



# Sleep and stroke

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## Abstract

*Obstructive Sleep-Disordered Breathing (OSDB) is an under-recognized risk factor for stroke. OSDB is associated with traditional vascular risk factors such as hypertension, obesity, and diabetes, and can influence the risk for stroke through direct and indirect mechanisms. Untreated OSDB may also influence rehabilitation efforts and functional outcome following a stroke, as well as the risk for stroke recurrence. Stroke risk is greatly reduced if the OSDB is adequately treated. Conversely, OSDB may be exacerbated or caused by stroke. Increasing awareness and improving screening for OSDB is paramount in the primary and secondary prevention of stroke, and in improving stroke outcomes.*

*The following review article is intended to highlight the current basics of epidemiology, clinical characteristics, pathophysiology, diagnosis, and treatment of OSDB in relation to stroke.*

## INTRODUCTION

Obstructive Sleep-Disordered Breathing (OSDB) describes a group of disorders characterized by abnormalities of respiratory pattern or ventilation during sleep related to upper airway obstruction. OSDB includes *habitual snoring, upper airway resistance syndrome (UARS), and obstructive sleep apnea (OSA)*, which is characterized by repetitive partial or complete collapse of the pharyngeal airway during sleep leading to oxygen desaturation and the need to arouse to resume ventilation (1, 2). Sleep is thus disrupted, yielding waking somnolence and diminished neurocognitive performance which may impede stroke rehabilitation, lengthen hospital stay, and influence stroke outcomes and risk of recurrence (3, 4). The recurrent sleep arousal in association with intermittent hypoxia and hypercapnia has been implicated in the occurrence of adverse cardiovascular outcomes. In addition, there is evolving evidence that OSDB may contribute to insulin resistance and other components of the metabolic syndrome.

## Epidemiology

It is estimated that over 90 million Americans, or up to 40% of the adult U.S. population, suffer from loud habitual snoring.<sup>5–7</sup> In the UK, an estimated 41.5% of the adult population snore, or 14.9 million adults, with a male to female ratio of approximately 2:1 (8).

Obstructive sleep apnea (OSA) affects up to 17% of the adult population, and up to 25% of patients over 65 years of age (9–11). The prevalence approaches 30–50% in patients with cardiovascular disease,

**TABLE 1**  
Sleep terms and definitions.

Term	Definition
Apnea	Cessation of airflow for at least 10 s, usually accompanied by oxygen desaturation
Hypopnea	Reduction in airflow by at least 30–50% of baseline, usually accompanied by oxygen desaturation or an arousal
Arousal	Awakening from sleep lasting 3 to 15 s
Apnea- hypopnea index (AHI)	Number of apneas and hypopneas per hour of sleep, a marker of sleep apnea severity
Sleep apnea syndrome	At least 5 apneas and hypopneas per hour of sleep, associated with complaints of snoring, breathing pauses, insomnia, unrefreshing sleep, excessive daytime sleepiness or fatigue

including hypertension, coronary artery disease, stroke, and congestive heart failure (CHF) (12).

There are ethnic differences in the prevalence of snoring and OSA with higher prevalence reported in Hispanics and African Americans (13–15).

Despite considerable progress, most patients with OSDB remain undiagnosed. It has been suggested that 93% of women and 82% of men with signs and symptoms of moderate to severe OSDB remain untreated (10).

### Clinical characteristics

Symptoms of OSA include snoring, gasping or choking during sleep, restless sleep, and excessive daytime sleepiness. It can also result in impaired cognition, irritability, and mood changes. Daytime sleepiness is one of the cardinal symptoms of OSA. Multiple models have been developed to assess the degree of daytime sleepiness. The *Epworth sleepiness scale* (ESS) is commonly used (16). It rates self-reports of dozing off unintentionally during the day in sedentary situations (Table 2).

Risk factors for OSBD include obesity, male gender, increased neck circumference ( $\geq 17$  inches in men;  $\geq 16$  inches in women), cranio-facial features (e.g. retrognathia and micrognathia), nasal obstruction, large tonsils (especially in children), ethnic background, and hypothyroidism (2, 10). The use of alcohol, tobacco, and sedatives further increases the risk.

Risk predictive models have also been proposed to identify individuals at high risk for obstructive sleep apnea. One of the most commonly used is the *Berlin questionnaire*, which combines risk factors such as snoring, daytime sleepiness, obesity, and hypertension to reliably predict OSA from polysomnography (PSG) (17); (Table 3, Table 4).

### Sleep, blood pressure, and risk of stroke

Stroke shares an identical double-peak 24 h pattern with many acute cardiovascular events with a major morning peak and secondary early evening peak, which parallels the circadian variation in blood pressure (18, 19). Blood pressure exhibits a prominent 24 hour rhythm, with two daytime peaks, the first around 9 a.m. and the second around 7 p.m., and a nadir during sleep (20).

**TABLE 2**

#### Epworth Sleepiness Scale

Likelihood of dozing off or falling asleep in the following situations.

Sitting and reading
Watching TV
Sitting inactive in a public place [theater/meeting]
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon when circumstances permit
Sitting quietly after a lunch without alcohol
Sitting and talking to someone
In a car, while stopped for a few minutes in traffic

0 = no chance of dozing

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

ESS score is  $\geq 10$  is consistent with Excessive Daytime Sleepiness.

**TABLE 3**

#### Berlin Questionnaire Sleep apnea risk stratification.

Check if present
Loud Habitual Snoring (at least 3 times per week)
Daytime Sleepiness (ESS $\geq 10$ ) (at least 3 times per week)
Hypertension
Obesity (BMI $> 30$ kg/m <sup>2</sup> )

Presence of two out of the four above factors predicts OSA with a sensitivity of 86%, specificity of 77%, and positive predictive value of 89%.

Excessive morning BP surge has been associated with a 2.7 fold increase risk of stroke in the elderly (21).

Normally, BP decreases by 10–20% during NREM sleep as compared to daytime levels (20). A variety of abnormal BP variation patterns have been described in which the nocturnal fall of BP may be  $> 20\%$  (extreme-

**TABLE 4**

Population at high risk for sleep disordered breathing.

Populations at high risk for Sleep disordered breathing and OSA	History and Symptoms prompting sleep evaluation by PSG
History of Stroke	Daytime sleepiness ( $\geq 10$ ESS)*
Obesity (BMI > 30)*	Loud and habitual snoring*
Congestive heart failure	History of hypertension*
Atrial fibrillation	Gasping/choking at night
Refractory hypertension	Witnessed apneas
Type 2 diabetes	Morning headaches
Nocturnal dysrhythmias	Frequent awakenings
Non- dipping BP	Memory loss
Pulmonary hypertension	Decreased concentration
Shift workers	Frequent nocturia

\* Berlin Questionnaire items.

ESS: Epworth Sleepiness Scale; BMI: body mass index; BP: blood pressure.

-dippers), < 10% (non-dippers), or < 0% (reversed-dippers), with nocturnal BP exceeding daytime BP) (22). Prospective studies have shown that patients who do not experience typical BP »dipping« during sleep are at increased risk for end organ damage, including left ventricular hypertrophy, myocardial infarction, congestive heart failure, vascular dementia and stroke (20, 22, 23). Extreme-dipper, non-dipper or reverse-dipper pattern have all been associated with intracranial hemorrhages, ischemic strokes, silent brain infarcts, and stroke deaths (24–26). The Ohasama study, a population-based study of the prognostic value of ambulatory BP monitoring in over 1,500 Japanese subjects, found that after an average follow up of 9.2 years, a 5% decrease in the nocturnal systolic BP in hypertensive patients was associated with

approximately a 20% increased risk of cardiovascular mortality (26). In addition, 'dipper hypertensives' had a risk of cardiovascular mortality (HR 2.4; 95% CI: 1.5–3.8) similar to that of 'non-dipper hypertensives' (HR 2.2; 95% CI: 1.3–3.6). These results suggest that loss of nocturnal BP dipping is a significant risk factor of cardiovascular mortality, independent of 24-hour mean BP. Hence, altered diurnal BP pattern with absence of nocturnal BP dipping represents an important risk factor for stroke and cardiovascular events.

### Obstructive Sleep-Disordered Breathing and Stroke

Habitual snoring is considered an independent risk factor for stroke, with a risk estimate of 1.7, similar to that of traditional risk factors (27, 28). It is more strongly associated with stroke during sleep (29). It has also been associated with carotid atherosclerosis, and was found to have an adverse effect on stroke outcome (30).

There seems to be a dose-response relationship between OSA and cardiovascular disease including stroke (31). The association between OSA and stroke has been established in multiple observational cohort studies (Table 5) (27, 28, 32, 33). In a cross-sectional analysis of 6,000 subjects from Sleep Heart Health Study, stroke prevalent (OR: 1.6; 95% CI 1.02–2.5) was greater among subjects with OSA (31). A cross-sectional analysis from the Wisconsin Sleep Cohort study of 1,475 individuals showed an increased risk of stroke in subjects with an AHI=20 (OR 3.8; 95% CI: 1.2–12.6) after controlling for covariates (32). In another observational cohort study of patients referred to an academic sleep center for the evaluation of sleep disordered breathing, OSA was associated with an increased risk of stroke or death (HR, hazard ratio 3.3; 95% CI: 1.7–6.3) independently of demographics and vascular risk factors. In the recent prospective analyses from the Sleep Heart Health Study with a median follow up of 8.7 years. OSA at all levels of severity was associated

**TABLE 5**

Sleep disorders, cardiovascular disease and stroke in epidemiological studies.

STUDY	DESIGN	N	OUTCOME	OR/HR (95% CI)
<b>OSA</b>				
SHHS Shahar et al., 2001	Cross- sectional	6,424	Heart failure	2.4 (1.2–4.6)
			CAD	1.3 (1.0–1.6)
			Stroke	1.6 (1.0–2.5)
WSC Arzt et al., 2005	Cross- sectional	1,475	Stroke	3.8 (1.2–12.5)
Yaggi et al., 2005	Prospective cohort	1,022	Stroke or death	2.0 (1.1–3.5)
Munoz et al., 2006	Prospective cohort	394	Stroke	2.5 (1.0–6.0)
SHHS Redline et al., 2010	Prospective cohort	5,422	Stroke	Men, 2.9 (1.1–7.4) Women, 1.2 (0.7–2.2)

OR, odds ratio; HR, hazards ratio; OSA, obstructive sleep apnea; SHHS, Sleep Heart Health Study; PSG, polysomnography; HTN, hypertension; CVD, cardiovascular disease; CAD, coronary artery disease; WSC, Wisconsin Sleep Cohort; ARIC, Atherosclerosis Risk In Communities

with an increased risk of stroke in men (for the top AHI quartile of >19, an adjusted HR 2.9; 95% CI: 1.1–7.4) but not in women (33). There was an increased risk of stroke in women only with an AHI of more than 25 (33). A recent meta-analysis of 29 studies has reported that up to 72% of stroke patients have OSA, as defined by an AHI greater than 5 (34). The patients with »cryptogenic stroke« had the highest incidence of OSA, raising the possibility that OSA may be an important cause of ischemic stroke of undetermined etiology (34).

### Mechanisms leading to stroke

Several direct and indirect mechanisms have been proposed to explain the increased risk of stroke in patients with OSDB. These include the effects of hypoxemia, sympathetic surges, nocturnal hypertension, reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, increased platelet activation, metabolic dysregulation (increased leptin levels and impaired glucose tolerance), increased inflammation, increased oxidative stress related to intermittent hypoxia, cardiac arrhythmias, and cardioembolism (35–37).

Damage to endothelial cells may occur by oxidative stress during hypoxemia related to apneas, and shear stress onto blood vessel walls from large fluctuations in blood pressure during the obstructive events and sustained hypertension (36, 37). Arousals from sleep associated to increased sympathetic surges, may play a significant role in the amount of »non-dipping« of BP in sleep leading to nocturnal hypertension (35). Obstructive events can lead to reductions in cerebral blood flow (CBF) and impaired cerebral autoregulation (38). Changes in intrathoracic pressures during obstructive events may reduce CBF increasing the risk of stroke in vulnerable patients (39). Also, decrease CBF and impaired vasomotor reactivity have been observed during wakefulness in subjects with OSA (38). These mechanisms may cause cerebral small vessel disease as well as cerebral white matter disease, and lead to subclinical cerebrovascular damage and permanent structural changes to the brain.

Another important mechanism which may cause clinical deterioration during an acute ischemic stroke is the Reversed Robin Hood Syndrome (RRHS). This is an intracranial steal phenomenon associated with neurological deterioration in up to 7% of acute stroke patients. Oxygen desaturations coupled with hypercapnia during obstructions in OSA can trigger this cerebral blood steal phenomenon (39).

### Obstructive Sleep Apnea and Stroke Risk Factors

The association between OSA and vascular disease may be in part mediated by the presence of major vascular risk factors including *hypertension, diabetes, and obesity*.

OSA is an independent risk factor for systemic hypertension, and increases the risk of hypertension in a dose-response pattern (40). An AHI greater than 5 and less than 15 is associated with a 2 fold increased risk of

developing hypertension at 4 year follow up, and an AHI > 15 is associated with a 3 fold increased risk (32, 41). A high prevalence of OSA is also described in treatment resistant hypertension (42).

Obstructive sleep apnea is linked to type 2 diabetes by its effect on insulin resistance and cortisol levels (43).

OSA is also associated with altered levels of leptin, a hormone secreted by adipocytes, which promotes the sensation of satiety and increases the metabolic rate (44). Untreated OSA causes resistance to the metabolic effects of leptin, promoting weight gain and obesity in this population.

### OSA and Cardioembolic Risk

OSA has also been linked to cardioembolic risk factors including patent foramen ovale (PFO) and cardiac arrhythmias. An increased risk of cardioembolism through paradoxical emboli has been suggested in patients with OSA (45). This may occur through increased intrathoracic pressure during apneas (46).

Heart rate variability is seen with sleep apneas and hypopneas with slowing of the heart rate during the event, followed by an increased rate or tachycardia with the initial restorative breath or hyperpnea phase, often associated with an arousal from sleep. This has been described as »brady-tachy« pattern and is the most common form of arrhythmia with OSA. Multiple arrhythmias have been documented in patients with OSA including sinus pauses, bradycardia, supraventricular tachycardia, ventricular tachycardia, second or third degree heart block, and atrial fibrillation. The majority of the arrhythmias are seen in stages N1, N2 and REM sleep.

An AHI greater or equal to 30 is associated with a 4 fold increased risk of Atrial Fibrillation, a 3.4 fold increased risk of non-sustained ventricular tachycardia, and 1.74 fold increased risk of complex ventricular ectopy (47).

Up to 40% of symptomatic Atrial Fibrillation (AF) episodes occur between midnight and 8 a.m. (48). Observational studies have shown an improvement or resolution of cardiac arrhythmias and atrial fibrillation with OSA treatment (49).

### OSA and subclinical vascular disease

The effect of OSA on subclinical vascular disease has been reported. In a cross-sectional study of Japanese men, brain magnetic resonance imaging revealed silent brain infarcts in 25% of patients with moderate to severe OSA but in only 8% of patients with mild OSA, and in 6% of control subjects, suggesting that OSA may elicit early and asymptomatic cerebrovascular damage (50). Subclinical carotid atherosclerosis (carotid intima-media thickness, IMT) has been proposed as an intermediary between OSA and stroke, but this relationship remains controversial. In the two large population based studies, Northern Manhattan Study and SHHS, snoring and insomnia were not associated with increased levels of carot-

id IMT (51, 52). However, another study reported a significant association between severe OSA and carotid atherosclerosis (53). This study however, involved a relatively small number of subjects referred to a tertiary care center.

### **Sleep Disorders and Stroke Rehabilitation and Outcomes**

Although data is limited, poor sleep quality or duration may significantly impair inpatient stroke rehabilitation efforts. Sleep disorders impede the restorative processes, which occur during undisturbed sleep (54). Obstructive sleep apnea is associated with depressive symptoms, daytime sleepiness, fatigue, and executive dysfunction, all of which can limit a patient's rehabilitation regimen (1, 4, 50). Stroke patients with untreated sleep disorders may also lack the motivation, energy, and concentration necessary to participate in intensive rehabilitation therapy. In a recent small randomized trial in 22 patients with OSA, CPAP treatment after stroke has been shown to improve motor functional recovery and depressive symptoms, but not cognitive impairment (55). Thus, treatment of sleep disorders in patients with stroke may help maximize stroke recovery.

### **Diagnosis and Treatment of obstructive sleep-disordered breathing**

Polyomnography (PSG) is the gold standard for the diagnosis of OSDB. A standard montage includes electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), electrocardiography (EKG), and respiratory activity with audiovisual correlation to detect sleeping disturbances.

Continuous positive airway pressure (CPAP) is the first-line treatment for patients with moderate to severe OSA. CPAP is administered by a small motorized unit that pushes pressurized air through a hose attached to a mask strapped on the patient's face. CPAP works as a »pneumatic splint« by delivering a positive intraluminal pressure, alleviating the repetitive episodes of upper airway collapse characteristic of sleep apnea, and completely or partially reversing its daytime consequences. Aside from improving sleep quality and daytime symptoms related to OSA, CPAP has been shown to decrease risk for cardiovascular events and has modest effects on BP (56, 57). Its benefits are directly related to its adherence with improvements in subjective sleepiness achieved with > 4 hours of nightly use while mild decreases in BP (1.89 mm Hg in systolic BP and 2.19 mm Hg in diastolic BP) require a minimum of 5.6 hours of nightly use (57).

The benefits and timing of CPAP therapy during an acute stroke however have not been established. The effects of CPAP therapy on BP during an acute stroke are not well known. CPAP treatment therefore may be problematic in acute stroke patients that are vulnerable to changes in cerebral blood flow. In addition, the severity and type of sleep apnea may evolve from the acute to the chronic stroke phase (4). Acute stroke patients may show

poor CPAP adherence due to cognitive and motor impairment that hinders appropriate mask fit and placement. An alternative option for inpatient treatment for OSA may be positional therapy (avoiding supine positioning), which has showed modest decreases in the AHI of about 20% compared to sleeping at lib (58). A 5-year prospective observational study of patients with OSA two months after stroke showed that those with moderate or severe OSA who were non-adherent to CPAP had increased mortality (HR 1.6; 95% CI: 1.0–2.5) from cardiovascular disease or stroke as compared to CPAP adherent patients (59). Randomized clinical trials studying the effects of CPAP therapy on stroke outcomes and recurrence are currently on-going; however, given its high benefit to risk ratio, stroke patients with OSA should be encouraged to use CPAP regularly as part of standard stroke care. Larger studies are needed to determine the optimal timing of CPAP therapy after stroke, determinants of CPAP adherence in stroke patients, and the effects of CPAP use on stroke risk reduction and mortality.

### **FUTURE DIRECTIONS**

Data is limited regarding the impact of sleep-disordered breathing and its treatment on incidence and recurrence of stroke, and regarding race-ethnic prevalence of sleep disorders. This may be of importance in stroke prevention, as Hispanics have a 2-fold increased risk for stroke in comparison to whites (60). A large multicenter epidemiological study, the Hispanics Community Health Study, will evaluate the effect of sleep disorders on adverse cardiovascular outcomes in the US Hispanic population (61). Several trials are currently investigating the effects of OSA treatment with CPAP on future cardiovascular events, including a large on-going trial in Australia (Sleep Apnea CardioVascular Endpoints Study, a China-Australia collaborative multi-centre trial). Studies are also needed to determine the effect of treatment of post-stroke sleep-disordered breathing on rehabilitation efforts and stroke outcomes. Increasing public awareness and improving healthcare professional education about the effects of sleep disorders, as well as screening methods, management, and prevention is an important first step given the emerging evidence that sleep-disordered breathing is a modifiable stroke risk factor. Finally, educating stroke patients and their caregivers regarding the impact of sleep-disordered breathing on stroke recovery and risk of stroke recurrence would help improve compliance with treatment.

### **CONCLUSION**

Sleep-disordered breathing is prevalent in the general population, especially in those with vascular risk factors, and in stroke victims. Screening for sleep disorders should become a standard part of stroke prevention, evaluation, and management. Collaboration between stroke and sleep specialists would further improve our understanding of the relationship between sleep-disordered breathing and stroke, may ensure early implementation of screening

and preventive strategies, and subsequently improve clinical outcomes for stroke patients. Finally, more innovative and effective strategies in educating health care professionals and the public about sleep disorders and their effect on stroke and cardiovascular disease are fundamental.

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