1	❍ 2	❍ 3
In a car, while stopped for a few minutes in traffic	❍ 0	❍ 1	❍ 2	❍ 3
			TOTAL SCORE:	

Fig. 11.5 The Epworth Sleepiness Scale [30, 32]

predict high or low risk for OSA; and (3) The STOP-Bang, a questionnaire focused on identifying SDB risk in the perioperative population. Overnight oximetry is not considered an adequate screening tool for SDB due to loss of data and risk of false-negative (which can be seen in mild, non-hypoxic SDB) and false-positive (movement artifacts) results.

The sleep study, including attended polysomnogram (PSG) and home sleep testing (HST) using portable monitoring (PM), remains the gold standard method to diagnose SDB. Attended or full montage PSG provides information on body position, respiratory pattern (flow and effort), oximetry, heart rate/rhythm (using single lead electrocardiogram), sleep architecture, motor activation, parasomnia activity, and when appropriate, capnography. Type III PMs, which include at least oximetry, nasal pressure and airflow, and respiratory effort (using plethysmography) and usually also body position (via an accelerometer), have been validated to

Berlin Questionnaire

BMI

Male / Female

Category 1

1. Do you snore?
   a. Yes
   b. No
   c. Don't know If you snore
2. Your snoring is:
   a. Slightly louder than breathing
   b. As loud as talking
   c. Louder than talking
   d. Very loud – can be heard in adjacent rooms
3. How often do you snore
   a. Nearly every day
   b. 3-4 times a week
   c. 1-2 times a week
   d. 1-2 times a month
   e. Never or nearly never
4. Has your snoring ever bothered other people?
   a. Yes
   b. No
   c. Don't Know
5. Has anyone noticed that you quit breathing during your sleep?
   a. Nearly every day
   b. 3-4 times a week
   c. 1-2 times a week
   d. 1-2 times a month
   e. Never or nearly never

Category 2:

6. How often do you feel tired or fatigued after your sleep?
   a. Nearly every day
   b. 3-4 times a week
   c. 1-2 times a week
   d. 1-2 times a month
   e. Never or nearly never
7. During your waking time, do you feel tired, fatigued or not up to par?
   a. Nearly every day
   b. 3-4 times a week
   c. 1-2 times a week
   d. 1-2 times a month
   e. Never or nearly never

Fig. 11.6 The Berlin Questionnaire [33]

8. Have you ever nodded off or fallen asleep while driving a vehicle?
   a. Yes
   b. No

If yes: 9. How often does this occur?
   a. Nearly every day
   b. 3-4 times a week
   c. 1-2 times a week
   d. 1-2 times a month
   e. Never or nearly never

Category 3:

10. Do you have high blood pressure?
   Yes
   No
   Don't know

Scoring :

High Risk: if there are 2 or more Categories where the score is positive.
Low Risk: if there is only 1 or no Categories where the score is positive.

Category 1 is positive if the total score is 2 or more.
   Item 1: if 'Yes', assign 1 point
   Item 2: if 'c' or 'd', assign 1 point
   Item 3: if 'a' or 'b', assign 1 point
   Item 4: if 'a', assign 1 point
   Item 5: if 'a' or 'b', assign 2 points

Add points.

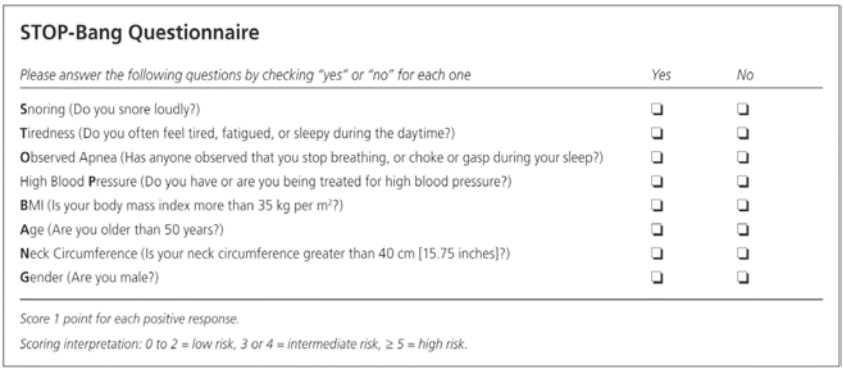
Category 2 is positive if the total score is 2 or more points
   Item 6: if 'a' or 'b', assign 1 point
   Item 7: if 'a' or 'b', assign 1 point
   Item 8: if 'a', assign 1 point
   (item 9 should be noted separately).

Add points.

Category 3 is positive if the answer to item 10 is 'Yes' OR if the BMI of the patient is greater than 30kg/m 2.

Fig. 12.6 (continued)

evaluate for OSA when there is a high pretest probability of moderate or severe disease as determined by a comprehensive sleep evaluation (clinical history, exam, comorbidities). PMs, which lack EEG data and thus provide no sleep stage information or arousal scoring, underestimate the true severity of SDB compared to attended PSG. PM is not recommended for use in conditions concerning for hypoventilation (such as neuromuscular disorders or advanced respiratory disease), cognitive impairment that may preclude ability to perform home testing, or CSA.



STOP-Bang Questionnaire

Please answer the following questions by checking "yes" or "no" for each one	*Yes*	*No*
Snoring (Do you snore loudly?)	❑	❑
Tiredness (Do you often feel tired, fatigued, or sleepy during the daytime?)	❑	❑
Observed Apnea (Has anyone observed that you stop breathing, or choke or gasp during your sleep?)	❑	❑
High Blood **P**ressure (Do you have or are you being treated for high blood pressure?)	❑	❑
BMI (Is your body mass index more than 35 kg per m^2?)	❑	❑
Age (Are you older than 50 years?)	❑	❑
Neck Circumference (Is your neck circumference greater than 40 cm [15.75 inches]?)	❑	❑
Gender (Are you male?)	❑	❑

Score 1 point for each positive response.

Scoring interpretation: 0 to 2 = low risk, 3 or 4 = intermediate risk, ≥ 5 = high risk.

Fig. 11.7 STOP-Bang Questionnaire to assess the risk of obstructive sleep apnea [34]

Table 11.3 Clinical sleep apnea questionnaire and diagnostic accuracy [35]

Questionnaire	Summary of questionnaire contents	Diagnostic accuracy compared with AHI (>15 events/h) [267]
Berlin Questionnaire	10 questions pertaining to the following 3 symptoms/signs:	• *Sensitivity*: 0.77 (0.73–0.81)
	• Snoring	• *Specificity*: 0.44 (0.38–0.51)
	• Daytime sleepiness	
	• Hypertension	
	Patients classified by score as having low risk or high risk of OSA	
STOP Questionnaire	4 questions regarding the following signs/symptoms:	• *Sensitivity*: 0.89 (0.81–0.94)
	• Snoring	• *Specificity*: 0.32 (0.19–0.48)
	• Sleepiness	
	• Observed apneas or choking	
	• Hypertension	
STOP-BANG Questionnaire	4 questions regarding signs/symptoms plus 4 clinical attributes:	• *Sensitivity*: 0.90 (0.86–0.93)
	• Snoring	• *Specificity*: 0.36 (0.29–0.44)
	• Sleepiness	
	• Observed apneas or choking	
	• Hypertension	
	• Obesity (BMI > 35 kg/m^2)	
	• Age (>50 years)	
	• Neck size	
	• Sex	
	Patients classified as low, intermediate, or high risk for OSA	
Epworth Sleepiness Scale	8 questions asking patients to rate the likelihood of falling asleep in various daytime contexts	• *Sensitivity*: 0.47 (0.35–0.59)
	Patients classified as having normal sleep, average sleepiness, or severe and possibly pathologic sleepiness	• *Specificity*: 0.62 (0.56–0.68)

AHI indicates apnea–hypopnea index, *BMI* body mass index, *OSA* obstructive sleep apnea

Treatment for SDB in General

The treatment goals for SDB include normalization of the AHI, preservation of oxygenation, resolution of symptomatology, as well as reduction in attributable cardiovascular disease morbidity and mortality.

Continuous positive airway pressure (CPAP) is considered the gold standard treatment for SDB, especially effective in OSA [28, 30, 36]. Depending upon disease severity, patient preference and comorbidities, and upper airway and physical exam characteristics, a mandibular advancement device (MAD or dental appliance) may be a PAP alternative [37–39]. Most upper airway surgeries are considered adjunctive, not curative for SDB, as they can improve upper airway obstruction to allow for lower efficacious PAP pressure. Maxillomandibular advancement (MMA), a jaw advancement surgery, can provide long-term effective control of OSA in appropriate candidates [40]. Hypoglossal nerve stimulation can be considered in ideal candidates, specifically those with moderate to severe OSA intolerant to CPAP, without severe obesity who have anterior-posterior predominant retropalatal collapse as determined by drug-induced laryngoscopy. The therapy, which involves an implantable device (similar to a pacemaker) that senses chest wall movement and stimulates the hypoglossal nerve during sleep, enlarges the upper airway via contraction of the genioglossus muscle and protrusion of the tongue [41, 42].

Treatment for CSA can be more challenging to optimize. In addition to positive airway pressure treatment, off-label therapies to stabilize breathing and prevent ventilatory overshoot may be needed. Such treatments include medications (acetazolamide, topiramate), carbon dioxide modulation, and supplemental oxygen [43, 44]. Phrenic nerve stimulation, a relatively new therapy for CSA, can also be considered [45].

Weight loss can lower the AHI and should be recommended in overweight and obese patients with SDB [46, 47]. A sleep study should be repeated after substantial weight loss (≥10% of body weight) to assess extent of residual SDB and whether treatment is still indicated or needs adjustment [29]. Body position during sleep impacts the size and patency of the upper airway, typically more narrowed and compromised in supine vs. side position [48, 49]. Positional training with maximization of side and avoidance of supine sleep may help in both OSA and CSA to minimize upper airways resistance and respiratory instability [46, 50–52]. Sedative hypnotic medications can be considered to increase arousal threshold and also to stabilize breathing [44].

Sleep Apnea and Heart Failure

Over 50% of patients with HF have comorbid SDB [53–58]. Moderate to severe SDB has been found to occur in 66% of patents with asymptomatic left ventricular systolic dysfunction [59]. More varied prevalence of SDB has been reported when the LV ejection fraction (EF) is preserved (HFpEF). Lanfranchi and colleagues found that only 25% of patients with HFpEF have SDB, while other studies report similar prevalence of SDB between HFrEF and HFpEF [59, 60]. The prevalence of diastolic dysfunction also increases with worsening severity of OSA [61]. CSA predominates in those with HFrEF, while OSA may be more common in HFpEF. Features of both types of SDB frequently coexist in the same patient, though OSA with high loop gain pathophysiology may be underrecognized clinically.

There are complex bidirectional interactions between HF and SDB pathophysiologies. Relative hypocapnia from pulmonary vascular congestion and heightened central and peripheral chemo-sensitization in HF contributes to ventilatory overshoot, respiratory instability, and central apnea. The prolonged circulation time in HFrEF leads to a long cycle length of PB [62, 63]. SDB promotes sympathoexcitation contributing to catecholamine induced myocyte injury; causes both systemic and pulmonary hypertension; and results in ischemic and inflammatory injury, cardiac remodeling, and cardiac interstitial fibrosis. Chronic exposure to SDB events impacts left ventricular filling resulting in reduction in stroke volume and cardiac output [64], contributes to diastolic dysfunction and chronic pressure overload [65], and is associated with increases in concentric cardiac remodeling (ratio of LV mass and volume) [66]. Echocardiographic indices of dysfunctional diastole (increased E/A ratio or the ratio of peak velocity blood flow from LV relaxation in early diastole to peak velocity flow in late diastole due to atrial contraction and reduced isovolumic relaxation) are more pronounced in patients with SDB compared to controls [61, 67, 68].

Asymptomatic LV dysfunction is a known predictor of incident symptomatic HF, and SDB is a likely contributing factor. In fact, prospective studies have demonstrated that SDB independently predicts new-onset HF in men [69] and in women [70]. A prospective study in which men and women without HF at the time of baseline PSG were followed over nearly 9 years showed that OSA predicted incident HF in men, but not in women, and that men with severe OSA had a 58% increased likelihood of developing HF compared to men without OSA [69]. Prospective data over 14 years from the Atherosclerosis Risk in Communities Study (ARIC) showed a 30% increased incidence of HF or death in women with vs. without SDB [70].

Cheyne-Stokes respiration (CSR) is a predictor of increased HF severity and worse prognosis [71]. The Outcomes of Sleep Disorders in Older Men Study (MrOS) demonstrated that in older men, the presence of CSA and CSR predicted a nearly twofold increased incidence of HF [72]. In patients with HF, SDB is also a predictor of HF exacerbations, impaired QOL, worsening functional status, more frequent hospitalizations, arrhythmias, and increased mortality in patient. A single-center prospective study of nearly 1000 patients with chronic stable HFrEF treated with guideline-based therapy found that patients with comorbid CSA had the lowest survival [73].

Treatment of SDB in HF

Regardless of SDB phenotype, cardiopulmonary and volume status should be medically optimized prior to pursuit of outpatient PSG, as rostral fluid shifts from the lower extremities to the neck and upper airway can worsen obstruction and pulmonary edema can exacerbate sleep hypoxemia and promote respiratory instability [53, 74, 75]. A meta-analysis evaluating the impact of cardiac resynchronization therapy (CRT), also called **biventricular pacing**, on sleep apnea in patients with HFrEF, found a significant reduction in AHI in CSA but not OSA [76]. In patients with HF, the presence of OSA has been shown to be associated not only with a decreased response to CRT but also with an increase in all-cause mortality [77]. Weight loss, when appropriate, and exercise are advised. Compression stockings can help reduce rostral fluid redistribution.

In HF as in any condition, treatment approaches for SDB and demonstrated clinical benefits vary depending on SDB phenotype.

In patients with HF and OSA, CPAP treatment has been show to promote cardiovascular benefits. CPAP use during sleep lowers awake sympathetic nervous system activity [78]. Several studies have shown that CPAP treatment improves LVEF [79–81], including a meta-analysis that found treatment of OSA with CPAP was associated with a 5.2% improvement in LVEF [82]. The reported impact of CPAP use on diastolic function has been inconsistent. While some studies have found no improvement [79], one RCT demonstrated improvement in diastolic dysfunction with CPAP treatment for OSA in patients with HFpEF [83]. In a large retrospective observational study of over 30,000 Medicare beneficiaries (from 2003 to 2005) with newly diagnosed HF and without prior diagnosis of SDB, Javaheri and colleagues found that SDB was highly underdiagnosed (only 4% were suspected to have SDB and only 2% of the cohort were tested). However, those subjects diagnosed with and treated for SDB had fewer readmissions, reduced overall health care cost, and reduced mortality [84]. In light of the available evidence supporting a pathophysiologic relationship between SDB and cardiovascular disease, the American Heart Association recommends screening for and if present treating SDB in patients with HF [85, 86].

Treatment for CSA in HF is more complicated and optimal treatment remains unclear.

While effective in the vast majority of OSA patients, CPAP is only partially effective in patients with CSA. When periodic breathing persists and CSA is not controlled, CPAP use in patients with HF may actually be harmful [87]. Respiratory stimulants, such as theophylline and acetazolamide, can stabilize breathing control in CSA, demonstrated in small studies and RCTs [88, 89]. Heart transplant cures CSA [90].

Adaptive servo-ventilation (ASV), a mode of non-invasive ventilatory treatment created for patients with central or complex sleep apnea, uses an algorithm that continuously adapts to the patient's breathing pattern by delivering an auto-adjusting pressure support to stabilize periodic breathing [91]. The Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure

(SERVE-HF) trial evaluated the impact of ASV (using the RESMED device) on all-cause mortality, life-saving cardiovascular interventions, or unplanned hospitalizations for worsening HF in 1325 patients with symptomatic HFrEF (<45%) and coexisting moderate to severe CSA. Results revealed a significantly higher (34%) increase in CVD mortality in the ASV arm compared to controls, with the most pronounced findings in those with lower LVEF [92]. Potential explanations for the results include notably low adherence in the treatment arm, suboptimal control of CSA with ongoing pressure cycling, excessive ventilation, and possible adverse effects on hemodynamics in vulnerable patients. Given results of the SERVE-HF trial, ASV is felt to be contraindicated to treat predominantly CSA in patients with HFrEF with EF < 35% [93].

Another ongoing Multi-Centre, Randomized Study, the Effect of ASV on Survival and Hospitalizations (ADVENT-HF), anticipated to be completed in August 2021, is testing an alternative ASV device in patients with OSA or CSA. Preliminary data shows superior adherence compared to prior studies.

Use of nocturnal oxygen supplementation (NOS) has been extensively evaluated in CSA. NOS stabilizes chemo-sensitization, reducing respiratory instability, loop gain, and periodic breathing and mitigates sleep hypoxemia and has also been shown to improve exercise capacity [94, 95]. Randomized studies have shown that NOS decreases muscle sympathetic nerve activity (MSNA), LVEF, and QOL [96, 97]. However, additional studies including RCTs are needed to clarify the role of NOS in the treatment of CSA in HF.

Transvenous unilateral phrenic nerve stimulation (**remedē System**, Respicardia, Inc., Minnetonka, MN, USA) is a potential therapy for patients with moderate to severe CSA. The system is a battery-powered device with two leads that is implanted in the upper chest. One lead provides therapy through stimulation of the phrenic nerve to cause movement of the diaphragm, while the other lead senses breathing via changes in intrathoracic pressure. Safety and efficacy data have been published [98]. The Pivotal trial, a prospective, multicenter, RCT of 151 patients with CSA (AHI > 20 events/h with at least 50% central apneas; 64% of those enrolled had HF, including both HFrEF and HFpEF), randomized to 6 months of transvenous unilateral phrenic nerve stimulation (PNS) vs. no stimulation, demonstrated improved severity of sleep apnea (reduction in AHI from 51% to 11%, $p < 0.001$; CAI, ODI), QOL, and daytime sleepiness in the treatment arm. At 12 months, 91% of subjects remained without serious therapy-related adverse events [99].

Sleep-Disordered Breathing and Arrhythmias

Data accumulated from epidemiologic and clinic-based studies shows that up to 60% of patients with SDB demonstrate some types of cardiac arrhythmia during sleep [100–102]. SDB is associated with a variety of cardiac rhythm disturbances including AF, ventricular fibrillation (VF), ventricular tachycardia (VT), premature ventricular complexes (PVCs), accelerated idioventricular rhythm (AIVR), and pronounced bradycardia and sinus arrhythmia [103]. Sudden cardiac death (SCD) has

also been linked to SDB. SDB events have been shown to directly trigger arrhythmia, including episodes of VT and AF, with a 17-fold increase in rate of arrhythmias following apneic episodes compared to normal breathing [104].

There are several proposed mechanisms, supported by experimental data from human and animal studies, linking SDB to cardiac arrhythmia, including intermittent hypoxia and hypercapnia, dysfunctional endothelium, atrial remodeling, inflammation, hypercoagulability, and autonomic dysfunction. Autonomic nervous system fluctuations from OSA may precipitate conduction changes, predisposing the atria to arrhythmia and resulting in atrial remodeling [105]. Repeated changes in intrathoracic pressure that occur during sleep apnea events impact cardiac afterload, atrial size, and also contribute to atrial remodeling [106]. Since increased respiratory effort is absent in CSA, other mechanisms causing sympathoexcitation including intermittent hypoxia, catecholamine excess, and repeated arousals are implicated [107].

Sleep Apnea and Atrial Fibrillation

AF is the most common cardiac arrhythmia. As seen with OSA, AF increases with age and BMI, though there is a stronger association between OSA and AF than between BMI and AF [108]. Both OSA and AF are often asymptomatic and thus are believed to be significantly underdiagnosed conditions.

Multiple epidemiologic, clinic-based, and experimental studies have established a direct association between SDB and AF [109]. Data from the Sleep Heart Health Study (SHHS) and the Osteoporotic Fractures in Men (MrOS) cohort of community dwelling older men show strong associations between SDB severity and arrhythmia [110, 111]. Findings from SHHC showed a two- to threefold higher odds of developing AF in CSA patients compared to controls [112], while data from MrOS showed a fivefold higher odds of AF in those with CSR compared to controls [111]. OSA severity and nocturnal hypoxia are strong predictors of new-onset AF [109]. AF patients with OSA compared to those without have a higher risk of hospitalization and more severe symptomatology [113]. Analysis of SHHS data reveals a temporal relationship between SDB events and episodes of arrhythmia, with an increased risk for paroxysms of AF observed during the 90 s after a respiratory disturbance as compared to normal breathing [104].

The 5-year AF recurrence rate following catheter ablation or cardioversion in general ranges from 25% to 60% [114]. The coexistence of OSA increases the AF recurrence rate by 40% [115].

While AF and OSA share important risk factors and comorbidities, including obesity, increasing age, HTN, and diastolic dysfunction, evidence supports independent causal effects of OSA on cardiac function and structure [116, 117]. Multiple observational studies support that CPAP decreases the risk of AF recurrence following cardioversion and ablation [9, 113, 118–120].

In a cohort ($n = 426$) of AF patients who underwent pulmonary vein isolation (PVI), in which 62 had confirmed OSA, those using CPAP ($n = 32$) had a significant AF-free interval (72% vs. 37%) compared to the untreated OSA patients ($n = 30$) and their

AF-free survival rate was similar to those without OSA [119]. A meta-analysis (which included eight studies, one of which was a RCT) of 698 CPAP users and 549 non-CPAP users after an AF intervention found a 42% decreased risk of AF in those treated with CPAP, with the most pronounced benefit seen in younger, male, and obese patients [121]. Evaluation for and treatment of OSA should be pursued in patients with AF, especially in those with recurrent arrhythmia after cardioversion or ablation procedures.

OSA, Bradycardia, and Sick Sinus Syndrome

SDB event-associated increases in vagal tone promote bradycardia and atrioventricular blocks and contribute to sick sinus syndrome (SSS). In a cohort of 98 patients with implanted pacemakers, 59% were found to have undiagnosed SDB identified by PSG [122, 123]. In patients with moderate to severe OSA who had loop recorders implanted, underwent two 24-Holter recordings, and were followed for 16 months, mostly nocturnal cardiac arrhythmias were detected in 47% of participants, with nearly half displaying severe bradycardic events or prolonged sinus pauses. Arrhythmias were significantly reduced by CPAP, within 8 weeks of use. There was significant weekly variation in the arrhythmia episodes such that the Holter recordings were insufficient at detecting the true prevalence or the beneficial impact of CPAP treatment [124]. A 2-year prospective study of 38 participants (mean age 67, 68% male and 58% with comorbid HTN) with SSS found a considerably higher prevalence of SDB (32%, AHI > 10/h) as compared to in the general population [125].

OSA and Ventricular Arrhythmias

SDB has also been associated with ventricular arrhythmias including ventricular premature complexes, VT, and VF. Patients with OSA have significantly higher frequency of premature ventricular contractions (PVCs) compared to non-OSA patients (67% vs. 0–12%) [100], with the majority occurring during sleep and in association with apneic, not hypopneic episodes [126, 127]. Conversely, in CSA, hypopneas, rather than apneas, are more frequently associated with ventricular ectopy [128]. Namtvedt et al. [129] studied 486 subjects of whom 271 (56%) had OSA and 72 (14.8%) had severe OSA (as defined by AHI ≥ 30/h). Those with increasing severity of OSA had more ventricular premature complexes at night and during the day compared to patients without OSA [129]. Night-time hypoxemia, acidosis, increased sympathetic tone, and alterations in intrathoracic pressure during sleep are plausible explanations for OSA-associated nocturnal ventricular arrhythmias [130–132]. CPAP treatment in OSA has been shown to decrease the 24-h heart rate and reduce PVC frequency during sleep [133, 134].

SDB and Stroke

SDB is not only extremely common, impacting nearly three-quarters of post-stroke patients [135–140], but is associated with worse outcomes, including higher mortality [141–143] and worse functional status [144, 145]. A majority of stroke patients have OSA, with only 7% having primarily CSA, though, as described earlier, central features tend to be underrecognized [146]. Several small studies, one of which identified a relationship only in men but not women, have found that patients with wake-up strokes have a higher prevalence of SDB than patients with non-wake-up strokes [147–149]. Multiple studies have established that SDB is an independent risk factor for incident (twofold increased risk) and recurrent stroke [150]. Given the high prevalence of SDB in patients with stroke, the American Academy of Sleep Medicine's Adult Obstructive Sleep Apnea Task Force considers patients with stroke as a high-risk group for SDB and recommends performing a sleep study in stroke or TIA patients with SDB symptoms [30].

In light of the relationship between SDB and stroke, many studies have evaluated whether CPAP, the gold standard treatment for SDB, improves outcomes after stroke or TIA. Older studies, including several RCTs, have shown inconsistent results, attributed to small numbers with insufficient sample size to detect a treatment effect [139, 140, 151, 152]. More recent studies remain conflicted, but suggest that CPAP treatment, when initiated early for ischemic stroke patients with moderate to severe OSA, improves long-term outcomes [153, 154]. Sleep Apnea Cardiovascular Endpoints (SAVE, 2016) trial, which included 2717 subjects between 45 and 75 years old with CAD or cerebrovascular disease and moderate to severe sleep apnea who were randomized to CPAP plus usual care verses usual care alone and followed for a mean of 3.7 years, found no difference in stroke incidence (a secondary endpoint and component of the primary endpoint) between the two groups [11]. However, interpretation of the study results was limited by exclusion of patients with excessive daytime sleepiness or recent stroke and suboptimal CPAP use in the intervention group (3.3 h overall mean nightly duration, with only 42% using CPAP for ≥4 h) leaving significant residual untreated disease and diminishing ability to identify a difference between the study arms.

Based on the accumulating evidence regarding a relationship between OSA and stroke and suspected benefit of OSA treatment on stroke outcomes, the American Heart Association/American Stroke Association 2014 Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack states "1. A sleep study might be considered for patients with an ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population 2. Treatment with CPAP might be considered for patients with ischemic stroke or TIA and sleep apnea given the emerging evidence in support of improved outcomes" [155].

OSA and Hypertension

Obstructive apneas during sleep are associated with marked oscillations in arterial pressure, heart rate, and ventricular function. In normal human subjects, arterial pressure consistently decreases from waking to stable non-REM sleep. This drop in pressure is primarily attributable to a decline in cardiac output that occurs as a consequence of decreases in heart rate. Numerous clinical studies have established that the normal decrease in arterial pressure is lacking in patients with OSA, i.e., "non-dipping" [9]. Instead, patients with sleep apnea experience repetitive surges in arterial pressure with the peak arterial pressure occurring 5–7 s following apnea termination. These hemodynamic events occur in association with changes in sleep state, chemo-stimulation, lung volume, as well as intrathoracic pressure. These oscillations in pressure may be extreme and are greater in REM than in non-REM sleep even when matching for degree of oxygen desaturation [156]. These pressure increases are further augmented after an arousal from apnea. MSNA recordings from the peroneal nerve in patients with sleep apnea demonstrate a crescendo increase from the beginning to the end of each episode and contribute to increases in systemic vascular tone from a state of chronic sympathoexcitation [130, 157–159]. These patients have elevated levels of circulating catecholamines, angiotensin II, endothelin-1, and aldosterone levels compared with control subjects (Fig. 11.8) [161].

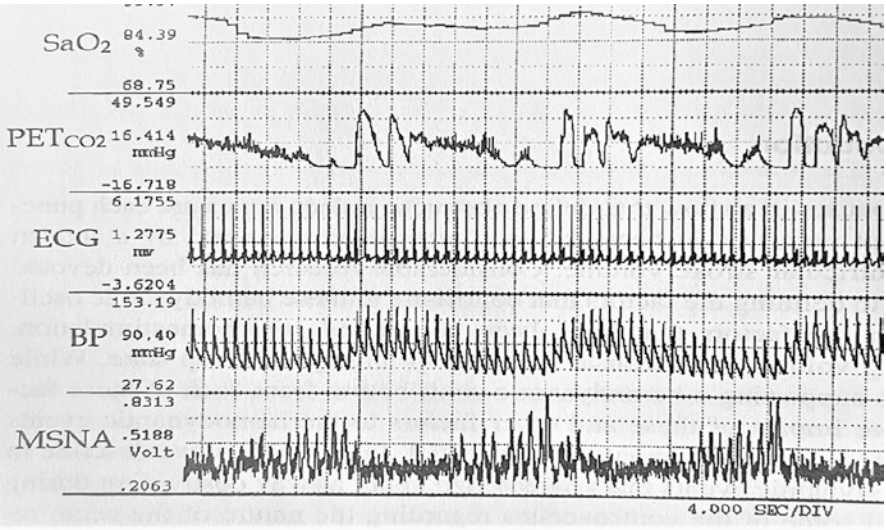


Fig. 11.8 Recording of oxygen saturation (SaO_2), end-tidal carbon dioxide ($PETCO_2$), heart rate on electrocardiogram (ECG), arterial pressure by digital photoplethysmography (PPG, BP below), and muscle sympathetic nerve activity (MSNA) in a patient experiencing repetitive obstructive apneas during sleep. The peaks of arterial pressure occur after the resumption of ventilation [160]

Epidemiologically, the relationship between HTN and SDB is well established. Approximately, 30% of patients with essential HTN have SDB and this increases to 70% in patients with resistant HTN [162]. Moreover, nearly 50% of patients with SDB have HTN [163]. There appears to be a dose response relationship between the severity of OSA and incidence of elevated diurnal blood pressures [164, 165]. The Sleep Heart Health Study (SHHS) ($n = 6132$ patients) found the prevalence of HTN was 59%, 62%, and 67% in mild, moderate, and severe sleep apnea, respectively [166, 167]. The correlation between OSA and isolated diastolic or combined systolic–diastolic HTN was stronger than that for isolated systolic HTN. A pooled meta-analysis estimated a 48% increased risk of HTN among individuals with OSA (pooled Hazard ratio 1.48; 95% CI 1.04–1.91) [168] even after controlling for confounders, such as age and obesity. The seventh national report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (J.N.C. 7) identified OSA as a treatable cause for HTN [169].

It is widely accepted that the use of CPAP for the treatment of sleep apnea portends benefit with respect to blood pressure control, even though the findings have not been universally consistent. Marin and colleagues followed a large cohort of patients for 12 years and found an increased risk for incident HTN among those with untreated OSA compared with those who adhered to a CPAP regimen and a control group (HR of 2.0 vs HR of 0.7) [170]. In a meta-analysis of nearly 1900 patients prescribed CPAP, there was a relatively small reduction in systolic blood pressure (2.6 mmHg) [171]. However, the presence of uncontrolled or resistant HTN at baseline, as well as excessive daytime sleepiness, may be important predictors of a reduction in blood pressure with CPAP therapy, independent of the severity of OSA [172, 173]. The effectiveness of other therapeutic measures, i.e., oral appliances or upper airway surgery on blood pressure are less well studied. A meta-analysis of patients prescribed mandibular advancement therapy for sleep apnea demonstrated similar reductions in systolic and diastolic blood pressures compared to patients prescribed CPAP [174]. It is well established that even small but sustained decreases in blood pressure are associated with meaningful reductions in major cardiovascular outcomes, such as stroke and HF [175]. It is conceivable that the lack of larger reductions in blood pressure with treatment may be attributable to the presence of vascular remodeling from long-standing disease and may suggest a role for early therapy of sleep apnea as primary prevention of HTN.

OSA and CAD

OSA and CAD share many risk factors, including obesity, advancing age, diabetes mellitus (DM), and male gender, promoting their coexistence in patients. Repetitive episodes of upper airway occlusion in OSA lead to intrathoracic negative pressure around the heart, increased left ventricular afterload, and increased myocardial oxygen consumption at a time when oxygen delivery is compromised due to obstructed breathing and hypoxemia. This imbalance between myocardial oxygen demand and

supply is most heightened during REM sleep when apneas are characteristically longer and the severity of intermittent hypoxemia is greater. REM sleep itself has been associated with nocturnal angina, possibly through associated changes in autonomic tone.

In the SHHS [105], a total of 1927 men and 2495 women 40 years of age or older and free of CAD and HF at the time of baseline PSG were followed for a median of 8.7 years in a prospective longitudinal manner. After adjustment for multiple risk factors, OSA was found to be a significant predictor of incident CAD (myocardial infarction, revascularization procedure, or CAD death) in men less than 70 years of age, but not in older men or in women of any age. Among men 40–70 years old, those with severe OSA (AHI $\geq$ 30/h) were 68% more likely to develop CAD than those without OSA (AHI $\leq$ 5/h).

Conversely, SDB is also highly prevalent in patients with CAD. In a cohort of 1425 patients with confirmed CAD starting cardiac rehabilitation who were screened for SDB, the prevalence of SDB (AHI $\geq$ 5/h) was 83%, with moderate to severe SDB (AHI $\geq$ 15/h) present in 53% [104]. Up to 70% of coronary artery bypass graft (CABG) recipients had an AHI $\geq$ 15/h vs. 33% of those who had not undergone CABG.

There is reasonable evidence that the development of significant hypoxemia during sleep in patients with coexisting OSA and CAD can provoke myocardial ischemia reflected by either nocturnal angina or ST segment depression on ECG monitoring. It also appears that the treatment of OSA with nasal CPAP not only treats the OSA but also significantly reduces the prevalence of accompanying myocardial ischemia during sleep.

Multiple prospective cohort studies have been conducted to better understand the relationship between CPAP use and its protective effects on CAD patients. Treatment with CPAP, even for a duration as short as 2 weeks, can reduce sympathetic activation, inflammation, endothelial dysfunction, and oxidative stress [122]. Increased duration of adherence to CPAP demonstrated greater benefits with respect to CAD end-points, such as myocardial infarction, ACS, or stroke [8, 123, 124]. While this was most evident in patients with severe OSA (mean AHI > 42/h) [176], there were also benefits in patients with mild to moderate disease [177]. Moreover, in a multicenter randomized (CPAP vs. no active intervention) trial including 725 patients without history of cardiovascular events who had moderate to severe OSA (AHI > 20/h) and no daytime sleepiness, a post-analysis of the data found that CPAP resulted in significant reduction of blood pressure and cardiovascular events when it was used for at least 4 h each night [178].

OSA and Sudden Cardiac Death

Sudden cardiac death is defined as an unanticipated natural death from cardiac pathology within 1 h of symptom onset in a person without a known prior condition that would appear to be fatal [179]. According to the American Heart Association

(AHA), SCD is a leading cause of CVD mortality, with greater than 379,000 SCDs occurring per year [180].

SDB and nocturnal hypoxia are associated with SCD. In a single-center study of 10,701 patients who underwent PSG and were followed for up to 5 years, Gami and colleagues discovered independent associations between nocturnal oxygen saturation nadir and SCD [181]. Every 10% decrease in nadir O_2 saturation (cohort mean [SD] 93% + 3) was associated with a 14% increase in the risk of SCD [182]. A 2005 retrospective study demonstrated that the relative risk of SCD was 2.57 times higher between midnight and 6 a.m. in patients with OSA compared to the general population and the risk increased with increasing OSA severity [183]. Mutations in SCN5A that alters repolarization and predisposes individuals to ventricular arrhythmias have become increasingly recognized as a contributing factor in SCD [184, 185]. The electrophysiological changes associated with OSA may contribute to nocturnal SCD in patients with channelopathies and altered repolarization [184, 185].

From multiple studies conducted, there is little statistical evidence showing CPAP prevents ventricular arrhythmias and SCD. A study done by Craig et al. which satisfied all four Cochran criteria showed no significant change in ventricular arrhythmias in OSA patients following initiation of CPAP [133]. In another study, the prevalence of PVCs was reduced but the prevalence of VT remained unchanged [186]. Gami et al. have proposed that OSA patients have higher levels of SCD during sleeping hours compared to the rest of the population since patient with OSA lose the cardioprotective period of increased vagal tone and autonomic stability seen in normal sleep [181–183].

Sleep Apnea and Diabetes

The prevalence of DM has increased dramatically in the last three decades, with an estimated 29 million people, or 9.3% of the U.S. population, suspected of having diagnosed or undiagnosed disease and an additional 86 million adults estimated to have pre-diabetes (Centers for Disease Control and prevention, Diabetes 2014 report card). T2DM represents 90–95% of all cases and with nearly 200,000 annual deaths, it ranks as the seventh leading cause of death in the U.S. Diabetes-related microvascular complications and cardiovascular disease are major causes of morbidity, mortality, and worsening QOL for affected patients [187].

Similarly, the adverse health outcomes associated with another global epidemic—the obesity epidemic—has also reached staggering proportions. Increasing rates of weight gain have no doubt played a pivotal role in the rise of pre-diabetes and T2DM. It is estimated that 35–40% of U.S. adults have "Metabolic Syndrome," a term used to ascribe the many health risks associated with "visceral" or "central" obesity (i.e., elevated blood pressure, insulin resistance, and abnormal lipid profiles) [188].

The increased prevalence of OSA (14–55% of the adult U.S. population) has mirrored the surge in obesity over the past two decades. A 4-year follow-up study of

the Wisconsin Sleep Cohort reported that a modest 10% weight gain predicted 32% increase in the AHI as well as sixfold odds of developing moderate to severe OSA. As a corollary, they reported that a 10% weight loss predicted a 26% decrease in AHI [189].

Not surprisingly, the prevalence of OSA is markedly elevated in both community and clinic-based, diverse ethnic cohorts of patients with T2DM, despite being underdiagnosed. Among individuals with OSA, the prevalence of T2DM has been estimated to be between 15% and 30%, with a higher prevalence in those with severe OSA [190–193]. Although obesity is often comorbid with T2DM and OSA, there is growing evidence that the relationship between OSA and T2DM is independent of obesity. OSA severity was shown to be positively associated with the incidence of T2DM independent of adiposity, during 12.8 years (median) of follow-up in a subpopulation ($n = 1453$) of participants of both the SHHS and Atherosclerosis Risk in Communities (ARIC) study [194]. A dose–response association was seen between severity of OSA and incident diabetes. Even after adjusting for adiposity, obese participants with severe OSA were at 2.03-times greater risk of incident diabetes than obese participants without OSA. A meta-analysis of ten studies that included a total of 64,101 participants showed OSA is associated with incident diabetes, with an unadjusted pooled relative risk of 1.62 (95% CI, 1.45–1.80) and an adjusted pooled relative risk of 1.35 (95% CI, 1.24–1.47). The effects size of OSA on T2DM is larger than that for physical inactivity (RR of 1.20) but smaller than that for having a family history of diabetes (RR of 2.33) [195, 196].

Pathophysiology in Relation to T2DM

OSA is a syndrome of cyclic upper airway obstruction that results in bouts of intermittent hypoxemia (IH) and intrathoracic pressure–volume changes that terminate in repetitive cortical micro-arousals and blood pressure surges. Accumulation of excess fat in the neck, which is associated with visceral abdominal obesity, contributes to upper airway narrowing, increased collapsibility, decreased efficiency of dilator muscle contractility, and skeletal muscle dysfunction due to lipid accumulation. There is a convincing literature showing that intermittent hypoxia (IH) and sleep fragmentation in OSA results in sustained increases in MSNA [130] and elevation in markers of local and systemic inflammation [197]. The local and systemic inflammation of OSA may have contributory roles in the development of metabolic derangements, including insulin resistance associated with OSA.

OSA-associated inflammation is thought to arise from mechanical de-formation of the upper airway and intermittent hypoxia. The pattern of oxidative stress seen in OSA is similar to that seen with ischemia–reperfusion injury [198], resulting in acceleration of redox-activated signal transduction pathways. Hypoxia-inducible factor 1-alpha (HIF-1α) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) play key roles in inflammation, especially in adipocytes, hepatocytes, and skeletal muscles [199, 200]. Gaines and colleagues [201] proposed that

central obesity, which precedes the development of OSA and metabolic dysfunction, may itself be a chronic low-grade inflammatory state as it creates conditions that perpetuate a vicious cycle of macrophage recruitment, impaired adipocyte function, and activation of genes that encode pro-inflammatory proteins.

The elevations in sympathetic activity and catecholamine secretion from the hypothalamic–pituitary–adrenal system induced by IH contribute to diurnal hypertension and reduction in insulin sensitivity and insulin-mediated glucose uptake in the peripheral tissues [202, 203]. Elevations in cortisol and norepinephrine levels also effect organs involved in glucose counterregulation (i.e., pancreatic β cell secretion, hepatic glucose production, and adipocyte regulation of energy balance) [204].

A recent analysis of the SHHS demonstrated that OSA in REM stage sleep was independently associated with insulin resistance after controlling for OSA in non-REM sleep [205]. The large declines in interstitial glucose concentration during REM stage sleep in diabetic patients without SDB, likely a result of an increase in cerebral glucose utilization, were abolished in those patients with OSA. Using continuous interstitial glucose monitoring simultaneously with polysomnography, Bialasiewicz and colleagues found that the mean glucose levels were 38% higher during REM stage sleep in those patients with OSA [206]. This finding that OSA during REM sleep is adversely associated with glucose metabolism in patients with T2DM may have important therapeutic implications regarding the duration/timing of nightly CPAP usage, as REM stage sleep tends to cluster in the second half of the sleep period [207].

The relationship between diabetes and OSA is felt to be bidirectional and insulin resistance is a suspected link. OSA is not only prevalent in patients with T2DM but also in those with Type I DM, including younger and non-obese patients [208, 209]. OSA is frequent in disorders in which insulin resistance is a primary pathophysiologic abnormality. Obese women with polycystic ovarian syndrome (PCOS) have significantly higher fasting insulin levels than non-obese women with PCOS. Vgontzas and colleagues have reported that insulin resistance is the strongest risk factor for OSA in women with PCOS, stronger than even BMI or testosterone levels [210]. A study of 30 patients with T2DM hospitalized for intensification of glycemic control found not only did nocturnal glycemic profiles improved significantly but this improvement was also accompanied by 32% reduction in the 4% AHI after just 5 days. These patients did not experience any change in body weight, neck circumference, or self-reported sleep duration [211].

Screening for OSA in Patients with T2DM

In 2008, the International Diabetes Federation Task Force on epidemiology and prevention recommended that health professionals caring for patients with either T2DM or SDB consider screening patients presenting with one condition for the other. The report acknowledged that untreated OSA is associated with worse

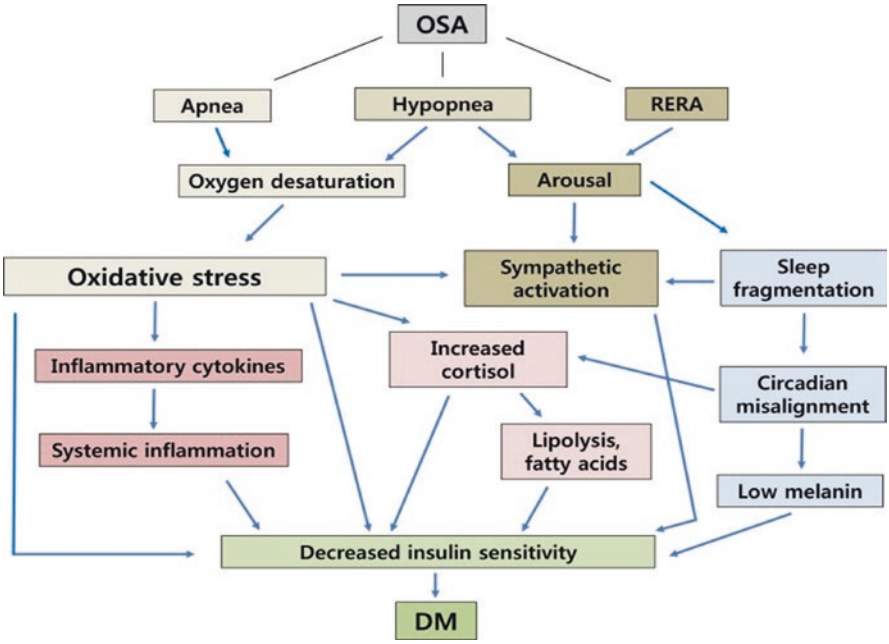


Fig. 11.9 Proposed interactions between obstructive sleep apnea (OSA) and diabetes. RERA: respiratory effort-related arousal; DM: diabetes mellitus [214]

glycemic control [212]. Westlake and colleagues compared the Berlin and Stop-Bang questionnaires with HST in 294 patients with T2DM and found that both questionnaires had low sensitivity and specificity [213]. In 2017, the American Diabetes Association recognized OSA as an important co-morbidity of T2DM and noted the benefits of OSA treatment on blood pressure control and QOL in patients with T2DM. Hence, clinicians should consider working up a diagnosis of sleep apnea using a HST monitoring devices in diabetic patients, if clinically appropriate (Fig. 11.9) [215].

Treatment

CPAP remains the gold standard treatment for patients with moderate to severe OSA with and without diabetes even though there are alternative therapies that may provide equivalent efficacy. The application of positive airway pressure establishes airway patency and has been associated with few arousals, lower AHI, improved oxygen saturation, and decreased daytime sleepiness. However, results from studies evaluating the effect of CPAP therapy on glycemic control and other markers of

inflammation have been inconsistent, despite showing evidence for improved insulin sensitivity in patients with severe disease.

In a proof-of-concept study, Mokhlesi at al. assigned 13 patients with OSA and T2DM to either nightly CPAP or sham CPAP for 1 week under nightly observation in the sleep laboratory to ensure full compliance with the allocated treatment. Using a 24-h blood sampling technique, the mean plasma glucose levels decreased significantly after 1 week of active versus sham CPAP treatment. This decrease was also associated with a trend toward lower 24-h mean insulin levels. Improvement in glucose levels was most prominent during the overnight period. Of interest, the beneficial effect with CPAP was larger in magnitude in patients with poor glycemic control at baseline [216].

There are many studies that have explored the effect of CPAP in patients with T2DM with follow-up of 1–6 months. Several randomized controlled trials have reported improvements in metabolic control, i.e., insulin sensitivity and glucose tolerance in patients with OSA treated with CPAP as compared to sham CPAP [217–219]. However, many of these studies showed no consistent effect of CPAP on glycemic control [220, 221]. In a randomized clinical trial consisting of 888 participants in the SAVE trial who were followed up for median of 4.3 years, there was no evidence that CPAP therapy affected glycemic control in those with diabetes, prediabetes, or diabetes risk over standard-of-care treatment [222]. Another recent randomized trial demonstrated improvements in inflammation, insulin resistance and serum triglycerides only in patients with OSA who combined their CPAP use with weight loss during a 24-week period [223].

These conflicting results are in large part a function of differences in baseline glycemic status, timing from disease onset/diagnosis, varying degrees of CPAP adherence and efficacy, different methodology to assess glucose metabolism, and the use of anti-hyperglycemic agents, the numbers of which have been increasing. Some of the newer diabetic medications have focused on weight loss effects along with improving glycemic control. Therapies designed to reduce visceral adiposity may address the systemic root cause of OSA and DM in many patients. Bariatric surgery is considered an effective treatment for both diabetes and sleep apnea. It is now a recommended treatment for patients with diabetes and a BMI of greater than 40 kg/m^2, with inadequate glycemic control despite lifestyle changes and optimal medical therapy.

Despite the inconclusive results, it is important to acknowledge the other benefits of CPAP in diabetic patients with OSA. Reduction in daytime sleepiness and improved QOL are favorable outcomes. CPAP does improve blood pressure control, likely a consequence of decreases in sympathetic tone which may have significant benefits on the microvascular complications of diabetes [224–226].

Additional longer-term and larger studies are needed to explore if effective treatment of sleep apnea can reduce the risk of developing T2DM. Such studies should explore the role of various lifestyle modifications, including weight reduction and physical activity, combined with CPAP therapy as a primary prevention strategy for pre-diabetes and T2DM early in the disease process.

Sleep-Disordered Breathing and High-risk Pregnancy Conditions

Preeclampsia, a potentially fatal, multisystem, progressive disorder of pregnancy impacting at least 5% of pregnancies worldwide, is a major cause of maternal and fetal morbidity and mortality. It is characterized by either new-onset HTN and proteinuria or HTN and end-organ dysfunction. The disorder typically occurs after 20-weeks gestation, but at times occurs post-partum, in previously normotensive women. The condition can also be superimposed on previously existing/chronic HTN. Gestational HTN is part of the preeclampsia spectrum. Gestational diabetes increases risk of developing both gestational HTN and preeclampsia.

The pathogenesis of preeclampsia is attributed to a combination of maternal and fetal/placental factors that promote placental oxidative stress and vascular reactivity and result in maternal systemic vascular and endothelial dysfunction, inflammation, and increased sympathoexcitation. Untreated OSA results in similar systemic pathophysiologic effects which are believed to be among the mediators linking OSA to cardiometabolic disease manifestations. Given the shared pathophysiology and mediators between OSA and preeclampsia, combined with weight gain, edema, and hormonal alterations of pregnancy that may increase the risk of developing or worsen pre-existing OSA, untreated OSA has been implicated as a potential contributor to the development of gestational diabetes, hypertensive disease of pregnancy, and preeclampsia.

The prevalence of OSA in pregnancy is not known. However, an increased report of snoring in pregnant women, compared to pre-menopausal non-pregnant women (14–45% compared to 4%) has been shown in numerous studies, though the presence of a bed partner may confound such findings [227–233]. Obesity, a major risk factor for OSA, is increasing in prevalence—between 2005 and 2014, 50% of women in the US were overweight or obese, 37% of reproductive-age women were obese, and 10% were morbidly obese (BMI 40 kg/m^2) [233]. Obese pregnant women are also more likely to have OSA [234]. Small studies using PSG to diagnose OSA in pregnant women have shown that OSA becomes more frequent later in pregnancy. In a study of 105 pregnant women with mean BMI of 33.4 kg/m^2, 26.7% in third trimester vs. 10.5% in first trimester were found to have OSA (AHI $\geq$ 5/h) [235], while another study found moderate OSA (AHI $\geq$ 15/h) in 20% of subjects studied at 48 h post-delivery [236]. In a small case–control study, the prevalence of OSA, as diagnosed by PSG (AHI 4% or arousal $\geq$5/h), was 14/17 (82%) in hypertensive, compared to 15/33 (45%) in normotensive pregnant women [237]. The primary risk factors for OSA in pregnancy include older maternal age, obesity, snoring, and history of chronic hypertension [236, 238].

OSA remains underdiagnosed both in the general population and in pregnancy. No SDB-related screening questionnaires have been specifically validated in pregnant women [239]. One prospective trial found low predictive parameters and high false-negative referral rates for pregnant woman with positive OSA screening by either the Epworth Sleepiness Scale or the Berlin questionnaire [240]. In a single,

large (over 1000 subjects analyzed) prospective trial of pregnant women, using generalized linear modeling, screening positive on the Berlin Questionnaire, but not with the Epworth Sleepiness Scale, was positively associated with hypertensive disorders of pregnancy [240]. The specificity of the STOP-Bang questionnaire increases from 37% to 85% for all OSA severities when the serum bicarbonate level is greater than 28 mEq/L in addition to a score ≥3 [241]. Although not validated in pregnancy, adding a serum bicarbonate level greater than 28 mEq/L to scores ≥3 for the STOP-Bang questionnaire may be useful in pregnancy, since serum bicarbonate levels in pregnant women are normally lower due to respiratory alkalosis [242].

Sleep apnea is more prevalent in pregnant women with high-risk pregnancy disorders than those without. While some small studies without objective testing to determine OSA have shown inconsistent results, studies that have used hypertensive disorders of pregnancy as an inclusion criteria and conducted objective testing for OSA via portable of attended PSG have found a greater prevalence of OSA in women with hypertensive disorders of pregnancy and preeclampsia [243, 244].

Pregnant women with sleep apnea also have a higher risk of adverse maternal and fetal outcomes compared to pregnant women without sleep apnea, shown in questionnaire studies, several large retrospective data-base studies, systematic reviews and meta-analyses. Associations between OSA symptoms and gestational HTN have been demonstrated [231, 232, 245–249]. Compared to pregnant women without OSA, pregnant women with OSA have a significantly higher risk of pregnancy-specific, medical and surgical complications including longer length of stay and need for Intensive Care Unit (ICU) admissions [249]. Data from the US National perinatal information center (from 2010 to 2014, including 1,577,632 pregnant women, using ICD 9 codes) showed that pregnant women with OSA have increased risk of GDM (adjusted OR 1.51, 95% CI 1.34–1.72), PEC (adjusted OR 2.22, 95% CI 1.94–2.54), and eclampsia (adjusted OR 2.95, 95% CI 1.08–8.02) and a 2.5- to 3.5-fold increase in risk of severe complications (cardiomyopathy, congestive heart failure, total abdominal hysterectomy, ICU stay and hospital length of stay) [249]. A large retrospective cross-sectional analysis using the Nationwide Inpatient Sample (NIS) database (which included almost 56 million pregnancy-related inpatient hospital discharges) found that OSA was associated with increased odds of pregnancy-related morbidities (including PEC, eclampsia, pulmonary embolism, cardiomyopathy) and that women with OSA had a fivefold increased odds of in-hospital death [250]. Pamidi and colleagues, in a systematic review and meta-analysis, found that maternal sleep apnea was significantly associated with gestational HTN and preeclampsia (pooled adjusted odds ratio (OR) 2.34; 95% confidence interval [CI], 1.60–3.09; 5 studies), and gestational diabetes (pooled aOR, 1.86; 95% CI, 1.30–2.42; 5 studies) [248]. Self-reported poor-quality sleep has been associated with longer labor, cesarean section, and preterm births [251, 252]. Obesity, which is becoming increasingly common in women at the time of conception [234], is a major risk factor for both OSA and preeclampsia, and is also associated with increased cesarean sections [253]. Diagnosed OSA in pregnancy has also been associated with poor fetal outcomes [254, 255].

Treating OSA in pregnancy may have important beneficial effects on maternal and fetal health. Two consecutive PSG studies (baseline followed by auto-titrating nasal CPAP) with simultaneous continuous blood pressure monitoring conducted in 11 women with preeclampsia found to have upper airways obstruction during sleep resulted in reduction in blood pressure on the treatment night [(128 ± 3)/(73 ± 3)] when compared with the initial non-treatment study night [(146 ± 6)/(92 ± 4)], p = (0.007)/(0.002) [256]. In women with gestational diabetes, HTN, and obesity who have OSA, CPAP treatment improves maternal and fetal outcomes, when compared to pregnant women with untreated OSA [256, 257]. Inspiratory airflow limitation and improvement in vascular reactivity and HTN have also been demonstrated with CPAP treatment in preeclampsia [258].

Rather than an isolated, though potentially morbid event of pregnancy, placental implantation disorders are actually a marker of future gestational complications and later in life cardiovascular events for both mothers and their offspring [259–261]. Since the mid-1990s evidence from retrospective and prospective epidemiological registries, clinical studies, systematic reviews, and meta-analyses has been accumulating showing that women with placental implantation disorders (such as gestation HTN and preeclampsia) are at an increased risk for long-term cardiovascular disease (including HTN, CAD, myocardial infarction, stroke, peripheral arterial disease, thromboembolism, and HF). Recent systematic reviews and meta-analyses provide strong support of the association of preeclampsia and future CVD [259, 262, 263], such that the American Heart Association now recommends that a history of preeclampsia be considered a major risk factor for cardiovascular and cerebrovascular disease [264, 265]. A large (n = 506,350 women) prospective registry-based study from Norway found that the severity of the placental implantation disorders resulted in additive risk for occurrence of major coronary events: 2.1-fold in those with history of preeclampsia, and 3.3-fold and 5.4-fold, respectively, when maternal preeclampsia was combined with intrauterine growth retardation or preterm birth [266].

OSA as a possible contributor to hypertensive disease of pregnancy and preeclampsia and may be an intervenable target to halt the progression of life-long cardiovascular disease in women with high-risk pregnancy conditions and their offspring. More studies are needed to inform optimal timing for OSA assessment and treatment and to better clarify the effect of treating OSA on maternal and fetal outcomes.

Summary and Future Directions

SDB is common in the general population, but even more prevalent in patients with comorbid cardiac and metabolic disease. Chronic exposure to SDB events is associated with a profile of systemic disturbances that are felt to contribute to and exacerbate the progression of cardiometabolic disease, while treatment of SDB has beneficial effects on these disorders and their progression. Treatment of OSA

lowers blood pressure, reduces rates of refractory HTN, increases left ventricular ejection fraction, decreases ventricular ectopy and the recurrences of and progression of AF, and may improve blood glucose control. CPAP, when used consistently in OSA and when the treatment is efficacious, leads to reduction in cardiac and cerebrovascular events and improvement in mortality. CSA is associated with worsened HF outcomes, though the impact of treatment of CSA on cardiovascular outcomes has not yet been clearly elucidated. Features of OSA and CSA often coexist in the same patient. Recognition of SDB phenotypes and their coexistence can inform treatment approaches and improve treatment tolerance, adherence, and clinical benefit. Randomized control trials, with attention to disease phenotype and optimal therapies, may provide further unbiased assessment of the impact of SDB treatment on cardiovascular disease morbidity and mortality.

References

1. Shahar E, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163(1):19–25.
2. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014;383(9918):736–47.
3. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387–94.
4. Berry RB, et al. AASM scoring manual updates for 2017 (Version 2.4). J Clin Sleep Med. 2017;13(5):665–6.
5. Zinchuk AV, Thomas R. Central sleep apnea: diagnosis and management. In: Kryger M, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia, PA: Elsevier; 2017. p. 1059–1075.e6.
6. Berry RB, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597–619.
7. Rapoport DM, Mitchell JJ. Pathophysiology, evaluation, and management of sleep disorders in the mucopolysaccharidoses. Mol Genet Metab. 2017;122S:49–54.
8. Peppard PE, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006–14.
9. Javaheri S, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. J Am Coll Cardiol. 2017;69(7):841–58.
10. Kendzerska T, et al. Untreated obstructive sleep apnea and the risk for serious long-term adverse outcomes: a systematic review. Sleep Med Rev. 2014;18(1):49–59.
11. McEvoy RD, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375(10):919–31.
12. Eckert DJ, et al. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med. 2013;188(8):996–1004.
13. Smith PL, et al. Upper airway pressure-flow relationships in obstructive sleep apnea. J Appl Physiol. 1988;64(2):789–95.
14. Wellman A, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol. 2011;110(6):1627–37.
15. Younes M, et al. Chemical control stability in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2001;163(5):1181–90.

16. Pepin JL, et al. The upper airway resistance syndrome. Respiration. 2012;83(6):559–66.
17. Patil SP, et al. Adult obstructive sleep apnea: pathophysiology and diagnosis. Chest. 2007;132(1):325–37.
18. Begle RL, et al. Effect of lung inflation on pulmonary resistance during NREM sleep. Am Rev Respir Dis. 1990;141(4 Pt 1):854–60.
19. Owens RL, et al. The influence of end-expiratory lung volume on measurements of pharyngeal collapsibility. J Appl Physiol. 2010;108(2):445–51.
20. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. Nat Sci Sleep. 2017;9:151–61.
21. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - new pathways for targeted therapy. Sleep Med Rev. 2018;37:45–59.
22. Dempsey JA, et al. The ventilatory responsiveness to CO(2) below eupnoea as a determinant of ventilatory stability in sleep. J Physiol. 2004;560(Pt 1):1–11.
23. Eckert DJ, et al. Central sleep apnea: pathophysiology and treatment. Chest. 2007;131(2):595–607.
24. Dempsey JA, et al. Pathophysiology of sleep apnea. Physiol Rev. 2010;90(1):47–112.
25. Thomas RJ, Pogach M. Sleep disordered breathing. In: Baliga RR, editor. Baliga's textbook of internal medicine: an intensive board review book with 1480 multiple choice questions. An imprint of MasterMedFacts LLC: Blendon-Miller; 2018.
26. Redline S, et al. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds. The Hispanic Community Health Study/Study of Latinos. Am J Respir Crit Care Med. 2014;189(3):335–44.
27. Chen X, et al. Racial/ethnic differences in sleep disturbances: the multi-ethnic study of atherosclerosis (MESA). Sleep. 2015;38(6):877–88.
28. Jonas DE, et al. Screening for obstructive sleep apnea in adults: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2017;317(4):415–33.
29. Kushida CA, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499–521.
30. Epstein LJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5(3):263–76.
31. Redline S. Screening for obstructive sleep apnea: implications for the sleep health of the population. JAMA. 2017;317(4):368–70.
32. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540–5.
33. Netzer NC, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131(7):485–91.
34. Chung F, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008;108(5):812–21.
35. Tietjens JR, et al. Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. J Am Heart Assoc. 2019;8(1):e010440.
36. Patel SR, et al. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. Arch Intern Med. 2003;163(5):565–71.
37. Chen H, et al. Phenotypes of responders to mandibular advancement device therapy in obstructive sleep apnea patients: a systematic review and meta-analysis. Sleep Med Rev. 2020;49:101229.
38. Kushida CA, et al. Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. Sleep. 2006;29(2):240–3.
39. Carvalho B, Hsia J, Capasso R. Surgical therapy of obstructive sleep apnea: a review. Neurotherapeutics. 2012;9(4):710–6.
40. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev. 2010;14(5):287–97.

41. Strollo PJ Jr, et al. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med. 2014;370(2):139–49.
42. Maresch KJ. Hypoglossal nerve stimulation: effective longterm therapy for obstructive sleep apnea. AANA J. 2018;86(5):412–6.
43. Edwards BA, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Physiol. 2012;590(5):1199–211.
44. Thomas RJ. Alternative approaches to treatment of Central Sleep Apnea. Sleep Med Clin. 2014;9(1):87–104.
45. Fudim M, et al. Phrenic nerve stimulation for the treatment of central sleep apnea: a pooled cohort analysis. J Clin Sleep Med. 2019;15(12):1747–55.
46. Morgenthaler TI, et al. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep. 2006;29(8):1031–5.
47. Kuna ST, et al. Effects of weight loss on obstructive sleep apnea severity. ten-year results of the sleep AHEAD study. Am J Respir Crit Care Med. 2021;203(2):221–9.
48. Kim WY, et al. The effect of body position on airway patency in obstructive sleep apnea: CT imaging analysis. Sleep Breath. 2019;23(3):911–6.
49. Pevernagie DA, et al. Effects of body position on the upper airway of patients with obstructive sleep apnea. Am J Respir Crit Care Med. 1995;152(1):179–85.
50. Jokic R, et al. Positional treatment vs continuous positive airway pressure in patients with positional obstructive sleep apnea syndrome. Chest. 1999;115(3):771–81.
51. Cartwright R, et al. A comparative study of treatments for positional sleep apnea. Sleep. 1991;14(6):546–52.
52. Benoist L, et al. A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. Sleep Med. 2017;34:109–17.
53. Lyons OD, Bradley TD. Heart failure and sleep apnea. Can J Cardiol. 2015;31(7):898–908.
54. Pearse SG, Cowie MR. Sleep-disordered breathing in heart failure. Eur J Heart Fail. 2016;18(4):353–61.
55. Javaheri S, Javaheri S, Javaheri A. Sleep apnea, heart failure, and pulmonary hypertension. Curr Heart Fail Rep. 2013;10(4):315–20.
56. Vazir A, et al. A high prevalence of sleep disordered breathing in men with mild symptomatic chronic heart failure due to left ventricular systolic dysfunction. Eur J Heart Fail. 2007;9(3):243–50.
57. Bitter T, et al. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail. 2009;11(6):602–8.
58. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):136–43.
59. Lanfranchi PA, et al. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation. 2003;107(5):727–32.
60. Herrscher TE, et al. High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function. J Card Fail. 2011;17(5):420–5.
61. Wachter R, et al. Impact of obstructive sleep apnoea on diastolic function. Eur Respir J. 2013;41(2):376–83.
62. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J Physiol. 2013;591(5):1179–93.
63. Dempsey JA, et al. Role of central/peripheral chemoreceptors and their interdependence in the pathophysiology of sleep apnea. Adv Exp Med Biol. 2012;758:343–9.
64. Querejeta Roca G, Shah AM. Sleep disordered breathing: hypertension and cardiac structure and function. Curr Hypertens Rep. 2015;17(12):91.
65. Bodez D, et al. Consequences of obstructive sleep apnoea syndrome on left ventricular geometry and diastolic function. Arch Cardiovasc Dis. 2016;109(8–9):494–503.
66. Alonderis A, et al. The association of sleep disordered breathing with left ventricular remodeling in CAD patients: a cross-sectional study. BMC Cardiovasc Disord. 2017;17(1):250.
67. Aslan K, et al. Early left ventricular functional alterations in patients with obstructive sleep apnea syndrome. Cardiol J. 2013;20(5):519–25.

68. Glantz H, et al. Obstructive sleep apnea is independently associated with worse diastolic function in coronary artery disease. Sleep Med. 2015;16(1):160–7.
69. Gottlieb DJ, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122(4):352–60.
70. Roca GQ, et al. Sex-specific association of sleep apnea severity with subclinical myocardial injury, ventricular hypertrophy, and heart failure risk in a community-dwelling cohort: the atherosclerosis risk in communities-sleep heart health study. Circulation. 2015;132(14):1329–37.
71. Andreas S, et al. Cheyne-Stokes respiration and prognosis in congestive heart failure. Am J Cardiol. 1996;78(11):1260–4.
72. Javaheri S, et al. Sleep-disordered breathing and incident heart failure in older men. Am J Respir Crit Care Med. 2016;193(5):561–8.
73. Oldenburg O, et al. Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. Eur Heart J. 2016;37(21):1695–703.
74. Mendelson M, et al. Effects of exercise training on sleep apnoea in patients with coronary artery disease: a randomised trial. Eur Respir J. 2016;48(1):142–50.
75. Chenuel BJ, et al. Increased propensity for apnea in response to acute elevations in left atrial pressure during sleep in the dog. J Appl Physiol. 2006;101(1):76–83.
76. Lamba J, et al. Cardiac resynchronization therapy for the treatment of sleep apnoea: a meta-analysis. Europace. 2011;13(8):1174–9.
77. Shantha G, et al. Role of obstructive sleep apnea on the response to cardiac resynchronization therapy and all-cause mortality. Heart Rhythm. 2018;15(9):1283–8.
78. Usui K, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. J Am Coll Cardiol. 2005;45(12):2008–11.
79. Johnson CB, et al. Acute and chronic effects of continuous positive airway pressure therapy on left ventricular systolic and diastolic function in patients with obstructive sleep apnea and congestive heart failure. Can J Cardiol. 2008;24(9):697–704.
80. Kaneko Y, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med. 2003;348(13):1233–41.
81. Mansfield DR, et al. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med. 2004;169(3):361–6.
82. Sun H, et al. Impact of continuous positive airway pressure treatment on left ventricular ejection fraction in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. PLoS One. 2013;8(5):e62298.
83. Arias MA, et al. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation. 2005;112(3):375–83.
84. Javaheri S, et al. Sleep apnea testing and outcomes in a large cohort of Medicare beneficiaries with newly diagnosed heart failure. Am J Respir Crit Care Med. 2011;183(4):539–46.
85. Writing Committee M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240–327.
86. Yancy CW, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136(6):e137–61.
87. Arzt M, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation. 2007;115(25):3173–80.
88. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med. 2006;173(2):234–7.
89. Javaheri S, et al. Effect of theophylline on sleep-disordered breathing in heart failure. N Engl J Med. 1996;335(8):562–7.

90. Javaheri S, et al. Prevalence of obstructive sleep apnoea and periodic limb movement in 45 subjects with heart transplantation. Eur Heart J. 2004;25(3):260–6.
91. Priou P, et al. Adaptive servo-ventilation: how does it fit into the treatment of central sleep apnoea syndrome? Expert opinions. Rev Mal Respir. 2015;32(10):1072–81.
92. Cowie MR, et al. Adaptive servo-ventilation for central sleep apnoea in systolic heart failure: results of the major substudy of SERVE-HF. Eur J Heart Fail. 2018;20(3):536–44.
93. Bradley TD, Floras JS, A.-H. Investigators. The SERVE-HF trial. Can Respir J. 2015; 22(6):313.
94. Andreas S, et al. Improvement of exercise capacity with treatment of Cheyne-Stokes respiration in patients with congestive heart failure. J Am Coll Cardiol. 1996;27(6):1486–90.
95. Bordier P, et al. Nocturnal oxygen therapy in patients with chronic heart failure and sleep apnea: a systematic review. Sleep Med. 2016;17:149–57.
96. Staniforth AD, et al. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. Eur Heart J. 1998;19(6):922–8.
97. Javaheri S. Pembrey's dream: the time has come for a long-term trial of nocturnal supplemental nasal oxygen to treat central sleep apnea in congestive heart failure. Chest. 2003;123(2):322–5.
98. Zhang XL, et al. Transvenous phrenic nerve stimulation in patients with Cheyne-Stokes respiration and congestive heart failure: a safety and proof-of-concept study. Chest. 2012;142(4):927–34.
99. Costanzo MR, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. Lancet. 2016;388(10048):974–82.
100. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol. 1983;52(5):490–4.
101. Hoffstein V, Mateika S. Cardiac arrhythmias, snoring, and sleep apnea. Chest. 1994;106(2):466–71.
102. Tilkian AG, et al. Sleep-induced apnea syndrome. Prevalence of cardiac arrhythmias and their reversal after tracheostomy. Am J Med. 1977;63(3):348–58.
103. European Heart Rhythm, A, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48(5):e247–346.
104. Monahan K, et al. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. J Am Coll Cardiol. 2009;54(19):1797–804.
105. Lu Z, et al. Increase in vulnerability of atrial fibrillation in an acute intermittent hypoxia model: importance of autonomic imbalance. Auton Neurosci. 2013;177(2):148–53.
106. Marinheiro R, et al. Ventricular arrhythmias in patients with obstructive sleep apnea. Curr Cardiol Rev. 2019;15(1):64–74.
107. Spicuzza L, et al. Autonomic modulation of heart rate during obstructive versus central apneas in patients with sleep-disordered breathing. Am J Respir Crit Care Med. 2003;167(6):902–10.
108. Trulock KM, Narayan SM, Piccini JP. Rhythm control in heart failure patients with atrial fibrillation: contemporary challenges including the role of ablation. J Am Coll Cardiol. 2014;64(7):710–21.
109. Gami AS, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007;49(5):565–71.
110. Mehra R, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. Am J Respir Crit Care Med. 2006;173(8):910–6.
111. Mehra R, et al. Nocturnal Arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. Arch Intern Med. 2009;169(12):1147–55.

112. Tung P, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. J Am Heart Assoc. 2017;6(7):e004500.
113. Holmqvist F, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2015;169(5):647–654.e2.
114. Bunch TJ, et al. Five-year outcomes of catheter ablation in patients with atrial fibrillation and left ventricular systolic dysfunction. J Cardiovasc Electrophysiol. 2015;26(4):363–70.
115. Ng CY, et al. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol. 2011;108(1):47–51.
116. Dimitri H, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. Heart Rhythm. 2012;9(3):321–7.
117. Iwasaki YK, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. J Am Coll Cardiol. 2014;64(19):2013–23.
118. Neilan TG, et al. Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. J Am Heart Assoc. 2013;2(6):e000421.
119. Fein AS, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol. 2013;62(4):300–5.
120. Naruse Y, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm. 2013;10(3):331–7.
121. Qureshi WT, et al. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. Am J Cardiol. 2015;116(11):1767–73.
122. Garrigue S, et al. High prevalence of sleep apnea syndrome in patients with long-term pacing: the European Multicenter Polysomnographic Study. Circulation. 2007;115(13):1703–9.
123. Rossi VA, et al. The effects of continuous positive airway pressure therapy withdrawal on cardiac repolarization: data from a randomized controlled trial. Eur Heart J. 2012;33(17):2206–12.
124. Simantirakis EN, et al. Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. Eur Heart J. 2004;25(12):1070–6.
125. Marti Almor J, et al. [Prevalence of obstructive sleep apnea syndrome in patients with sick sinus syndrome]. Rev Esp Cardiol. 2006;59(1):28–32.
126. Shepard JW Jr, et al. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. Chest. 1985;88(3):335–40.
127. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation. 2000;101(4):392–7.
128. Ryan CM, et al. Timing of nocturnal ventricular ectopy in heart failure patients with sleep apnea. Chest. 2008;133(4):934–40.
129. Namtvedt SK, et al. Cardiac arrhythmias in obstructive sleep apnea (from the Akershus Sleep Apnea Project). Am J Cardiol. 2011;108(8):1141–6.
130. Somers VK, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96(4):1897–904.
131. Somers VK, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation. 2008;118(10):1080–111.
132. Narkiewicz K, et al. Sympathetic activity in obese subjects with and without obstructive sleep apnea. Circulation. 1998;98(8):772–6.
133. Craig S, et al. Continuous positive airway pressure treatment for obstructive sleep apnoea reduces resting heart rate but does not affect dysrhythmias: a randomised controlled trial. J Sleep Res. 2009;18(3):329–36.

134. Ryan CM, et al. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax. 2005;60(9):781–5.
135. Wessendorf TE, et al. Sleep-disordered breathing among patients with first-ever stroke. J Neurol. 2000;247(1):41–7.
136. Turkington PM, et al. Prevalence and predictors of upper airway obstruction in the first 24 hours after acute stroke. Stroke. 2002;33(8):2037–42.
137. Harbison J, et al. Sleep-disordered breathing following acute stroke. QJM. 2002;95(11): 741–7.
138. Iranzo A, et al. Prevalence and clinical importance of sleep apnea in the first night after cerebral infarction. Neurology. 2002;58(6):911–6.
139. Parra O, et al. Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. Eur Respir J. 2011;37(5):1128–36.
140. Bravata DM, et al. Continuous positive airway pressure: evaluation of a novel therapy for patients with acute ischemic stroke. Sleep. 2011;34(9):1271–7.
141. Good DC, et al. Sleep-disordered breathing and poor functional outcome after stroke. Stroke. 1996;27(2):252–9.
142. Turkington PM, et al. Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. Thorax. 2004;59(5):367–71.
143. Sahlin C, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. Arch Intern Med. 2008;168(3):297–301.
144. Cherkassky T, et al. Sleep-related breathing disorders and rehabilitation outcome of stroke patients: a prospective study. Am J Phys Med Rehabil. 2003;82(6):452–5.
145. Morcos Z, Phadke J. Re: Kaneko Y, Hajek VE, Zivanovic V et al. Relationship of sleep apnea to functional capacity and length of hospitalization following strok. Sleep 2003;26(3):293-7e. Sleep. 2003;26(6):761; author reply 762.
146. Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. J Clin Sleep Med. 2010;6(2):131–7.
147. Hsieh SW, et al. Obstructive sleep apnea linked to wake-up strokes. J Neurol. 2012;259(7):1433–9.
148. Koo BB, et al. Observational study of obstructive sleep apnea in wake-up stroke: the SLEEP TIGHT study. Cerebrovasc Dis. 2016;41(5–6):233–41.
149. Brown DL, et al. Wake-up stroke is not associated with sleep-disordered breathing in women. Neurol Clin Pract. 2018;8(1):8–14.
150. Li M, et al. Obstructive sleep apnea and risk of stroke: a meta-analysis of prospective studies. Int J Cardiol. 2014;172(2):466–9.
151. Giles TL, et al. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev. 2006;1:CD001106.
152. Brown DL, et al. Sleep apnea treatment after stroke (SATS) trial: is it feasible? J Stroke Cerebrovasc Dis. 2013;22(8):1216–24.
153. Parra O, et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. J Sleep Res. 2015;24(1):47–53.
154. Kim Y, et al. Can continuous positive airway pressure reduce the risk of stroke in obstructive sleep apnea patients? A systematic review and meta-analysis. PLoS One. 2016;11(1):e0146317.
155. Kernan WN, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160–236.
156. Mokhlesi B, et al. Obstructive sleep apnea during REM sleep and hypertension. Results of the Wisconsin Sleep Cohort. Am J Respir Crit Care Med. 2014;190(10): 1158–67.
157. Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. Sleep. 2003;26(1):15–9.

158. Hedner J, et al. Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? J Hypertens Suppl. 1988;6(4):S529–31.
159. Tamisier R, et al. Blood pressure increases in OSA due to maintained neurovascular sympathetic transduction: impact of CPAP. Sleep. 2015;38(12):1973–80.
160. Krzysztof Narkiewicz FHSK, Somers VK, Phillips BG. Influence of sleep and sleep apnea on autonomic control of cardiovascular system. In: Bradley TD, Floras JS, editors. Sleep apnea: implications in cardiovascular and cerebrovascular disease, vol. 146. Boca Raton, FL: CRC Press LLC; 2019.
161. Jin ZN, Wei YX. Meta-analysis of effects of obstructive sleep apnea on the renin-angiotensin-aldosterone system. J Geriatr Cardiol. 2016;13(4):333–43.
162. Pedrosa RP, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58(5):811–7.
163. Phillips CL, O'Driscoll DM. Hypertension and obstructive sleep apnea. Nat Sci Sleep. 2013;5:43–52.
164. Young T, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med. 1997;157(15):1746–52.
165. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ. 2000;320(7233):479–82.
166. Nieto FJ, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000;283(14):1829–36.
167. O'Connor GT, et al. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2009;179(12):1159–64.
168. Hou H, et al. Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. J Glob Health. 2018;8(1):010405.
169. Chobanian AV, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289(19):2560–72.
170. Marin JM, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307(20):2169–76.
171. Fava C, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea a systematic review and meta-analysis. Chest. 2014;145(4):762–71.
172. Bakker JP, et al. Blood pressure improvement with continuous positive airway pressure is independent of obstructive sleep apnea severity. J Clin Sleep Med. 2014;10(4):365–9.
173. Parati G, Lombardi C. Control of hypertension in nonsleepy patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2010;181(7):650–2.
174. Bratton DJ, et al. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. JAMA. 2015;314(21):2280–93.
175. Turnbull F, C. Blood Pressure Lowering Treatment Trialists. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362(9395):1527–35.
176. Marin JM, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046–53.
177. Buchner NJ, et al. Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. Am J Respir Crit Care Med. 2007;176(12):1274–80.
178. Barbe F, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307(20):2161–8.
179. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation. 1998;98(21):2334–51.

180. Virani SS, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020;141(9):e139–596.
181. Gami AS, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. J Am Coll Cardiol. 2013;62(7):610–6.
182. Adabag S, et al. Obesity related risk of sudden cardiac death in the atherosclerosis risk in communities study. Heart. 2015;101(3):215–21.
183. Gami AS, et al. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med. 2005;352(12):1206–14.
184. Zheng J, et al. Sudden unexplained nocturnal death syndrome: the hundred years' enigma. J Am Heart Assoc. 2018;7(5):e007837.
185. Tobaldini E, et al. Cardiac autonomic control in Brugada syndrome patients during sleep: the effects of sleep disordered breathing. Int J Cardiol. 2013;168(4):3267–72.
186. Abe H, et al. Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients. Heart Vessel. 2010;25(1):63–9.
187. Rawshani A, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med. 2017;376(15):1407–18.
188. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care. 2005;28(11):2745–9.
189. Peppard PE, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000;284(23):3015–21.
190. Marshall NS, et al. Is sleep apnea an independent risk factor for prevalent and incident diabetes in the Busselton Health Study? J Clin Sleep Med. 2009;5(1):15–20.
191. Reichmuth KJ, et al. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med. 2005;172(12):1590–5.
192. Mahmood K, et al. Prevalence of type 2 diabetes in patients with obstructive sleep apnea in a multi-ethnic sample. J Clin Sleep Med. 2009;5(3):215–21.
193. Kent BD, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. Chest. 2014;146(4):982–90.
194. Nagayoshi M, et al. Obstructive sleep apnea and incident type 2 diabetes. Sleep Med. 2016;25:156–61.
195. Anothaisintawee T, et al. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. Sleep Med Rev. 2016;30:11–24.
196. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. Chest. 2017;152(5):1070–86.
197. Wieser V, Moschen AR, Tilg H. Inflammation, cytokines and insulin resistance: a clinical perspective. Arch Immunol Ther Exp. 2013;61(2):119–25.
198. Drager LF, et al. Chronic intermittent hypoxia induces atherosclerosis via activation of adipose angiopoietin-like 4. Am J Respir Crit Care Med. 2013;188(2):240–8.
199. Htoo AK, et al. Activation of nuclear factor kappaB in obstructive sleep apnea: a pathway leading to systemic inflammation. Sleep Breath. 2006;10(1):43–50.
200. Yamauchi M, et al. Oxidative stress in obstructive sleep apnea. Chest. 2005;127(5):1674–9.
201. Gaines J, et al. Obstructive sleep apnea and the metabolic syndrome: the road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. Sleep Med Rev. 2018;42:211–9.
202. Deibert DC, DeFronzo RA. Epinephrine-induced insulin resistance in man. J Clin Invest. 1980;65(3):717–21.
203. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–807.
204. Ota H, et al. Relationship between intermittent hypoxia and type 2 diabetes in sleep apnea syndrome. Int J Mol Sci. 2019;20(19):4756.
205. Chami HA, et al. Association between glucose metabolism and sleep-disordered breathing during REM sleep. Am J Respir Crit Care Med. 2015;192(9):1118–26.

206. Bialasiewicz P, et al. Sleep disordered breathing in REM sleep reverses the downward trend in glucose concentration. Sleep Med. 2011;12(1):76–82.
207. Grimaldi D, et al. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. Diabetes Care. 2014;37(2):355–63.
208. Banghoej AM, et al. Obstructive sleep apnoea is frequent in patients with type 1 diabetes. J Diabetes Complicat. 2017;31(1):156–61.
209. Reutrakul S, et al. Sleep characteristics in type 1 diabetes and associations with glycemic control: systematic review and meta-analysis. Sleep Med. 2016;23:26–45.
210. Vgontzas AN, et al. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab. 2001;86(2):517–20.
211. Lecube A, et al. Effect of glycemic control on nocturnal arterial oxygen saturation: a case-control study in type 2 diabetic patients. J Diab. 2015;7(1):133–8.
212. Shaw JE, et al. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes Res Clin Pract. 2008;81(1):2–12.
213. Westlake K, et al. Screening for obstructive sleep apnea syndrome in patients with type 2 diabetes mellitus: a prospective study on sensitivity of Berlin and STOP-Bang questionnaires. Sleep Med. 2016;26:71–6.
214. Song SO, et al. Metabolic consequences of obstructive sleep apnea especially pertaining to diabetes mellitus and insulin sensitivity. Diabetes Metab J. 2019;43(2):144–55.
215. Marathe PH, Gao HX, Close KL. American Diabetes Association standards of medical care in diabetes 2017. J Diab. 2017;9(4):320–4.
216. Mokhlesi B, et al. Effect of one week of 8-hour nightly continuous positive airway pressure treatment of obstructive sleep apnea on glycemic control in type 2 diabetes: a proof-of-concept study. Am J Respir Crit Care Med. 2016;194(4):516–9.
217. Shaw JE, et al. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. Am J Respir Crit Care Med. 2016;194(4):486–92.
218. Martinez-Ceron E, et al. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. Am J Respir Crit Care Med. 2016;194(4):476–85.
219. Weinstock TG, et al. A controlled trial of CPAP therapy on metabolic control in individuals with impaired glucose tolerance and sleep apnea. Sleep. 2012;35(5):617–625B.
220. West SD, et al. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax. 2007;62(11):969–74.
221. Morariu EM, et al. Effect of continuous positive airway pressure (CPAP) on glycemic control and variability in type 2 diabetes. Sleep Breath. 2017;21(1):145–7.
222. Reutrakul S, Mokhlesi B. Can long-term treatment of obstructive sleep apnea with CPAP improve glycemia and prevent type 2 diabetes? Diabetes Care. 2020;43(8):1681–3.
223. Chirinos JA, et al. CPAP, weight loss, or both for obstructive sleep apnea. N Engl J Med. 2014;370(24):2265–75.
224. Loffler KA, et al. Continuous positive airway pressure treatment, glycemia, and diabetes risk in obstructive sleep apnea and comorbid cardiovascular disease. Diabetes Care. 2020;43(8):1859–67.
225. Prasad B, et al. Effects of positive airway pressure treatment on clinical measures of hypertension and type 2 diabetes. J Clin Sleep Med. 2012;8(5):481–7.
226. Jullian-Desayes I, et al. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. Sleep Med Rev. 2015;21:23–38.
227. Calaora-Tournadre D, et al. [Obstructive Sleep Apnea Syndrom during pregnancy: prevalence of main symptoms and relationship with pregnancy induced-hypertension and intrauterine growth retardation]. Rev Med Interne. 2006;27(4):291–5.
228. Higgins N, et al. The Berlin Questionnaire for assessment of sleep disordered breathing risk in parturients and non-pregnant women. Int J Obstet Anesth. 2011;20(1):22–5.

229. Bourjeily G, et al. Patient and provider perceptions of sleep disordered breathing assessment during prenatal care: a survey-based observational study. Ther Adv Respir Dis. 2012;6(4):211–9.
230. Bourjeily G, Ankner G, Mohsenin V. Sleep-disordered breathing in pregnancy. Clin Chest Med. 2011;32(1):175–89.
231. Bourjeily G, et al. Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. Eur Respir J. 2010;36(4):849–55.
232. Ursavas A, et al. Self-reported snoring, maternal obesity and neck circumference as risk factors for pregnancy-induced hypertension and preeclampsia. Respiration. 2008;76(1): 33–9.
233. Ogden CL, et al. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013-2014. JAMA. 2016;315(21):2292–9.
234. Maasilta P, et al. Sleep-related disordered breathing during pregnancy in obese women. Chest. 2001;120(5):1448–54.
235. Pien GW, et al. Risk factors for sleep-disordered breathing in pregnancy. Thorax. 2014;69(4):371–7.
236. Zaremba S, et al. Elevated upper body position improves pregnancy-related OSA without impairing sleep quality or sleep architecture early after delivery. Chest. 2015;148(4): 936–44.
237. Champagne K, et al. Obstructive sleep apnoea and its association with gestational hypertension. Eur Respir J. 2009;33(3):559–65.
238. Louis JM, et al. Predictors of sleep-disordered breathing in pregnancy. Am J Obstet Gynecol. 2018;218(5):521.e1–521.e12.
239. Lockhart EM, et al. Obstructive sleep apnea in pregnancy: assessment of current screening tools. Obstet Gynecol. 2015;126(1):93–102.
240. Antony KM, et al. Association of adverse perinatal outcomes with screening measures of obstructive sleep apnea. J Perinatol. 2014;34(6):441–8.
241. Chung F, et al. Serum bicarbonate level improves specificity of STOP-Bang screening for obstructive sleep apnea. Chest. 2013;143(5):1284–93.
242. Dominguez JE, Krystal AD, Habib AS. Obstructive sleep apnea in pregnant women: a review of pregnancy outcomes and an approach to management. Anesth Analg. 2018;127(5): 1167–77.
243. Reid J, et al. Pregnant women with gestational hypertension may have a high frequency of sleep disordered breathing. Sleep. 2011;34(8):1033–8.
244. O'Brien LM, et al. Hypertension, snoring, and obstructive sleep apnoea during pregnancy: a cohort study. BJOG. 2014;121(13):1685–93.
245. Franklin KA, et al. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest. 2000;117(1):137–41.
246. Perez-Chada D, et al. Snoring, witnessed sleep apnoeas and pregnancy-induced hypertension. Acta Obstet Gynecol Scand. 2007;86(7):788–92.
247. Facco FL, et al. Association between sleep-disordered breathing and hypertensive disorders of pregnancy and gestational diabetes mellitus. Obstet Gynecol. 2017;129(1):31–41.
248. Pamidi S, et al. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;210(1):52.e1–52.e14.
249. Bourjeily G, et al. Obstructive sleep apnea in pregnancy is associated with adverse maternal outcomes: a national cohort. Sleep Med. 2017;38:50–7.
250. Louis JM, et al. Obstructive sleep apnea and severe maternal-infant morbidity/mortality in the United States, 1998-2009. Sleep. 2014;37(5):843–9.
251. Lee KA, Gay CL. Sleep in late pregnancy predicts length of labor and type of delivery. Am J Obstet Gynecol. 2004;191(6):2041–6.
252. Okun ML, Schetter CD, Glynn LM. Poor sleep quality is associated with preterm birth. Sleep. 2011;34(11):1493–8.
253. Chu SY, et al. Maternal obesity and risk of cesarean delivery: a meta-analysis. Obes Rev. 2007;8(5):385–94.

254. Louis JM, et al. Maternal and neonatal morbidities associated with obstructive sleep apnea complicating pregnancy. Am J Obstet Gynecol. 2010;202(3):261.e1–5.
255. Micheli K, et al. Sleep patterns in late pregnancy and risk of preterm birth and fetal growth restriction. Epidemiology. 2011;22(5):738–44.
256. Edwards N, et al. Nasal continuous positive airway pressure reduces sleep-induced blood pressure increments in preeclampsia. Am J Respir Crit Care Med. 2000;162(1):252–7.
257. Blyton DM, et al. Treatment of sleep disordered breathing reverses low fetal activity levels in preeclampsia. Sleep. 2013;36(1):15–21.
258. Guilleminault C, et al. Pre-eclampsia and nasal CPAP: part 1. Early intervention with nasal CPAP in pregnant women with risk-factors for pre-eclampsia: preliminary findings. Sleep Med. 2007;9(1):9–14.
259. Wu P, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2):e003497.
260. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122–31.
261. Valdes G. Preeclampsia and cardiovascular disease: interconnected paths that enable detection of the subclinical stages of obstetric and cardiovascular diseases. Integr Blood Press Control. 2017;10:17–23.
262. Brown MC, et al. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28(1):1–19.
263. McDonald SD, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156(5):918–30.
264. Bushnell C, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(5):1545–88.
265. Mosca L, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American heart association. Circulation. 2011;123(11):1243–62.
266. Riise HK, et al. Incident coronary heart disease after preeclampsia: role of reduced fetal growth, preterm delivery, and parity. J Am Heart Assoc. 2017;6(3):e004158.
267. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13:479–504.