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Sleep Disorders and Risk of CVD

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According to Thomas Dekker quote “Sleep is that golden chain that ties health and our bodies together”.

Insufficient and inadequate sleep quality is a growing health problem affecting more than one in three adults. Sleep disorders are critical contributors to obesity, diabetes, cardiovascular (CV) disease, heart failure (HF), stroke and depression. Sleep debt increases the risk of motor vehicle crashes, fatal injury, and disability each year.

Sleep can be disrupted by ‘sleep and circadian rhythm disorders’ (i.e., sleep apnoea, insomnia, narcolepsy, restless leg syndrome, parasomnias, sleep bruxism), work, social or lifestyle behaviours. Unhealthy sleep patterns defined as short (<7 hours) and long sleep (>8 hours), late chronotype, insomnia symptoms, snoring and excessive daytime sleepiness (EDS) have been associated with an increased risk of coronary heart disease (CHD), CV disease, stroke, and all-cause mortality. While patients with a healthy sleep score (Figure 1a) demonstrated a reduced risk of CV disease by 35%, CHD by 34% and stroke by 34% independently of genetic risk score¹, and HF² suggesting that treating sleep disorders should be considered for CV prevention.

Obstructive sleep apnoea (OSA) is the most common type of sleep-disordered breathing [3]. Nearly 1 billion of the worldwide adults’ population aged 30–69 years have OSA, and the number of people with moderate to severe OSA, for which treatment is generally recommended, is estimated 425 million⁴. Given the already high and increasing prevalence of obesity and aging, the number of people presenting with OSA symptoms continues to grow.

OSA is characterized by recurrent episodes of closure (apnoea) and hypopnea (narrowing) of the upper respiratory airflow resulting in shallow or paused breathing (Figure 1b), intermittent hypoxemia, and arousal associated with maintained or increasing ventilator efforts³. Apnoea is defined as at least 90% airflow limitation through the respiratory tract which is maintained for 10 seconds and associated with increased inspiratory efforts from chest and/or abdomen, whereas hypopnea refers to a drop in the airflow of $\geq 30\%$ for ≥ 10 seconds and is associated with a $\geq 3\%$ oxygen desaturation or arousal. Based on the index denoting average number of apnoeic and hypopneic episodes per hour of sleep (apnoea-hypopnea-index [AHI], OSA is classified as: mild AHI ≥ 5 and <15 events per hour, moderate AHI ≥ 15 and ≤ 30 events per hour, and severe AHI >30 events per hour.

The most common symptoms, risk factors and OSA associated conditions are summarized in **Table**.

OSA mediated intermittent hypoxia has been suggested as the critical contributor to increased morbidity and mortality. Evidence is emerging on the casual relationship between OSA and development and management of hypertension, diabetes, cardiac arrhythmia, HF, sudden cardiac death (SCD), chronic obstructive pulmonary disease, stroke, erectile dysfunction (ED), depression, cognitive impairment, Alzheimer disease (AD) and cancer-related death. Recent data suggests that COVID-19 may adversely affect OSA and that treated OSA patients may be at increased risk of death from COVID-19.

While not all OSA patients are obese, undoubtedly excess weight is as an independent causative factor to the development of OSA, with the severity of disease strongly associated with an increase in body weight³. OSA alone can promote obesity related effects further potentiating increased CV morbidity and mortality.

OSA is primarily important in the context of hypertension. Blunted nocturnal BP dipping (defined as a <10% decrease in BP during sleep) is a common feature of sleep disturbances. OSA has been reported in approximately 40% hypertensive patients, increasing to nearly 90% in resistant hypertension patients⁵. OSA should rise the suspicion of secondary hypertension and should be recognized as an important risk modifier increasing CV risk estimated by the SCORE system.

OSA, resulting sleep fragmentation and intermittent hypoxia promotes metabolic disturbances and is highly associated with prevalent and incident type 2 diabetes. The J-curve phenomena on the relationship between daytime napping (i.e., excessive marker of underlying sleep disorder) and the risk of diabetes or metabolic syndrome was found, with no effect of napping below 40 minutes/day.

Severe OSA is associated with significant coronary artery plaque burden independent of traditional CV risk factors. Moderate to severe OSA increases the risk of developing NSTEMI compared to STEMI, with the risk increasing with AHI severity⁶. Patients with moderate to severe OSA demonstrate less severe cardiac injury during an acute non-fatal myocardial infarction (MI) when compared to patients without or with mild OSA, suggesting that

OSA may have a cardioprotective effect in the acute phase of MI, likely via ischemic preconditioning.

OSA and AF are strongly associated and may coexist with ED forming a clinical OSAFED syndrome that considerably potentiated the global CV risk. OSA promotes AF via acute apnoea-related arrhythmogenic changes during sleep and long-term atrial remodelling. OSA is highly prevalent in AF patients referred for cardioversion⁷. However, most of AF patients present no symptoms of EDS, indicating that this marker is not a reliable indication for occult OSA. Further relevant findings are related to night-to-night variability in OSA severity (which cannot be detected over one sleep study) demonstrating that OSA severity on a specific night directly corresponds to AF incidence on the same day⁸.

Patients with OSA present with a higher prevalence of sleep-related bradycardia and conduction delay, primarily during apnoeic episodes. Undiagnosed OSA is common in patients referred for pacemaker implantation to treat nocturnal bradycardia which in addition to prolong sinus pauses and atrioventricular conduction are substantially reduced following OSA therapy with no need for pacemaker. In this context the 2018 ACC/AHA/HRS Guidelines highlighted OSA evaluation and treatment in patients with documented or suspected bradycardia or conduction delays.

SDB plays a critical role in the development and worsening of HF, and its prognosis⁹. OSA more commonly occurs in HF preserved ejection fraction (EF), whereas central sleep apnoea and cyclic episodes of hypopnea-apnoea breathing (Cheyne-Stokes) increasingly characterize patients with HF reduced EF contributing to arrhythmias and SCD. Thus, screening for SDB in HF patients is urgently required.

OSA is highly prevalent in patients with cerebral infarction, transient ischemic attack (TIA), ischemic stroke or haemorrhagic stroke, reaching 62% in patients with AHI > 10 events per hour and 30% in severe OSA, and is associated with increased poststroke mortality. SDB often precedes acute stroke and TIA. Clinically relevant are findings showing that stroke and TIA patients presents specific phenotype of OSA such as significantly shorter apnoeas and hypopneas¹⁰, suggesting that optimal therapeutic approach requires routine OSA screening in patients with cerebrovascular disease even in the absence of a previous OSA diagnosis.

The link between OSA and increased risk of dementia and AD is of clinical importance. OSA may impair amyloid- β clearance and affect the link between slow wave activity and amyloid- β .

Awareness of OSA has increased over time but still remains low. Early detection and identification of patients with SDB is integral to curb the disease burden as its CV consequences impose a large

economic burden on the global healthcare system. OSA and CV disease commonly coexist sharing multiple risk factors. Thus, the implementation of the AHA Life's Simple 7 recommendations (i.e., not smoking, having a healthy diet habits, being physically active, losing excess weight, controlling cholesterol, glucose and BP levels) are vital for ideal CV health and can prevent from OSA mediated CV disease.

Figure 1a

Figure 1a. Healthy sleep pattern.

Figure 1b

Figure 1b. Airway during normal sleep and obstructive sleep apnoea (republished with permission)

Table

Pay attention to the risk factors for OSA ✓ Waist circumference of >94 cm for men, >80 cm for women Alarming: >102 cm for men, >88 cm for women ✓ Neck circumference $\geq$ 43 cm in men, $\geq$ 41 cm in women ✓ Male gender ✓ Postmenopausal state ✓ Smoking ✓ Alcohol / Sedative use ✓ Craniofacial bony abnormalities	
OSA attributable to high-risk population ✓ Hypertension ✓ Pre-diabetes / Diabetes type 2 ✓ Coronary artery disease (acute coronary syndrome) ✓ Cardiac arrhythmia (atrial fibrillation, nocturnal bradycardia, sinus pauses) ✓ Transient ischemic attack / Stroke ✓ Heart failure ✓ Dementia / Alzheimer disease	
OSA nighttime symptoms ✓ Loud snoring ✓ Often insomnia ✓ Abrupt awakenings / gasping / choking ✓ Witnessed apneas ✓ Nocturia ✓ Reflux symptoms	
OSA daytime symptoms ✓ Excessive daytime sleepiness ✓ Dry mouth ✓ Morning headache ✓ Elevated blood pressure ✓ Difficulty concentrating ✓ Depression, irritability ✓ Decreased libido / Erectile dysfunction ✓ Cognitive dysfunction	

Table. Common symptoms, risk factors and high-risk population associated with obstructive sleep apnoea (OSA).

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Pathophysiology of Sleep Disordered Breathing

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Introduction

Twenty years ago, it would have been easy to summarise the pathophysiology of sleep disordered breathing as repetitive nocturnal apnoea in obese persons causing sympathetic nerve system activation, hypertension and over time general cardiovascular disease, heart failure and stroke. The continuing studies in the field have added considerable knowledge but also

many exceptions to this simplified description. Furthermore, despite the wealth of physiological understanding, the evidence for best treatment beyond weight loss and life-style modifications is limited. Part of the explanation for this is that most trials have excluded symptomatic patients, as it has been considered unethical not to offer them treatment. Nonetheless the strong association between sleep disordered breathing and obstructive sleep apnoea (OSA) in particular,