Sleep Deprivation & Cardiovascular Risk

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Sleep is a universal experience shared by all humans and is necessary to sustain life.[1] Yet the influence of sleep on other physiological processes is still poorly understood. Increasing evidence is supporting the importance of adequate sleep for overall health, quality of life, decreased risk of disease and all-cause mortality.[2, 3] More recently, the relationship between sleep and cardiovascular disease risk has been investigated and is emerging as an area that deserves increased attention.

The most recent guidelines from the American Academy of Sleep Medicine and Sleep Research Society state that an average adult needs approximately 7 hours of sleep each night for optimal health.[4] Yet, sleep patterns amongst humans are widely variable and are influenced by cultural, social, psychological, behavioural, pathophysiological and environmental factors.[3] Particularly in Western society and developed nations, sleep patterns have drastically changed over the past few decades. With the advent of longer working hours and commuting times, higher rates of shift-work, continuous access to commodities, increased environmental lighting and exposure to LED light sources, regulated indoor temperatures, consumption of caffeine and alcohol as well as the pervasive use of technology, average nightly sleep duration has decreased significantly.[1,3] So much so, the World Health Organization has described a 'global epidemic of sleeplessness' with approximately two-thirds of adults failing to obtain the recommended 8 hours of sleep each night.[5] Alarmingly, only 48% of adults in the USA report regularly sleeping between 7-9 hours nightly, 26% of the population reports sleeping 6-7 hours nightly and 20% have reported to sleep less than 6 hours nightly.[6]

In 2015, an expert panel formed by The National Sleep Foundation conducted a rigorous evaluation of the scientific literature to provide an update to sleep duration recommendations across the lifespan. It was determined that adults aged 18-64 years are recommended to obtain 7-9 hours of sleep nightly.[7] Decreased sleep duration has not only led to increased reports of fatigue and daytime sleepiness, but has also resulted in harmful effects on human physiology with deleterious impacts on metabolic, endocrine, immune and cardiovascular systems.[3] Failing to obtain adequate sleep is associated with increased risk of immune system dysfunction and susceptibility to infection, Alzheimer's disease, reproductive (fertility) challenges, blood sugar dysregulation, obesity, all major psychiatric conditions (including but not limited to depression, anxiety and suicidality) as well as cardiovascular disease and all-cause mortality.[1,3]

With increasing rates of inadequate amounts of sleep in the adult population, the cardiovascular consequences alone are substantial and highly significant.[6] Specifically, short sleep duration has been identified as an independent marker for morbidity and mortality associated with cardiovascular disease, mainly from coronary artery disease, arrhythmias and hypertension.[8] This is of high clinical significance as following cancer, cardiovascular disease is the second leading cause of death in Canada and is estimated to cost the Canadian economy more than $20.9 billion dollars annually.[9, 10]

Cardiovascular disease encompasses a variety of disorders that affect the heart and blood vessels, but for the purposes of this research paper, the risk of hypertension, coronary heart disease, myocardial infarction, cerebrovascular disease and metabolic disorders in relation to sleep deprivation will be explored. The intent of this paper is to review the available data regarding the relationship between inadequate sleep duration (qualitative and quantitative) and cardiovascular disease outcomes and risk, including the importance of screening for sleep as a risk factor for CVD, potential pathophysiologic mechanisms underlying the relationship and potential sleep-related interventions to reduce CVD risk.

Sleep, the Sleep Cycle & Disordered Sleeping

Simply defined, sleep is the prolonged period of unconsciousness that typically occurs for several hours each night. Sleep is clinically and objectively identified and defined by polysomnography (PSG), which records specific brainwave, eye movement and muscle activity by the placement of electrodes on the head and body. With the development of the PSG in the 1950s, sleep was originally divided into two stages, non-rapid eye movement (NREM) and rapid eye movement (REM). In following years, NREM was further sub divided into four separate stages (NREM Stage 1 through 4), with stages 3 and 4 being the deepest states of sleep in which it becomes increasingly difficult to wake an individual.[1]

Interruption in the quality and/or quantity of sleep that allows an individual to transition through continuous sleep cycles may be secondary to environmental or organic causes. The Diagnostic and

Statistical Manual of Mental Disorders (DSM-5) has identified 10 sleep-wake disorders, which include individual disorders as well as several disorder groups. In the past number of years, the relationship between disordered sleep and risk of cardiovascular disease has been investigated by a number of studies.[11]

DSM-5 SLEEP-WAKE DISORDERS
Insomnia disorder
Hypersomnolence disorder
Narcolepsy
Breathing-related sleep disorders • Obstructive sleep apnea • Central sleep apnea • Sleep-related hypoventilation
Circadian rhythm sleep-wake disorders • Delayed sleep phase type • Advanced sleep phase type • Irregular sleep-wake type • Non-24-hour sleep-wake type • Shift work type
Non-rapid eye movement sleep arousal disorders
Nightmare disorder
Rapid eye movement sleep behavior disorder
Restless legs syndrome
Substance/medication-induced sleep disorder

The Association Between Sleep & CVD Risk

In a recent meta-analysis (2017) of more than 5 million participants from 153 studies, short sleepers (those sleeping <6 hours nightly) had a relative risk of increased mortality of 1.12 (this translates to a 12% absolute increase). With regards to outcomes related to cardiometabolic disease, the review reported a point estimate of an absolute increase of 37% for diabetes mellitus, 17% for hypertension, 16% for cardiovascular disease, 26% for coronary heart disease and 38% for obesity.[12] An exploration of the relationship between specific cardiometabolic conditions and sleep follows.

Hypertension

In 2012-2013, hypertension (defined as blood pressure ≥ 140/90 mmHg) affected 22.6% of the Canadian adult population and the lifetime incidence of developing hypertension is estimated to be 90%[13, 14]. The prevalence of self-reported hypertension has nearly doubled in the past two decades and the annual cost attributed to managing hypertension in Canada is forecasted to reach $20.5 billion by 2020[15]. Hypertension is a clinically relevant and significant risk factor for developing other cardiovascular disorders, such as coronary artery disease, congestive heart failure and cerebrovascular disease (stroke).[16] Epidemiological evidence has reported a U-shaped relationship between extremes of sleep duration and the risk of hypertension, and in corroboration of this, a recent meta-analysis has indicated that short sleep is an independent marker for the incidence of hypertension.[17–19]

An epidemiologic and experimental evidence review completed by Covassin and Singh in 2016 identified that the risk of hypertension is lowest in those sleeping 7 to 8 hours nightly with progressive increases in risk with extremes of sleep length distribution[6]. The greatest risk is seen in those sleeping less than 6 hours nightly; it is estimated that these individuals are 20-32% more likely to develop hypertension in comparison to those obtaining 7-8 hours of sleep. This review also highlighted a 60% increased likelihood of an individual developing hypertension if they are sleeping ≤5 hours and are between 32 to 59 years old.[6]

Interestingly, different populations may be more greatly affected by the curtailing of sleep. Women appear to be more susceptible to developing hypertension due to sleep restriction; the Whitehall II study identified a higher prevalence and incidence of hypertension in middle-aged women sleeping <5 hours nightly compared to those sleeping 7 hours. This was not observed in men.[20] In a study by Stranges et al., the authors found a 66% higher prevalence of hypertension in women who were sleeping less than 6 hours nightly compared to those sleeping 6 hours or more. This study was the first to identify that the effect of short sleep duration on hypertension was more than doubled in premenopausal versus postmenopausal women (OR 3.25 versus 1.49).[21] The impact of sleep duration may also differentially affect various ethnicities. Both white and black individuals sleeping less than 6 hours have a greater likelihood of reporting hypertension; however, hypertension rates were reportedly higher in African-American subjects who were sleeping less than 6 or more than 8 hours nightly as compared to White subjects in the National Health Interview Survey (NHIS), even after adjustment for confounding factors.[6]

The U-shaped relationship between hypertension and sleep hours is most robust for systolic values. Both short and long, typically defined as less than 6 or more than 8 hours respectively, sleep durations have been correlated with loss of nocturnal reduction in blood pressure, a sensitive prognostic marker for CVD.[6]

Coronary Heart Disease

Coronary heart disease (CHD), includes a spectrum of acute and chronic cardiovascular conditions and is one of the leading causes of death worldwide.[6] CHD is caused the atherosclerosis of the coronary vessels, which can lead to ischemic heart disease, the underlying cause of angina pectoris, myocardial infarction and cardiac arrest.[22] Numerous studies have identified the negative correlation between sleep duration and coronary heart disease, demonstrating an increased risk of coronary artery calcification, myocardial infarction and heart failure highest in those with short sleep duration.[8] Furthermore, the recurrence of cardiac events is strongly associated with disturbed sleep patterns and disturbed sleep is now known to be an independent prognostic marker for cardiac prognosis.[23]

In similarity to hypertension, epidemiologic studies show a U-shaped curve with respect to sleep duration and risk of CHD; prevalence of CHD is higher in those sleeping <6 hours/night or >9 hours/night.[6] The incidence of fatal and non-fatal CHD events follows a similar pattern; greatest risk of CHD occurs in those with regular sleep duration above or below 7-8 hours nightly. A 10-year follow up with the participants in The Nurses' Health Study reported a 1.39 relative risk in women reporting <5 hours of sleep each night and a 1.37-fold higher relative risk in those sleeping >9 hours nightly compared to those sleeping 8 hours.[6] A meta-analysis in 2014 identified a 45% increased risk of morbidity and/or mortality from cardiovascular disease in subjects who reported difficulty initiating and maintaining sleep or experienced disturbed sleep during the night in comparison to subjects who reports good sleep quality.[11]

In a 2019 systematic review investigating the relationship between sleep and coronary heart disease, Madsen et al completed a review of 64 articles. The authors reported that both disturbed sleep architecture and amount of sleep are commonly experienced by those with CHD, with sleep disturbances being most aggravated in relation to an acute coronary event.[23] Importantly, this systematic review was the first to account for CHD and sleep disturbances in patients with anxiety, depression and sleep-disordered breathing, as these are known to co-occur. The authors also noted that the majority of literature investigating sleep disturbances and CHD is in relation to sleep disordered breathing (SDB).

Sleep-disordered breathing

Diagnosed with overnight polysomnography, sleep disordered breathing (SDB) is "characterized by repetitive episodes of shallow breathing or apnea during sleep", resulting in intermittent hypoxemia.[24] In a vicious cycle, the risk factors for developing and the sequelae of SDB include sympathetic nervous system activation, metabolic abnormalities (insulin resistance and dyslipidemia), systemic inflammation and increased oxidative stress, obesity and cardiovascular dysfunction (hypercoagulability, uncoupling of myocardial workload, vascular endothelial dysfunction and arteriosclerosis). SDB is in return associated with a high risk of CVD, including sudden death, atrial fibrillation, stroke, coronary heart disease and heart failure.[24]

SDB encompasses obstructive sleep apnea (OSA; characterized by the cessation or reduction of airflow still in the presence of respiratory effort) and central sleep apnea (CSA; in which both the airflow and respiratory effort stop during sleep). The gold-standard treatment for SDB is continuous positive airway pressure (CPAP) therapy, which attenuates apneic and hypoxic episodes by preventing collapse of the pharynx and reducing the cessation of airflow and oxygen desaturation. Treatment with CPAP therapy has been reported to improve sleep quality, heart rate variation, daytime sleepiness and overall quality of life.[24] However, the effect of CPAP therapy on various cardiovascular conditions is mixed.

A 2015 review highlighted that the strongest evidence of CPAP use is for the reduction of hypertension.[25] A 2018 review reported that observational studies indicate CPAP therapy is effective at reducing the incidence of hypertension, nonfatal cardiovascular events in men and fatal cardiovascular events in men, women and the elderly.[26] However, the authors noted that more recent randomized trials failed to demonstrate benefit for secondary prevention of cardiovascular events. It is noteworthy that this discrepancy may be due to the failure to adjust for confounding variables unknown in observational studies as well as poor CPAP adherence and compliance in randomized trials.[25] Given the nature of the device, users often remove their CPAP machine over the course of the night, particularly in the early hours of the morning during REM sleep periods.[26] This is of additional significance, as REM sleep is already associated with an increased cardiometabolic demand and occurs when noncompliant individuals have removed their CPAP. However, numerous studies have indicated that the longer the duration of use of a CPAP machine on a nightly basis, the more benefit on CVD.[26]

Metabolic Disorders

Several epidemiological studies have demonstrated the relationship between short sleep duration, circadian rhythm disruption and metabolic derangement, including insulin resistance, glucose intolerance, changes in leptin and ghrelin hormone release and negative alterations in lipid profiles.[16] These metabolic changes, although not described in detail here, can lead to an increased risk of obesity, hypercholesterolemia, metabolic syndrome and type 2 diabetes mellitus, further increasing the risk of CVD in the presence of prolonged sleep deprivation.[16]

Pathophysiological Mechanisms

The underlying mechanisms relating the increased risk of CVD and sleep complaints have been investigated by both epidemiologic and experimental studies, but remain incompletely understood. [11] This is complicated by the fact that there is considerable heterogeneity in experiments investigating the effects of short sleep time in humans and population-based studies have associated limitations. Regardless, epidemiological observational findings are accompanied by experimental and laboratory-based evidence, which provide some insight into the mechanisms of increased CVD risk due to inadequate sleep.

Inflammation – Considered to be one of the most important underlying pathophysiological mechanisms in the development of CVD, the creation of a pro-inflammatory state in short sleepers has been proposed as a possible mechanism increasing the risk of CVD in these individuals. Although conclusive evidence is lacking, several studies consistently report a pro-inflammatory state after both partial and total sleep deprivation. This pro-inflammatory state is thought to play into the increased oxidative stress, endothelial dysfunction, release of prothrombotic factors and ultimately, the development of atherosclerosis, increasing the risk of CVD. Exactly how an inflammatory state develops after sleep deprivation is not fully understood, but it appears that increased sympathetic nervous system activation plays a role.[16]

Autonomic Nervous System Dysfunction – In studies in both humans and rodents, sleep deprivation and sleep restriction are associated with increases in sympathetic nervous system (SNS) activity and the hypothalamic pituitary adrenal (HPA) axis dysfunction.[27] Activation of these systems in the presence of an acute or chronic stressor results in the release of catecholamines (adrenaline and noradrenaline) and glucocorticoids (cortisol). Under normal circumstances, these hormones have pronounced diurnal variation and rapidly decline during sleep, as sleep has suppressive effects on these systems.

There is now evidence that clearly illustrates the effect of sleep loss on our neuroendocrine system. Almost all the data investigating the mechanisms of increased risk of CVD risk and sleep deprivation indicate that any form of sleep disruption is associated with sympathetic nervous system activation.[16] Understandably, the relationship between stress and sleep is bidirectional, as increased stress may lead to insufficient and/or poor quality sleep and vice versa.[27] However, studies investigating heart rate variability (HRV), a marker of the response of the SNS on cardiovascular function, demonstrate that SNS activity is indeed affected by sleep, and lack thereof.[27] HRV is an independent risk factor for morbidity and mortality; accumulating evidence is identifying the relationship between HRV and modifiable and non-modifiable CVD risk factors. Interestingly, increasing HRV (by decreasing sympathetic activity and increasing parasympathetic dominance), lowers CVD risk profiles.[28]

While there is reported variation on the degree to which SNS activation occurs after sleep deprivation, increases in sympathetic outflow can in turn increase coronary vasomotor tone, blood pressure and heart rate, ultimately affecting the supply and demand of oxygen, even in healthy individuals.[1, 8] The result of chronic sympathetic activation is endothelial dysfunction, compromising the oxygenation of the myocardium, increasing the risk of atherosclerosis and platelet activation. Accompanying this chronic activation of the SNS are changes in other neuroendocrine pathways, including the renin angiotensin system, the thyroid and leptin/ghrelin release.[8] Figure 1, from Cappuccio and Miller (2017) eloquently illustrates the interconnectedness of sleep deprivation and possible pathological mechanisms affecting the cardiovascular system.[29]

Clinical Significance

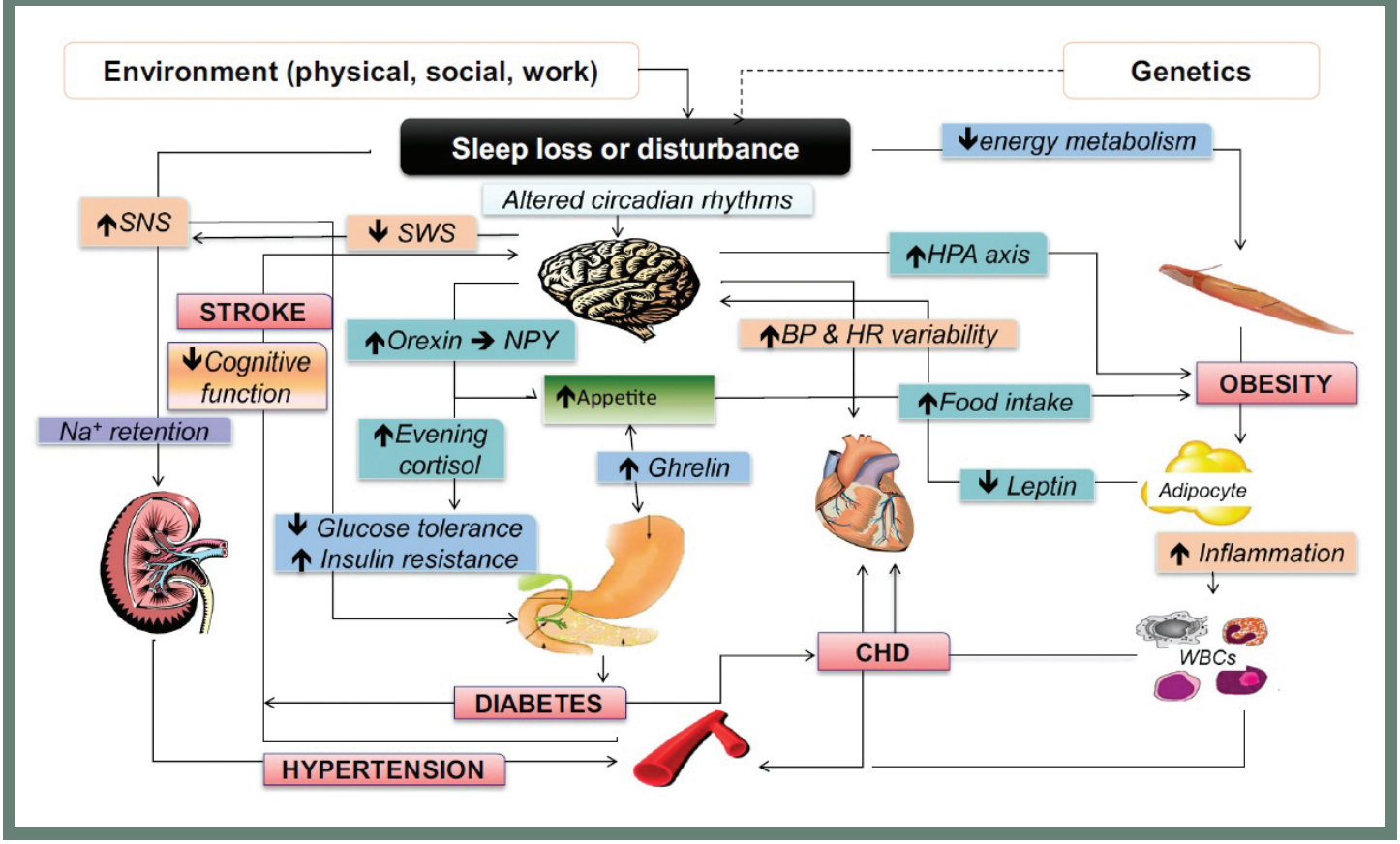
The pathophysiological outcomes associated with short sleep duration are established major risk factors for the development of cardiovascular and metabolic disease.[16] The complex interplay and combination of metabolic and circulatory abnormalities can contribute to the development of cardiovascular diseases, however, there is still debate over whether the relationship between these outcomes and risk factors are mono- or bidirectional.[12, 16] Due to the limitation of the fact that the majority of clinical evidence investigating short sleep duration and the increased risk of cardiovascular disease comes from cross-sectional studies, a causal link cannot be confirmed. However, experimental evidence does support this hypothesis.[16]

Regardless, the clinical significance of disturbed sleep and its negative impact on cardiovascular disease is well-established. Therefore, it is important that clinicians, especially in the primary care setting, screen for sleep disorders, yet data suggests this is not routinely the case.[30] Considering the presented information, primary care providers should take into consideration the power of and importance of sleep on overall health, particularly related to the risk of cardiovascular disease. Primary care providers are at the epicenter of this process, as the screening for cardiovascular risk factors and the development of CVD is widely implemented in Western medicine to identify high-risk individuals and implement risk reduction. A recent 2016 systematic review of guidelines for cardiovascular risk assessment included the review of 21 sets of guidelines, 5 of which were specific to total cardiovascular risk. Sleep was not identified as a recommended risk factor to screen for.[31]

A number of ways to increase the screening of sleep disorders have been proposed, including raising awareness through improved communication and educational measures, incorporating chart reminders as well as providing sleep intervention support.[32] As Mollayeva *et al.* report in a systematic review and meta-analysis of 37 studies, the Pittsburgh Sleep Quality Index (PSQI) is the most commonly used subjective assessment of sleep in the clinical and research settings and is currently the only standardized clinical instrument that covers a wide range of factors relevant to sleep quality.[33] Together with a detailed clinical history of the patient, other factors not included on the PSQI may also be identified, including circadian rhythm disruption and medication effects. It is important to note that to date, there is no agreed upon method among clinicians in assessing quality of sleep in a patient, nor has a study to investigate this been completed.[33]

Despite the fact that primary care physicians find screening for sleep disorders and the implementation of preventative strategies to reduce the risk of CVD challenging, approaches to improve the quality and duration of sleep are worthwhile considerations for both the primary and secondary prevention of CVD, as management of those with increased risk of CVD remains suboptimal.[31] While there is plenty of evidence and studies investigating the impact of lifestyle interventions like physical activity, diet, alcohol, smoking

FIGURE 1



and body composition on CVD risk modification, there is limited evidence available including sleep duration.[34] However, despite the lack of volume, the existing evidence is promising and many authors investigating the relationship between short sleep duration and CVD risk emphasize the need and importance of future studies in this area.

In the first study of its kind to identify the impact of sufficient sleep in addition to four other well-established lifestyle factors that reduce the risk of CVD (adequate physical activity, consuming a Mediterranean diet, appropriate alcohol consumption and non-smoking), sufficient sleep (≥ 7 hours nightly) was shown to significantly reduce the risk of CVD.[34] The study involved tracking 10,571 adults aged 20-65 years free of CVD at baseline over 10-14 years. Compared to those who did not implement any or implemented only one of the healthy lifestyle factors, those who implemented all four had a 57% lower risk of CVD (HR 0.43, 95% CI) and a 67% lower risk of fatal CVD (HR 0.33, 95% CI). When sufficient sleep was added to these four healthy lifestyle factors, there was a 65% lower risk of CVD and an 83% lower risk of fatal CVD. This translated to a theoretical prevention of 36% reduction in the number of CVD cases when either all four or five lifestyle factors were implemented and a 46% and 57% reduction in the number of fatal CVD events with adherence to all four or five factors, respectively. Withstanding limitations of the study, this equates to the possible prevention of 14 fatal CVD events amongst the study participants.

Interventions to Improve Sleep & Reduce CVD Risk

With the demonstrated relationship between sleep disturbances and increased risk of cardiovascular disease, the clinical relevance lies in whether improving sleep quality and duration decreases CVD risk. Although limited, there are studies targeting CVD risk reduction with sleep interventions that show promising results.

Cognitive behavioural therapy (CBT) is an evidence-based intervention that teaches cognitive restructuring and behavioural modification to improve mental and physical health outcomes. CBT for insomnia (CBT-I) is considered the gold standard therapy for insomnia recommended by the American College of Physicians and the American Academy of Sleep Medicine. CBT-I focuses on sleep hygiene principles with individualized recommendations for the patient, after accounting for their sleep challenges and lifestyle. CBT-I appears to have more long-lasting benefit than sleeping medications, provides substantial benefit with minimal risk, can address comorbid conditions (i.e. depression and anxiety, which are often present in individuals with CVD) and can be combined with pharmacotherapy for increased efficacy.[35]

Individuals with CVD who receive CBT have been shown to improve health behaviours and positively modify their lifestyle to reduce their overall CVD risk.[36] Although limited, available evidence

does suggest that CBT-I improves biomarkers related to CVD risk, insomnia, sleep patterns and daytime symptoms.[37] In the first of its kind, a recent 2019 study that tailored CBT-I to patients with CVD reported significant improvement in sleep outcomes (duration, continuity, efficiency, latency and quality) while also reporting significantly fewer symptoms of anxiety, depression and insomnia (p value <0.05).[38] The authors, Heenan et al (2018) highlighted the need for randomized trials further investigating CBT-I specific for the CVD patient population.

Furthering the mind-body connection and its implication on reducing risk of CVD, decreased Heart Rate Variability (HRV) (governed by the sympathetic nervous system) is an established risk factor for CVD, and interventions to increase HRV are worthwhile considering. Modifiable factors such as smoking cessation, physical exercise and weight loss are associated with increased HRV.[39] There is also some evidence that suggests that dietary changes (the consumption of fruits and vegetables, moderate alcohol consumption and intake of omega-3 fatty acids and vitamin D) may also increase HRV. Mindfulness and meditation may also reduce stress and worry through the modulation of HRV.[39]

Conclusion

Accumulating evidence is demonstrating a profound relationship between sleep disturbances and the risk of cardiovascular disease, including a clinically significant risk of hypertension, diabetes mellitus, myocardial infarction and coronary heart disease. Short sleep duration is also associated with activation of the sympathetic nervous system, impairing heart rate variability, while also increasing the activity of the HPA axis, leading to elevated secretion of catecholamines and glucocorticoids. The result is a negative cycle in which sleep disturbances may be exacerbated, further increasing the risk of CVD.

The screening for sleep disorders is insufficient in the primary healthcare setting, but may easily be introduced by simply inquiring about sleep habits and administering the PSQI. The importance of identifying sleep disturbances as a significant risk factor for CVD should not be overlooked; in a systematic review and meta-analysis with over 5.1 million cumulative participants from 153 studies, short sleep is significantly associated with mortality (RR 1.12, 95% CI, 1.08-1.16), hypertension (1.17, 1.09-1.26), CVD (1.16, 1.10-1.23) and coronary heart disease (1.26, 1.15-1.38).[12]

With this significant increase in CVD risk associated with short sleep duration, multiple studies emphasize the existing positive evidence as well as the need for future investigation on psychosocial interventions to ultimately lower CVD risk. As naturopathic doctors, we are well positioned within the healthcare system to identify, assess and address sleep disturbances to not only improve the overall quality of life of our patients, but also to reduce the risk of CVD.

About the Author

Dr. Leigha Saunders, ND is a graduate of the Canadian College of Naturopathic Medicine and the owner and founder of Uxbridge, Ontario's premiere wellness clinic, True Roots Healthcare. Dr. Saunders maintains a private practice with a special interest in sleep medicine and the impact sleep has on all aspects of heath. She believes that when you have your health you have everything. Dr. Saunders holds general, IVIT and therapeutic prescribing certification with the College of Naturopaths of Ontario and is a member of the CAND and the OAND.

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