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Sleep: Important Considerations for the Prevention of Cardiovascular Disease

Michael A. Grandner, PhD MTR[1,2,3,*], **Pamela Alfonso-Miller, MD**[1], **Julio Fernandez-Mendoza, PhD**[4], **Safal Shetty, MD**[3], **Sundeep Shenoy, MD**[3], and **Daniel Combs, MD**[3]

[1]Sleep and Health Research Program, Department of Psychiatry, University of Arizona College of Medicine, Tucson, AZ

[2]Sarver Heart Center, University of Arizona College of Medicine, Tucson, AZ

[3]Department of Medicine, University of Arizona College of Medicine, Tucson, AZ

[4]Department of Psychiatry, Penn State Hershey Medical Center, Hershey, PA

Abstract

Purpose of Review—Sleep plays many roles in maintenance of cardiovascular health. This review summarizes the literature across several areas of sleep and sleep disorders in relation to cardiometabolic disease risk factors.

Current Findings—Insufficient sleep duration is prevalent in the population and is associated with weight gain and obesity, inflammation, cardiovascular disease, diabetes, and mortality. Insomnia is also highly present and represents an important risk factor for cardiovascular disease, especially when accompanied by short sleep duration. Sleep apnea is a well-characterized risk factor for cardiometabolic disease and cardiovascular mortality. Other issues are relevant as well. For example, sleep disorders in pediatric populations may convey cardiovascular risks. Also, sleep may play an important role in cardiovascular health disparities.

Summary—Sleep and sleep disorders are implicated in cardiometabolic disease risk. This review addresses these and other issues, concluding with recommendations for research and clinical practice.

Keywords

Sleep; cardiovascular; diabetes; insomnia; sleep apnea

INTRODUCTION

Sleep is responsible for many regulatory and maintenance functions in human physiology. Although this has been well-established, the specific mechanisms of these functions, and the

*CORRESPONDING AUTHOR: Michael A. Grandner PhD MTR, University of Arizona Department of Psychiatry, 1501 N Campbell Ave, Suite 8326, PO Box 245002, Tucson, AZ 85724-5002, (520) 626-6346, grandner@email.arizona.edu.

relation of this physiology to relevant clinical outcomes, has only more recently received increased attention. With this in mind, much recent work has focused on the role of sleep in the maintenance of cardiometabolic health. This includes laboratory, clinical, and epidemiologic research, focusing on issues such as insufficient sleep and sleep disorders such as sleep apnea and insomnia. Also, research has focused on issues pertaining to special groups, such as pediatric populations and racial/ethnic minorities. This review summarizes the work in these areas and proposes some considerations for addressing sleep duration and sleep disorders in the context of preventing cardiovascular disease.

HABITUAL SLEEP DURATION AND CARDIOVASCULAR DISEASE

Recently, the American Academy of Sleep Medicine and the Sleep Research Society jointly established a consensus panel to determine recommended guidelines for sleep duration. As a result of this process, a final guideline document was released(1-3) in addition to a companion manuscript that detailed methodological and other considerations(4, 5). In a parallel effort, the National Sleep Foundation developed its own guideline document(6) and companion manuscript(7). Both of these efforts agreed that a typical adult should get at least 7 hours of sleep on a typical night in order to maintain optimal health and functioning. (The document by the National Sleep Foundation also suggested an upper limit of 9 hours.) The American Thoracic Society also recently released a document that made a similar statement(8). Taken together, these documents identify 7 hours as the minimum amount of habitual sleep duration that is recommended for health and functioning. As a part of all of these efforts, the respective panels examined a growing body of literature that identifies associations between insufficient habitual sleep duration and cardiometabolic disease risk.

Prevalence of insufficient sleep

Data from two survey cycles (2005-2006 and 2007-2008) of the National Health and Nutrition Examination Survey (NHANES) show that adults aged 20-39 and adults aged 40-59 reported sleeping less than 7 hours in a 24 hour period more frequently (37.0% and 40.3% respectively) than those aged over 60 years (32%)(9). These results are further supported by a recent CDC report, utilizing data from the Behavioral Risk Factor Surveillance System, that over 30% of US adults report less than 7 hours of habitual sleep duration(10).

Rather than being distributed evenly across the geographic landscape, Grandner and colleagues found unevenness in the distribution of such phenomenon. Using county-level data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS), Grandner et al. identified insufficient sleep 'hotspots' in the Appalachian region that connects Tennessee, Virginia, West Virginia, Kentucky, and Ohio. Similar hotspots were found in the Midwest and southeast United States(11).

Sleep duration, cardiovascular events and mortality

Sleep duration and mortality are associated in a U-shaped fashion, where lowest risk is usually found in those who sleep between 7-8 hours, and mortality risk increasing with further deviation on either end of the range. This pattern of findings has been explored in

multiple narrative reviews(12, 13) and meta-analyses(14, 15). Mechanisms for this relationship are still not completely delineated, but short sleep duration has been linked to chronic illness, cardiovascular disease (CVD), increased BMI and risk for obesity, accidents, hypertension, hypercholesterolemia heart attack and stroke(12, 16-26) [3-11]. To investigate the association between short and long sleep duration and total CVD and coronary heart disease incidence, Hoevenaar-Blom et al. conducted a 12-year prospective study of 20,432 healthy men and women in the Netherlands and found that those individuals who slept   6 hours had a 15% higher risk of CVD incidence and a 23% higher risk of CHD incidence compared to people who slept 7-8 hours. When sleep quality was compared, individuals with short sleep duration and poor subjective sleep has a 63% higher risk of CVD and 79% higher risk of CHD than those with normal sleep duration and good sleep quality(22). In another relevant study, Altman and colleagues examined data from the 2009 BRFFS and found that short sleep duration was associated with elevated prevalence of hypertension, hyperlipidemia and history of heart attack and stroke(16).

Sleep duration and obesity

While the relationship between sleep duration and BMI can vary across age and age-related sleep need(19), insufficient sleep has been linked to lower energy expenditure, altered glucose homeostasis and alterations in hormones that mediate hunger(24, 25, 27-31). Altered sleep patterns may also be tied to lifestyle choices that are related to higher BMI and obesity(32). One possible mechanism for this could be explained by the metabolic hormones leptin and ghrelin. Leptin is secreted by adipose cells and it acts on the hypothalamus by regulating appetite through hunger inhibition. In laboratory sleep deprivation studies, decreased leptin secretion has been shown(26, 33). Ghrelin is a neuropeptide produced in the gastrointestinal tract. It acts on hypothalamic cells to increase hunger and has been shown to be increased in deprived sleep states in laboratory studies(26, 28, 33). This hormonal interaction may lead to an eating pattern that may lead to a dysregulation of energy balance through appetite stimulation that might predispose to cardiometabolic disease and weight gain. Along with the situational aspect of being awake longer leading to increased calorie intake, sleep deprived individuals are prone to indulge in late night snacks and make unhealthy food choices(34-40).

Sleep duration and behavioral risk factors

A variety of behavioral risk factors have been positively linked to insufficient sleep, such as unemployment, increased alcohol consumption, self-reported poor mental health days, and active cigarette smoking(41, 42). Additionally, sleep deprivation leads to cognitive impairment and reduced attention(43-46). Chronic sleep insufficiency has played a role in motor vehicle accidents, industrial disasters, medical and other occupational errors, for instance(41, 42, 47-51). Others have found that short self-reported sleep duration is associated with risk of depression(4, 52-54), the same association has been found for long sleepers (>8-9 hours) (13).

Sleep duration and inflammation

Inflammation is a well-established key mechanism in CVD risk and could be a possible mechanism linking sleep duration and CVD(55). Sleep deprivation has been associated with

increased inflammation and negative cardiovascular outcomes. Proinflammatory processes that promote the development of atherosclerotic plaques and Proinflammatory markers (such as tumor necrosis factor α [TNFα], interleukins 1 (IL-1), 6 (IL-6), and 17 (IL-17), C-reactive protein (CRP), cellular adhesion molecules, and visfatin) have demonstrated or suggested an association with sleep deprivation in laboratory studies(55). Cytokines (specifically IL-6) and elevated CRP are a clinically useful measure of systemic inflammations that have been shown to be present in healthy individuals exposed to partial and total sleep deprivation(56).

A recent meta-analysis did not find a consistent association between short sleep and inflammation(57). A study using the 2007-2008 NHANES(56) (not included in that meta-analysis) and a subsequent review(55) present some potential explanations. For example, using the 2007-2008 NHANES, levels of CRP were distributed in a U-shape across the US population. A few elements of this relationship suggest reasons why other studies could not find this relationship. First, these elevations were only seen at the extreme ends of the sleep duration spectrum (<5 and >9 hours), which most studies are not powered to examine. Second, there were significant race/ethnicity and sex patterns, suggesting that the makeup of the sample also played a role in findings. Third, since CRP does not demonstrate a circadian rhythm(58), a single measurement (common in epidemiologic studies) is more appropriate for this analyte. Finally, the NHANES sample may be one of the few samples that is sufficiently large and diverse (regarding age, sex, race/ethnicity, and geography) to detect the elevation associated with short sleep.

Sleep duration and Diabetes Mellitus (DM) risk

Sleep deprivation alters glucose homeostasis, leading to insulin resistance and risk of diabetes(17, 18, 24, 59-61). Sleep extension in restricted sleepers may lessen this relationship by improving glucose tolerance(17). Current research is exploring mechanistic pathways involved, including adipose tissue physiology and the role of circadian genetics.

In the Western New York Health Study, Rafalson and colleagues found that sleep duration <6 h was associated with impaired fasting glucose [30]. In another study, Shankar and colleagues found that self-reported insufficient sleep was positively associated with prevalence of Diabetes(62). In a cross sectional study, Hall et al. found that both short (>7h) and long sleepers (>8) were associated with metabolic syndrome in midlife adults despite adjusting for traditional risk factor components(63).

Several reviews on this topic have been published elsewhere(24, 60, 64, 65), including several meta-analyses(3, 66-69), which show that habitual short sleep duration was associated with a 30-50% increased incidence of diabetes.

Sleep duration and blood pressure

In a study of ambulatory blood pressure in 18 healthy subjects, Lusardi and colleagues observed that when sleep was restricted to the second half of the night for only a week, elevated diastolic and systolic blood pressure were present, compared to the week prior where a typical night of sleep was observed with no alterations(70).

At the population level, Altman and colleagues found increased risk of hypertension associated with both short (5-6 hours)(16). In an analysis of the 2004–2005 NHIS data, Buxton and Marcelli found that short sleep duration is associated with increased prevalence of hypertension and CVD(21). Using the 2007-2008 NHANES data, Grandner and colleagues established an association between short sleepers and elevated risk for self-reported history of hypertension, but not recorded blood pressure(20).

Sleep duration and lipids

Increased CVD morbidity risk is tied to a decrease in High-Density Lipoprotein (HDL) and an increase in Low-Density lipoprotein (LDL). This relationship might be mediated by age and gender, as lipoprotein metabolism is strongly associated with sex hormones. In one study, elevated triglyceride and LDL profiles were found in Japanese women who slept <6 hours and >8 hours and were lowest among women who slept 6-7 hours. Risk of high LDL was low in men sleeping 8 hours(71). Short sleep duration has also been identified as a risk factor for hyperlipidemia and hypercholesterolemia in adolescents(72). Although a different study found relationships to hyperlipidemia only in very short sleepers, this association was most evident in non-Hispanic whites and Asians/others(20). It should be noted that in this study population, women were less likely to report as short or long sleepers. Very short sleep (>5) and increased incidence of hyperlipidemia was also found by Altman et al(16).

Taken together, habitual short sleep duration is highly prevalent in the US population. Regarding cardiometabolic risk, short sleep duration (6 hours or less), and especially very short sleep duration (less than 5 hours) is associated with increased cardiometabolic morbidity and mortality, including weight gain and obesity, hypertension, hyperlipidemia, and diabetes.

SLEEP APNEA AND CARDIOVASCULAR DISEASE

Prevalence of Sleep Apnea

In a recent review of 11 published epidemiological studies, the prevalence of obstructive sleep apnea (OSA), defined as an Apnea-Hypopnea Index (AHI) greater or equal to 5, was estimated to be 22% in men and 17% in women(73). More recent studies indicate that this is increasing, with an estimated prevalence of 37% in men and 50% in women(74, 75). The reason for the rising prevalence is thought to be secondary to differences in diagnostic equipment, the definition of OSA, study design, and patient characteristics such as age and obesity.(73) The prevalence of OSA in obesity is about 50% (76), with much higher prevalence in morbidly obese individuals.(77)

Drager and colleagues, studied 152 consecutive patients with metabolic syndrome (MetS) with a standard polysomnogram (PSG) and found the prevalence of moderate-severe sleep apnea, defined as an AHI greater than or equal to 15, to be about 60%. Patients with MetS and OSA were found to have greater cardiometabolic morbidity in comparison with those without OSA.(78)

Obstructive sleep apnea (OSA) and cardiovascular mortality

The association between OSA and cardiovascular mortality is complicated due to associated factors such as obesity, insulin resistance, and dyslipidemia. However, OSA is an independent risk factor for atherosclerotic heart disease(79). Epidemiological data supports the idea that OSA can initiate not only cardiovascular conditions such as hypertension and ischemic heart disease but also worsen existing disease(80).

The key pathology resulting in the adverse cardiovascular outcomes stems from the intermittent hypoxia, hypercapnia, intrathoracic pressure changes and the resulting autonomic changes(80). The intermittent hypoxia induces oxygen free radical production and sets off an inflammatory response, over time causing adverse cardiovascular damage(81, 82).

A prospective study from Punjabi and colleagues, showed increased all-cause mortality, specifically from coronary artery disease, in men aged 40-70 years with severe OSA characterized by apnea-hypopnea index (AHI) of greater than 30(83). Similar results were noted in an observational study where severe OSA was linked to an increased risk of fatal cardiovascular events (odds ratio of 2.87; 1.17 – 7.51) as well as non-fatal cardiovascular events (odds ratio of 3.17, 1.12 –7.51) compared to a control of healthy individuals(84). The intermittent hypoxia-hypercarbia results in myocardial oxygen demand-supply mismatch and can trigger nocturnal angina as well as ischemic electrocardiographic (EKG) changes(85).

OSA is a common treatable cause of drug-resistant hypertension(86). Independent of confounders, the odds of developing hypertension was 2.89 (95% CI; 1.46 –5.64) for patients with an AHI of >15 compared to the control group(87). A higher prevalence of arrhythmias such as paroxysmal supraventricular tachycardia and atrial fibrillation is noted in patients with OSA. An observational study reported patients with untreated OSA had twice the risk of recurrence of atrial fibrillation compared to the group who were treated with Continuous Positive Airway Pressure (CPAP) therapy(88).

Patients with congestive heart failure can have a component of central sleep apnea atop their obstructive component(89). Mansfield and colleagues, in a randomized trial, showed that patients treated with CPAP in addition to standard heart failure therapy had improved ejection fraction as well as improved quality of life(90). Similar results were noted by Kaneko et al., who noticed an improvement in ejection fraction as well morning blood pressures with CPAP treatment. This improvement was observed as early as one month from the initiation of CPAP therapy(91). Promising results were also noted by Ryan and colleagues who reported a 58% reduction in the frequency of ventricular arrhythmias during sleep in patients with OSA and heart failure(92).

A prospective observational study involving patients with CAD and moderate OSA with AHI >15 showed patients on CPAP had a significantly decreased cardiovascular mortality, acute coronary syndrome, hospitalization from heart failure exacerbation as well as need for coronary revascularization compared to the group which did not use the CPAP(93). Hence, a

consistent finding is that there is an improved cardiovascular outcome with regular use of CPAP in patients with OSA.

Syndrome Z and Metabolic Syndrome

Syndrome Z describes the association between OSA and metabolic syndrome (MetS). The odds for the presence of MetS in OSA ranges from five to nine fold when compared to individuals without OSA.(94) OSA may be an independent risk factor for metabolic syndrome.(95)

Sleep Apnea and Heart Failure

The prevalence of OSA among heart failure patients is about 30-50% while that of central sleep apnea (CSA) is about 25-40%. The presence of Congestive heart failure (CHF) may exacerbate or contribute to the development of OSA(96). Nocturnal fluid shift rostrally from the lower extremity towards the neck is believed to contribute to the pathogenesis of both OSA and CSA.(97)

Episodes of apnea and hypopnea related to pharyngeal collapse associated with OSA leads to negative inspiratory intrathoracic pressure. As a consequence, the venous return to heart increases increasing the right ventricular (RV) preload. Intermittent hypoxia, causes pulmonary vasoconstriction and hence increases RV after load. This may lead to the development of pulmonary hypertension and RV dysfunction. The post apneic related increase in sympathetic drive can persist during the day and lead to neurohormonal dysregulation and can adversely affect cardiac remodeling(96). Patients with HF may not present with typical symptoms of sleep apnea, such as excessive daytime sleepiness due to the heightened sympathetic activity(98). Intermittent hypoxia results in oxidative stress and release of inflammatory mediators involved in the progression of atherosclerosis. Wang and colleagues, in a study of patients with HF to determine the effect of untreated moderate to severe OSA versus mild to no OSA, found that the mortality was significantly higher in the untreated moderate to severe OSA group(99). Treatment with CPAP therapy has been shown to improve left ventricular ejection fraction, functional class, reduce hospitalization and consequently survival.(96)

Patients with HF have a high prevalence of Central sleep apnea (CSA). Cheyne stokes respiration (CSR), a pattern of breathing characterized by a cyclic crescendo decrescendo pattern of hyperventilation followed by apnea in the absence of upper airway obstruction(100). CSR in low output HF is thought to be due to an impaired feedback mechanism with delayed messaging to the respiratory control center resulting in respiratory oscillation in response to a fluctuating PCO2 level(101). The presence of wake hypocapnia, as demonstrated on an arterial blood gas may help predict the presence of CSR during sleep. (101) Treatment consists of targeted optimization of medical therapy to HF status. CPAP improves CSR by multiple mechanisms, such as by increasing lung volume, stabilization of the upper airway, and improved oxygenation and cardiac function.(102)

Sleep Apnea and Diabetes Risk

The prevalence of OSA in patients with history of diabetes mellitus (DM) ranges from 58-87%.(94) OSA has been linked with increased risk of developing DM due to deregulation of glucose metabolism and alteration in the hypothalamic –pituitary adrenal axis (HPA) axis(103, 104). Intermittent hypoxia and sleep fragmentation related to OSA have been shown to independently increase insulin resistance, increase sympathetic activity and serum cortisol, and impair glucose clearance(94, 105) . The severity of OSA has a direct correlation with the worsening of glucose metabolism. In a study done to assess the effect of the severity of OSA and glycemic control by measurement of Hemoglobin A1c, it was found that HbA1c increased by 1.49% in mild OSA, 1.93% in moderate OSA, and 3.69% in severe OSA, compared with individuals without OSA.(106)

Improvement in glycemic control has been demonstrated after 3 months of CPAP use, with improvement related to number of hours of nightly CPAP use(107, 108). In a recent randomized control trial, patients who received CPAP when compared to the control group who did not receive CPAP were found to have improved glucose control and insulin sensitivity.(109) Also, CPAP therapy has been shown to improve insulin sensitivity in patients with OSA with or without diabetes(110, 111).

Sleep Apnea and Hypertension

Epidemiologic studies support the strong relationship between OSA and hypertension.(112) The prevalence of OSA in individuals with hypertension is estimated to be about 40-50%(112) and approaches 83% in patients with resistant hypertension(86). In a large prospective longitudinal study on participants of the Wisconsin sleep cohort study, the odds for the presence of hypertension were 2.03 for apnea-hypopnea index (AHI) between 5.0 to 14.9 events per hour and 2.89 for AHI greater than 15 events per hour(113). Epidemiologic studies suggest the relationship between hypertension and OSA to be bidirectional. Activation of the sympathetic nervous system and renin-angiotension-aldosterone system, along with oxidative stress and endothelial dysfunction, implicate OSA as an independent risk factor for the development of hypertension. Inhibition of upper airway muscles, volume overload and rostral shift of fluid nocturnally can contribute to pharyngeal edema and the development of OSA in hypertensive patients.(114)

Schein and colleagues performed a recent met analysis and systematic review of 16 RCTs involving over 1000 patients, to study the effects of CPAP therapy on hypertension in OSA patients. Modest reduction in mean systolic blood pressure (SBP) (−4.92 mm Hg; 95%CI −8.70 to −1.14) and mean (−2.56 mm Hg; 95% CI −4.43 to −0.68 mmHg) nighttime blood pressure were seen. No significant change in daytime SBP (−0.74 mm Hg; 95% CI −3.9 to 2.41) and daytime diastolic blood pressure (−1.86 mm Hg; 95% CI −4.55 to 0.83) were observed, however.(115)

The effect of CPAP therapy is more pronounced in patients with resistant hypertension. In a recent meta-analysis, to study the effect of CPAP therapy on OSA patients on this subset of patients, showed the mean improvement of ambulatory SBP and DBP of −6.74 mm Hg (95% CI −9.98 to −3.49;P value <0.001) and −5.94 mm Hg (95% CI;-9.40 to

−2.47;P=0.001) respectively(116). The improvement correlated with the duration of CPAP use. Blood Pressure improved by 1.3 mm Hg for each additional hour of CPAP use.(117)

Sleep Apnea and Dyslipidemia

Murine experiments reveal that it is the intermittent hypoxia which upregulates triglyceride and phospholipid synthesis and inhibits cholesterol uptake in the liver resulting in dyslipidemia(118, 119). OSA has been associated with dyslipidemia and its associated higher CV mortality. However, the causal relation between OSA and dyslipidemia remains to be elucidated due confounders such as obesity, diet, and physical activity.

The evidence is limited to cross-sectional studies and a few randomized studies. The major limitation of all these studies being their duration of follow-up. The majority of the studies indicate that the total cholesterol and LDL were unchanged. However, an increase in triglyceride levels and decrease in the HDL levels were noted in patients with OSA(120, 121). Non-randomized trials studying the effects of treatment of OSA with CPAP revealed a decrease in total cholesterol, LDL, homocysteine, and triglycerides, while on treatment; however, there was mixed data on HDL(122-127). Robinson and colleagues demonstrated a decrease in total cholesterol while on treatment with CPAP(128). Similarly, Phillips and colleagues, in a randomized, placebo-controlled trial looking at the role of CPAP on postprandial lipid levels in patients with OSA, concluded that treatment of severe OSA with CPAP improved postprandial triglyceride levels as well as total cholesterol levels(129). These trials, although randomized, have limitations such as a lack of adjustment for CPAP adherence and the role of lipid-lowering medications. An observational study in Portugal followed patients for an eight year period and concluded that CPAP treatment improves daytime sleepiness in patients with OSA but does not play as significant a role in improving their lipid profile comparable to the lipid-lowering medications(130). Although a direct causal relation of OSA and dyslipidemia is yet to be determined, there is increasing evidence that an association exists(131). The actual impact of the treatment of OSA in the improvement of the lipid profile is debatable and will require large RCTs.

INSOMNIA AS A CARDIOVASCULAR DISEASE RISK FACTOR

Insomnia has long been viewed as a symptom of the "worried well." However, accumulating evidence indicates that insomnia disorder is a significant risk factor for CVD(132, 133). Insomnia, especially when coupled with short sleep duration, is associated with hyperactivity of the hypothalamic-pituitary-adrenal axis (e.g., increased cortisol secretion) and sympathetic system (e.g., impaired heart rate variability) and, consequently, with a clinically significant risk of CVD (e.g., hypertension, type-2 diabetes, myocardial infarction, and coronary heart disease).

Epidemiology of Insomnia: Scope of the Problem

The prevalence of insomnia in the general population ranges between 8-40%, depending on the definition used. While 20-30% of the general population has "poor sleep" (i.e., difficulty falling asleep, staying asleep, early morning awakening or non-restorative sleep at any given time), another 8-10% of the population has insomnia(134, 135).

Natural history studies indeed show that insomnia is a highly persistent condition, whereas the course of "poor sleep" is more unstable and likely to remit(136-140), which indicates that insomnia is a disorder while "poor sleep" is a symptom of underlying physical or mental health problems(137, 138, 140). Despite the fact that the objective sleep of people with insomnia is different than that of normal sleepers(135, 141) and that objective short sleep duration has been shown to predict the development of "poor sleep" into insomnia(138) and the persistence of insomnia(140), polysomnographic (PSG) studies are not required for the diagnosis of insomnia(141), which contrasts with the current indication of PSG for the evaluation of patients with sleep disordered breathing and their associated CVD risk. Actually, the associations between insomnia and significant CVD risk has not been systematically examined until recently.

Insomnia as a Behavioral Risk Factor

Insomnia may be associated with increased CVD risk through its association with poor health behaviors. Indeed, individuals with "poor sleep" or insomnia are more likely to report increased alcohol and caffeine use, smoking, and lack of physical activity and to show lower cardiorespiratory fitness as compared to normal sleepers(142). Moreover, individuals with insomnia may be at increased CVD risk through poor diet, as subjective and objective sleep has been associated with dietary macronutrient and micronutrient composition(143). For example, a recent study of the 2007-2008 National Health and Nutrition Examination Survey (NHANES) found inadequate intake of alpha-carotene, calcium, selenium, salt, carbohydrates, vitamin D, lycopene, dodecanoic, hexadecanoic, butanoic or hexanoic acids to be associated with "poor sleep"(144). It is likely that the relationship between insomnia and "poor sleep" with many of these health behaviors is bidirectional(137, 138, 140). Interestingly, however, sleep hygiene therapy alone, which targets poor health behaviors, is not effective in the treatment of insomnia. Importantly, most studies on the independent association of insomnia with CVD risk have controlled for alcohol and smoking but not diet or physical activity. More work is needed to establish the relative contribution of health behaviors to the CVD risk associated with insomnia.

Insomnia Pathophysiology and Cardiovascular Risk

Current models of insomnia posit the joint effect of stressful life events(145) and stress-related psychological factors as central to the pathogenesis of insomnia(146, 147); thus, activation of the stress system, i.e., hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, should be a key pathophysiologic mechanism of the persistence of insomnia. While early studies reported no difference between "poor sleepers" and controls in cortisol levels, later studies found that 24-h urinary free cortisol, norepinephrine, and catecholamine metabolites levels were increased in patients with insomnia or were correlated with PSG indices of sleep disturbance in insomnia patients(148-151). Also, other studies, with a few exceptions(152-155), have found that insomnia is associated with increased nocturnal heart rate, blunted heart rate variability (HRV)(156-160), altered sympathovagal balance, as measured by impedance cardiography(156, 161), increased overall oxygen consumption (VO2), a measure of increased whole-body metabolic rate(162, 163), increased pupil size, indicative of sympathetic system activation(164), increased central nervous system activation during sleep(165-167), increased or altered systemic

inflammation(57, 168), and increased daytime sleep latencies in the Multiple Sleep Latency Test (MSLT), a test of physiologic sleep propensity(155, 169). The shorter the objective sleep duration, the longer the sleep latencies in the MSLT in persons with insomnia(170, 171).

In summary, increased peripheral and central markers of HPA axis dysfunction and sympathetic activation are primarily found in insomniacs with objective short sleep duration, who suffer from a disorder of 24-hour hyperarousal(172). Thus, proposed physiologic mechanisms of the association of insomnia with CVD risk include neuroendocrine dysregulation, autonomic imbalance, and increased inflammation.

Insomnia and Cardiovascular Disease Risk

Although the association of insomnia with cardiovascular disease has been reported for several years(173), its association with clinical risk factors (e.g., hypertension, diabetes, metabolic syndrome) and cardiovascular disease has remained largely unexplored until recently(174). In fact, only in the past few years several systematic reviews and meta-analyses have been published on the association of insomnia with CVD risk. For example, the estimated risk for incident hypertension associated with "poor sleep" or insomnia ranges between 5% and 20%(175), that for type-2 diabetes (T2D) about 57%(3), and that for incident myocardial infarction (MI) and coronary heart disease (CHD) between 41% and 55%, respectively(176, 177). Although these studies have shown a significant association between insomnia, mainly "poor sleep", and CVD risk, the effect sizes reported were modest and most studies did not include PSG and could not control for SDB.

Based on the physiologic mechanisms reviewed above, recent work from the Penn State Adult Cohort has shown a synergistic effect between insomnia and PSG-measured short sleep duration (i.e., < 6 hours) on the risk for hypertension and T2D even after controlling for multiple confounders, including SDB(178-180). Specifically, the odds of T2D in individuals with insomnia who slept < 6 hours were 2.1- to 3.0-fold cross-sectionally and the odds of hypertension were 3.5- to 5.1-fold cross-sectionally[71] and 3.8-fold longitudinally, while the odds of hypertension or T2D in individuals who reported insomnia but slept objectively > 6 hours were not significantly increased (e.g., OR = 1.3 and 0.85). Importantly, these findings have been replicated in two recent studies in patients with insomnia using PSG-measured short sleep duration(181) and MSLT-measured increased sleep latency(182).

While SDB is strongly associated with the metabolic syndrome (MetS), the evidence for insomnia is limited and inconsistent(63, 183, 184). A potential explanation may be related to different physiologic mechanisms in SDB and insomnia; for example, central obesity is strongly associated with incident SDB and "poor sleep", but not as much with incident insomnia. In fact, patients with insomnia are typically non-obese(185) and in a recent longitudinal study(186), despite sleeping objectively shorter than controls or "poor sleepers", non-obese insomniacs were less likely to become obese than controls or "poor sleepers", a finding consistent with the presence of increased whole-body metabolic rate(162). These data indicate that insomnia with short sleep duration may be linked to insulin resistance and CVD independent of central obesity.

Current literature indicates that insomnia is a premorbid risk factor of CVD. Accumulating evidence suggests that the association of insomnia with CVD risk is more pronounced when insomnia is associated with objective short sleep duration or other measures of physiologic arousal. Evidence suggests that measures of insomnia, and especially objective sleep measures, should be included in the estimation of CVD risk in the clinical and general population.

SLEEP AND CARDIOVASCULAR DISEASE RISK IN PEDIATRICS

Factors that increase cardiovascular risk have been shown to emerge early in life. For example, blood pressure and body mass index in adolescence predict future adult cardiovascular risk (187). Similar to what has been shown in adults; sleep-related factors are important contributors to cardiovascular risk in childhood. These factors include both sleep duration, as well as factors that disrupt sleep quality, particularly sleep-disordered breathing.

Sleep duration and cardiovascular disease risk in children

Sleep curtailment and short sleep duration have been linked to increased adiposity and elevated BMI in longitudinal studies spanning from infancy to adolescence (188, 189). Additionally, there is robust evidence linking short sleep duration to impaired glucose metabolism. A recent study showed that shorter sleep duration, as well as worse sleep efficiency, was associated with impaired glucose tolerance (190). This is consistent with most prior literature, which generally has shown that short sleep in children and adolescents is associated with impaired glucose metabolism (191). One prior study identified a U-shaped relationship, with short and long sleep duration both predicting impaired glucose tolerance, similar to adults (192). A recent cross-sectional study has also identified that short sleep duration in obese children is associated with elevated homocysteine levels compared to obese children who obtain sufficient sleep (193).

Pediatric sleep-disordered breathing and cardiovascular disease risk

SDB is a prevalent condition in children, with obstructive sleep apnea seen in 1.2-5.7% of all children (194). In children with cardiovascular risk factors, the prevalence may be even higher. A recent retrospective study found that 55% of children with hypertension referred for polysomnography were found to have sleep-disordered breathing (195). Sleep-disordered breathing in children is associated with adverse cardiovascular effects including dysregulation of blood pressure (196, 197) and cardiac dysfunction (198, 199). Children with sleep-disordered breathing have significantly elevated pulmonary arterial pressures as well as right ventricular hypertrophy and dysfunction (199). There is also evidence for left ventricular dysfunction (198). The underlying pathophysiologic effects of sleep-disordered breathing that may cause these deleterious effects include endothelial dysfunction (200), autonomic dysfunction (201), and chronic inflammation (202). Importantly, these adverse cardiovascular effects appear to be reversible with treatment (199). Sleep disordered breathing is also associated with significant metabolic adverse effects. The presence of OSA has been shown to be associated with increased serum triglycerides, blood glucose and insulin resistance (203).

In general, recent evidence in children has continued to identify sleep as an important factor in cardiovascular risk. Both short sleep duration and sleep-disordered breathing appear to be important modifiable risk factors that contribute towards overall cardiovascular risk. Targeted sleep interventions during childhood may be an important strategy to lower cardiovascular risk throughout the lifetime.

SLEEP AND CARDIOVASCULAR HEALTH DISPARITIES

Cardiovascular Health Disparities as a Public Health Priority

Health disparities exist when one group of people is at a disadvantage as a virtue of their socioedemographic category and not inherent physiologic risk. In these cases, increased risk for morbidity and mortality are a product of social-environmental influences and as such represent a societal concern. Although health care advances have proceeded at a dramatic pace over the last half-century, racial/ethnic and socioeconomic health disparities are still well-documented in the United States.(204-206). In particular many racial/ethnic minority groups (particularly Blacks/African-Americans and Hispanics-Latinos) are at greater risk of obesity, heart disease, diabetes, and cardiovascular events (204, 206, 207). These effects persist even after accounting for socioeconomics (204, 206). It is likely that a complex combination of structural, physiological, psychological and behavioral differences drive these relationships (205, 206, 208-210). In addition, environmental factors such as neighborhood may play a significant role through differential exposures to social, psychological, and physical influences (211, 212). Understanding and reducing health disparities has been identified as a key public health priority(206, 213).

Sleep Disparities in the Population

Several studies have documented sleep disparities in the US population. A meta-analysis by Ruiter and colleagues(214) showed that Blacks/African-Americans obtained less polysomnographic sleep than Non-Hispanic Whites. Blacks/African-Americans also obtained less Slow Wave Sleep. Other studies have also found that Blacks/African-Americans obtained less Slow Wave Sleep(215-219) and had poorer sleep efficiency(217, 219) than Non-Hispanic Whites.

Several epidemiologic studies have examined population-level sleep disparities. Using the 2007-2008 NHANES, Whinnery and colleagues(220) found that relative to non-Hispanic Whites, Blacks/African-Americans were 3.5 times as likely to report very short (<5 hours) sleep duration and twice as likely to report short (5-6 hours) sleep duration. In this same sample, non-Mexican Hispanics/Latinos were 87% more likely to report very short sleep and 35% more likely to report short sleep. And Asians/Others were 2.5 times as likely to report very short sleep and 67% more likely to report short sleep. These findings are mirrored in many other studies, which have shown increased prevalence of habitual short sleep duration among racial/ethnic minority groups(221-225).

Regarding sleep disorders, Ruiter and colleagues(226) found that African-Americans were more likely to have sleep disordered breathing, of greater severity, compared to Whites. Data from the 2007-2008 NHANES(227) also showed that Blacks/African-Americans were more

likely to report sleep latency >30 minutes, but self-reported difficulties initiating or maintaining sleep were all reported less frequently among minority groups, suggesting that despite differences in sleep, these are not perceived as "difficulties." In this sample, Non-Mexican Hispanics/Latinos were more likely to report choking/gasping during sleep and snoring(228). Other studies have found inconsistent relationships between race/ethnicity and sleep symptoms. Although some studies have found that sleep quality is worse among racial/ethnic minorities(229-232), others have not(233-235). A potential explanation is the variable, interactive roles of race/ethnicity, socioeconomic, and cultural factors.

Could Sleep be a Modifiable Risk Factor for Cardiovascular Health Disparities?

If racial/ethnic minorities are at increased risk of cardiometabolic disease, and if insufficient sleep is also associated with cardiometabolic disease, and if racial/ethnic minorities are more likely to experience insufficient sleep, it is plausible to suggest that sleep may play a role in disparities and therefore may serve as an intervention target. Although this has not yet been directly tested, several studies have shown that the relationship between sleep and cardiometabolic disease risk does depend on race/ethnicity. Knutson and colleagues(236) found that racial differences in 5-year blood pressure change were explained by differences in sleep duration. Also, Grandner and colleagues(56) found that the relationship between sleep duration and C-reactive protein (a cardiovascular risk marker) differed by race/ethnicity. This was followed up by another analysis that showed that the relationship between sleep duration and obesity, diabetes, hypertension and hyperlipidemia depended on self-identified race/ethnicity(20).

PREVENTING CARDIOVASCULAR DISEASE: A ROLE FOR SLEEP DISORDERS SCREENING

Sleep disorders have been robustly implicated in cardiometabolic disease risk. In particular, sleep apnea is a well-characterized risk factor for cardiometabolic morbidity and even cardiovascular events. Strikingly, as described above, studies that evaluated the prevalence of sleep apnea in obesity, cardiology, and diabetes clinics routinely find that most patients meet criteria for sleep apnea, though few are diagnosed and even fewer are successfully treated. For this reason, clinics that treat patients with cardiovascular disease, diabetes, and/or obesity should routinely screen patients for sleep apnea risk and refer for diagnosis appropriately.

Insomnia is also shown to be an important marker of cardiometabolic disease risk. It is, however, often ignored in the context of treatment for these conditions. Screening for insomnia is not difficult, though, with brief instruments such as the Insomnia Severity Index(237) and other brief screening measures. Of note, the recommended first line treatment for insomnia is not pharmacotherapy, although pharmacotherapy remains the most widely-utilized approach(238). This particularly important since prescription hypnotic medications may carry significant risks(239-243). The recommended first-line treatment, Cognitive Behavioral Therapy for Insomnia (CBTI) does not carry these risks and is therefore preferable for reasons beyond demonstrated efficacy(244-248), efficacy relative to medications(249-253), and effectiveness(254). Despite this, knowledge about the existence

of CBTI is limited in the medical community, and providers may be difficult to locate(255). Still, patients with insomnia should be directed to CBTI when it is available.

PREVENTING CARDIOVASCULAR DISEASE: A ROLE FOR HEALTHY SLEEP DURATION

In addition to sleep disorders, it has been repeatedly shown that insufficient sleep duration is an important risk factor for cardiometabolic disease risk. In addition to many cross-sectional studies, prospective studies show that insufficient sleep is a risk factor for incident obesity, hypertension, and diabetes. For this reason (and others), achieving adequate sleep duration has been included as a Healthy People 2020 goal(213). This should be reflected in practice. Clinicians should be asking about sleep duration and consider short sleep duration among other behavioral risk factors such as poor diet, inactivity, smoking, and excessive alcohol use.

CONCLUSIONS

Over 50 years ago, epidemiologic studies began to show that habitual sleep was associated with mortality(256). Since that time, substantial knowledge about the role of sleep in cardiometabolic health has emerged. Habitual short sleep duration is associated with weight gain and obesity, hypertension, hyperlipidemia, inflammation, diabetes, heart attack, and stroke. Sleep apnea is associated with cardiac and vascular dysfunction, hypertension, dyslipidemia, diabetes, inflammation, heart attack and stroke. Even insomnia, which has been traditionally seen as relatively benign, is a risk factor for cardiometabolic morbidity and mortality. Taken together, sleep represents an important domain of cardiometabolic health risk. Future studies are needed to better characterize the mechanisms by which sleep leads to morbidity and to identify and refine interventions to better ameliorate this risk. In the meantime, healthy sleep should be a consideration in the clinical care of heart disease patients.

ACKNOWLEDGEMENTS

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KEY POINTS

- Insufficient sleep duration is prevalent in up to 1/3 of US adults and is associated with weight gain, diabetes, hypertension, inflammation, and mortality.

- Insomnia disorder is prevalent in 5-15% of US adults and is associated with cardiometabolic disease risk, especially when paired with objective short sleep duration.

- Sleep apnea is prevalent among men and women in the US and is a strong predictor of cardiometabolic morbidity and mortality, especially if left untreated.

- Pediatric sleep disorders such as insomnia and sleep apnea are related to cardiovascular disease risk.

- Sleep may play an important and potentially modifiable role in cardiovascular health disparities.