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Cardiovascular Disease in Women Across the Lifespan: The Importance of Sleep

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Abstract

Cardiovascular disease (CVD) and sleep disturbances are both common and associated with significant morbidity and mortality. Compared with men, women are more likely to report insufficient sleep. During the 2018 Research Conference on Sleep and the Health of Women sponsored by the National Heart, Lung, and Blood Institute, researchers in cardiology, integrative physiology and sleep medicine reviewed the current understanding of how sleep and sleep disturbances influence CVD in women across the lifespan. Women may be particularly vulnerable to the negative effects of sleep disturbances at important stages of their life, including during pregnancy and after menopause. The proposed pathways linking sleep disturbances and adverse cardiovascular outcomes in women are numerous and the complex interaction between them is not well understood. Future research focused on understanding the scope of sleep disorders in women, defining the underlying mechanisms, and testing interventions to improve sleep are critical for improving the cardiovascular health of all women.

Keywords: sleep, women, cardiovascular outcomes, hypertensive disorders of pregnancy, autonomic function

Introduction

Cardiovascular disease (CVD), which includes coronary heart disease, heart failure, stroke, and hypertension, is extremely common and affects nearly half of adults in the United States.[1] Disturbances in sleep are also common; one-third of U.S. adults report some form of sleep disorder or insufficiency.[2,3] Over recent years, there has been growing interest in understanding the relationships between sleep disturbances and CVD.[3–5] Women are more likely to report insufficient sleep than men; the importance of sleep for the cardiovascular health of women is of particular interest.[2] During the 2018 Research Conference on Sleep and the Health of Women sponsored by the National Heart, Lung, and Blood Institute (NHLBI), researchers in cardiology, integrative physiology and sleep medicine reviewed the current understanding of how sleep and sleep disturbances influence CVD in women across the lifespan. The following is a summary of the information presented including the scope of CVD in women, and the evidence associating sleep disturbances with adverse cardiovascular outcomes during pregnancy and the development of hypertension throughout a women's life.

An Overview of CVD in Women

CVD is common in women

CVD remains the leading cause of death worldwide and affects the majority of adults past the age of 60 years. Historically, CVD has been viewed as a disease that primarily affected men. According to U.S. estimates from 2017, CVD is almost as common in women as it is in men (35.9% vs. 37.4%, respectively).[6] In a 2019 updated report using new definitions of hypertension, these prevalence estimates for total CVD are even higher (51.2% in men, 44.7% in women).[1] The prevalence of CVD varies across the lifespan. Approximately 17% of women aged 20–39 years have CVD; by age 40–59 years the prevalence of CVD in women increases to >50%.[1] CVD is more prevalent in men until the age range of 60–79 years when the prevalence becomes higher in

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women than in men (78.2% vs. 77.2%, respectively). After age 80 years, >90% of women have some form of CVD.[1]

CVD remains the number one cause of death for women overall.[1,6] From 1980 to 2010, the absolute number of women dying each year from CVD in the United States was higher than the absolute number of men.[6] The greater number of deaths in women is largely because, on average, women live longer than men and constitute a higher proportion of older adults. As of 2014, this gender gap closed and the absolute number of CVD deaths in men and women was similar.[6]

Although CVD is the leading cause of death in women overall, the leading cause of death in women varies across the lifespan.[6] Deaths in younger and middle-aged women are less common, but when they occur, cancer is more commonly the cause than CVD.[7] Older women have higher rates of death than younger women and CVD is the most common cause of death in women >80 years.[7] Therefore, CVD continues to outpace cancer overall as the leading cause of death; this difference is largely driven by the larger proportion of deaths in older women compared with younger women.

Women have worse cardiovascular outcomes

Women with CVD are known to have worse outcomes than men with CVD. Women with CVD have more symptoms, more frequent hospitalizations, worse health status, and more complications after many procedures.[8–17] Of particular concern is the significant difference in mortality from CVD by age. Mortality rates from CVD have significantly declined for both men and women in the past several decades (−5% estimated annual percentage change), however, young women (<55 years of age) have seen minimal improvement in CVD mortality (−1% estimated annual percentage change) since 2000.[18,19] Many potential mechanisms for these gender differences have been proposed including differences in how CVD manifests, delays in seeking treatment, higher rates of comorbid conditions, biological sex differences and management disparities based on gender.[13,18,20,21] Multiple studies have demonstrated treatment disparities by gender in the diagnosis and treatment of CVD disease. For example, after an abnormal stress test, women are less likely to get referred for additional testing.[22] Eligible women are less likely to receive implantable cardioverter defibrillator therapy for the primary prevention of sudden cardiac death.[23] Some evidence also suggests that differences in invasive procedure use may be related to gender bias.[24] These gender differences in management persist even after considering important patient factors that may explain variation such as differences in comorbidities, health risk behaviors, and socioeconomic factors—suggesting that these differences represent meaningful disparities.[25]

Women have both traditional and unique cardiovascular risk factors

Traditional risk factors for CVD in women are similar to those in men and include obesity, dyslipidemia, diabetes, older age, hypertension, inactivity, and smoking.[20,26,27] The prevalence of many of these risk factors varies across the lifespan. By midlife, >80% of women have one or more traditional cardiac risk factors.[20,27] The overall number of risk factors is prognostic in both genders; however, some risk factors portend greater risk in women than in men.[28–32] For example, diabetes conveys a higher risk of CVD mortality in women than in men.[33–41] Smoking is another potent risk factor for women as it imparts 25% greater risk of coronary heart disease than in men independent of smoking intensity or other risk factors.[33–41] These gender differences exist across all age groups with the largest difference seen in young women smokers compared with women nonsmokers.[42] Women also have several unique CVD risk factors that can develop across the lifespan, including exposure to oral contraceptives, pregnancy complications (*i.e.*, pre-eclampsia, pregnancy-associated hypertension, and gestational diabetes), polycystic ovarian syndrome, autoimmune inflammatory diseases (more prevalent in women), menopause, and exposure to hormone replacement therapy.[11,20]

Sleep and CVD risk

Sleep duration and quality is increasingly recognized as an important contributor to cardiovascular health.[3–5,43] Both short- and long-duration sleep and sleep disorders such as sleep disordered breathing and insomnia are associated with adverse cardiovascular risk and outcomes.[3] Poor sleep has been shown to be associated with high blood pressure, arrhythmia, stroke, heart attack, and heart failure.[3] The mechanisms linking sleep disruption to increased cardiovascular risk are not fully understood. Several studies suggest disruptions in underlying health conditions such as glucose metabolism and blood pressure, as well as disturbances in biological processes such as inflammation.[2,3] Women are more likely to report insufficient sleep than men and some studies suggest women may be more vulnerable to the negative cardiometabolic consequences of poor sleep.[2] Furthermore, the effects of poor sleep in women may vary across the lifespan. The following sections overview the current understanding of the association between sleep and cardiovascular outcomes during pregnancy and its effects on hypertension.

Sleep, Pregnancy, and Cardiovascular Risk

Pregnancy is a unique period in a woman's life from a sleep perspective, and there are numerous reasons to focus on this population when understanding potential links between sleep, pregnancy-related cardiovascular outcomes, and long-term cardiovascular outcomes. Nearly six million women become pregnant in the United States each year.[44] This section of the symposium focused on highlighting reasons why sleep should be an important research focus for the pregnant population, and showcased epidemiological data linking sleep disordered breathing to hypertensive disorders of pregnancy. Finally, an overview of potential mechanisms behind the association with hypertensive disorders of pregnancy was also presented.

Sleep patterns during pregnancy

In national polls and large epidemiological studies, pregnant women frequently reported sleep disturbances such as poor sleep, frequent naps, snoring, and restless legs.[45–47] A third of all pregnant women report snoring by late pregnancy[46] and 9%–26% of all pregnant women have obstructive sleep apnea (OSA) by objective criteria,[48,49] with higher estimates in medically complicated pregnancies.[50] These disturbances are likely worsened by anatomical changes that

may predispose to snoring and sleep fragmentation, physiological changes that impact sleep disordered breathing, and metabolic changes of pregnancy that may impact disorders such as restless legs syndrome.[51] Bidirectional interaction between sleep and sleep disturbances on the one hand and pregnancy physiology on the other hand are also likely.

Pregnancy exposures and future health risks

Unlike other industrialized countries, maternal mortality in the United States is on the rise.[52] CVD and hypertensive disorders of pregnancy are leading causes of maternal mortality according to recent statistics by the center for disease control.[53] Pregnancy has also been argued to be a window into future health from a cardiovascular and a metabolic perspective, where exposures and complications of pregnancy have been associated with long-term maternal outcomes. Numerous national registry data have shown that the development of pre-eclampsia or maternal placental syndrome during a given pregnancy is associated with increased risk of developing a future adverse major cardiovascular event.[54,55] The development of gestational diabetes is also associated with a sevenfold increased risk of developing type 2 diabetes, a major cardiovascular risk factor, later in life.[56] In addition, maternal health and exposures have the potential to impact and influence the offspring's health from the fetal stages to neonatal life and childhood.[57,58] Although no studies have examined epigenetic regulation of placental genes in human pregnancies with sleep disordered breathing, recent animal data showed evidence of DNA methylation in the offspring of mice exposed *in utero* to intermittent hypoxia[59] and sleep fragmentation[60] in late gestation. Exposure to late gestation intermittent hypoxia was also associated with a worse metabolic profile in the pups, consisting of higher body mass index, food intake, adiposity index, and insulin levels.[59] In summary, evidence suggests that exposures and complications during pregnancy have long-term consequences on women's health, as well as that of their offspring.

Sleep disordered breathing during pregnancy and cardiovascular risk

Sleep disordered breathing is an under-recognized condition during pregnancy[61] and is associated with hypertension, adverse cardiovascular outcomes, and type 2 diabetes.[62] Data from the past decade have consistently shown an association between snoring, a mild form of sleep disordered breathing, and hypertensive disorders of pregnancy,[46,63,64] even after adjusting for potential confounders such as body mass index, age, and medical comorbidities.[46] OSA has also been associated with hypertensive disorders of pregnancy in multiple registry and population-based studies.[65–68] Most recently, a multicenter prospective study in the United States has shown that OSA, defined as a respiratory event index of ≥5 events per hour using an in-home sleep monitor, was associated with an increased risk of developing pre-eclampsia in low-risk primiparous women.[69]

OSA has also been linked to severe cardiovascular morbidity among pregnant women. In a study based on >55 million women from the national inpatient sample, Louis et al. showed that pregnant women with a diagnosis code of OSA had an increased risk of severe complications such as eclampsia, a ninefold increased risk of cardiomyopathy (including peripartum cardiomyopathy) and congestive heart failure, an eightfold increased risk of pulmonary edema, and a threefold increased risk of developing a cerebrovascular event, after adjusting for demographics, obesity, and comorbidities, compared with women without the diagnosis.[68] Another study based on the national perinatal information center demonstrated similar associations except that in that sample, there was no significant association between OSA and the risk of cerebrovascular events.[67] In addition, this study demonstrated a threefold increased risk of requiring an admission to the intensive care unit, after adjusting for multiple comorbidities, age, and obesity.[67] In summary, several studies have demonstrated a significant association between sleep disordered breathing and hypertensive disorders of pregnancy, as well as an association with severe cardiovascular morbidity.

Mechanisms linking sleep disordered breathing and adverse pregnancy outcomes

Mechanistic data linking sleep disordered breathing to adverse pregnancy outcomes are sorely lacking. The mechanistic link between these conditions may be bidirectional; however, there is biological plausibility to sleep disordered breathing having a causal relationship with at least hypertensive disorders of pregnancy and likely other cardiovascular conditions. The consistency of the association across study designs, the strength of the association, and the analogous association identified in the nonpregnant population also suggest causality. A temporal relationship has also been demonstrated in prospective longitudinal studies between sleep disordered breathing and the clinical manifestation of pre-eclampsia.[69] However, as pre-eclampsia is biologically determined late in the first trimester, sleep disordered breathing would need to be confirmed before conception to establish a temporal relationship with biological changes of pre-eclampsia.

The pathophysiology of sleep disordered breathing and mechanisms underlying its association with adverse cardiovascular outcomes are likely different in the pregnant versus nonpregnant state for numerous reasons. Some of the main reasons include physiological changes to the cardiopulmonary, metabolic, and immunological systems, together with the profound hormonal changes during pregnancy. In addition, the timeframe from exposure to sleep disordered breathing to an incident outcome is significantly contracted during pregnancy, compared with the nonpregnant population. This suggests that mechanistic pathways underlying the outcomes may be somehow accelerated or at least modified. Animal studies have also shown that reproductive hormones such as estradiol alter mechanistic pathways of intermittent hypoxia. For instance, recent data by Laouafa et al. have shown an elevation in mean, diastolic, and systolic blood pressure in ovariectomized animals exposed to intermittent hypoxia.[70] However, the rise in blood pressure measurements was not seen in ovariectomized animals that received estradiol replacement, suggesting that estradiol may protect against the detrimental effects of intermittent hypoxia.

The proposed biological pathways linking sleep disordered breathing to hypertensive disorders of pregnancy are likely similar to those linking it to cardiovascular outcomes. Several potential pathways include oxidative stress, inflammation, sympathetic activation, thrombosis, endothelial dysfunction,

and activation of the renin angiotensin system.[71] Given the short duration of time for the development of cardiovascular outcomes during pregnancy, the potential effect of steroid hormones,[72,73] and the physiological changes of pregnancy, the interplay of all these factors in the pathobiology of these associations remains to be studied.

Animal studies and limited human data support the hypothesis that oxidative stress pathways are suppressed by sex steroid hormones. In one study, expression of NADPH oxidase activity was significantly increased in the cortex and brainstem of ovariectomized animals exposed to intermittent hypoxia compared with sham and ovariectomized animals exposed to room air, as well as ovariectomized animals that received estradiol replacement.[70] In a case–control study of pregnant women with OSA, total antioxidant capacity was increased, and levels of oxidative and carbonyl stress markers were decreased compared with pregnant controls without a diagnosis of sleep apnea.[74] Collectively, these studies suggest oxidative stress is likely not the predominant pathway linking sleep disordered breathing to CVD in the presence of sex steroid hormones. However, further human studies are needed to examine the interplay between levels of sex steroid hormones and oxidative markers.

In contrast, other animal and human studies point to inflammation as potentially being an important pathway linking sleep disordered breathing and adverse pregnancy outcomes, even in the setting of female sex steroid hormones. In an experimental study in a mouse model, intermittent hypoxia led to considerable increases in interleukin (IL)-6 and IL-8 gene expression in the heart and brain.[75] However, the same experiment conducted in oophorectomized animals failed to show differences in the gene expression of these cytokines, suggesting that female reproductive hormones enhance inflammation in response to intermittent hypoxia and sleep disordered breathing. In a small cohort of pregnant women at high risk for sleep disordered breathing, Bublitz et al. demonstrated elevated levels of proinflammatory markers (IL-6 and IL-8) in the late second trimester in women with sleep disordered breathing compared with pregnant women without the disorder at a similar gestational age.[76] These studies suggest that in the setting of female reproductive hormones, inflammation may play an important role in the association of sleep disordered breathing and adverse pregnancy outcomes.

Finally, several other biological pathways have been proposed linking sleep disturbances and adverse cardiovascular outcomes among pregnant women. Sympathetic activation assessed by pulse transit time has been found to be significantly more prevalent in women with OSA and snoring than in nonsnoring controls.[77] Another important difference in the pregnant population is the unique presence of an additional organ—the placenta—that may play an important role in the association with hypertensive disorders and other outcomes. The placenta likely plays a role in mediating the association of sleep disordered breathing with hypertensive disorders of pregnancy, as evidence of alteration in placenta-secreted markers linked to pre-eclampsia,[78] and placental tissue hypoxia,[79] has been found in women with sleep apnea compared with controls. It is also possible that the placenta may potentially play a role in the pathogenesis of sleep disordered breathing during pregnancy.[80] In summary, numerous pathways linking sleep disordered breathing with cardiovascular disorders have been proposed, but research is still very limited. This major gap in our knowledge base severely limits the ability to understand these associations and offer novel interventions that may positively change the course of the pregnancy, and even potentially impact offspring health.

Small experimental data show promise that treatment of sleep disordered breathing with positive airway pressure may improve hemodynamics during pregnancy.[81,82] A multicenter randomized controlled trial aimed at examining the impact of positive airway pressure on maternal blood pressure is ongoing and will inform clinicians on the utility of such therapy in preventing adverse cardiovascular outcomes.

Areas for future research in sleep and pregnancy

Much remains to be done to close the gap in our knowledge of the association of sleep and sleep disordered breathing with adverse cardiovascular risk and outcomes during pregnancy. It is still unclear whether sleep disturbances are causal factors, mediators, or modifiers of adverse outcomes. Research to further our understanding of processes underlying these associations is sorely needed, and ongoing trials evaluating the impact of treatment of sleep apnea on blood pressure outcomes will help shed light on the issue and offer new hope to women with these devastating pregnancy outcomes.

Sleep and Hypertension: Why Sex Matters

This portion of the symposium focused the growing evidence that associations between sleep deprivation and hypertension are impacted by sex, and presented experimental evidence that sympathetic neural responsiveness to sleep deprivation may be an important contributing factor.

CVD and autonomic function

Since the pioneering work of Claude Bernard[83] and Walter Cannon,[84] the autonomic nervous system has been acknowledged as a key contributor to cardiovascular homeostasis in humans. Dysfunction of the autonomic nervous system, and particularly the sympathetic nervous system, plays a key role in the pathogenesis of hypertension, atherosclerosis, congestive heart failure, and stroke. Over the past 15 years, numerous studies have shown that sympathetic neural activity, as well as sympathetic reactivity to various stressors, can differ between men and women.[85–88]

In humans, the gold standard for measuring sympathetic neural activity is microneurography, a technique that involves the insertion of a tungsten microelectrode to *directly* record postganglionic sympathetic nerve activity.[89,90] Using the microneurographic approach, Narkiewicz et al.[91] demonstrated that sympathetic neural activity is disproportionately impacted by age and sex. Specifically, when compared with age-matched men, women tend to have lower resting sympathetic nerve activity early in life (20–39 years), roughly similar levels at mid-life (40–49 years), and significantly elevated levels when older (>60 years). In fact, resting sympathetic nerve activity increases threefold over each decade of life in women when compared with men.[91] This aggressive increase of sympathetic tone throughout a woman's

lifespan is believed to be a contributor to the higher incidence of hypertension in postmenopaual women when compared with age-matched men.

Epidemiological studies on sleep, hypertension, and sex

In 2006, Gangwisch et al.[92] and Gottlieb et al.[93] independently explored two major health databases that collected information on self-report sleep and hypertension (*i.e.*, the National Health and Nutrition Examination Survey and Sleep Heart Health study, respectively). Both studies reported significant cross-sectional associations between self-report short sleep duration and hypertension, but sample sizes were not sufficient to adequately explore the impact of sex. However, 1 year later, a larger data set from the United Kingdom (Whitehall II study) allowed for comparisons between men and women, and reported that short sleep durations were associated with hypertension in women, but not in men.[94] More recently, Grandner et al.[95] utilized the 2013 Behavioral Risk Factor Surveillance System and 2007–2016 National Health Interview Surveys (>700,000 adults in total) to report that the associations between short sleep and hypertension were stronger in women than in men, and that this relationship persisted across the lifespan. Taken together, epidemiological studies are converging to document that the association between insufficient sleep and hypertension is stronger in women than in men.

Experimental studies on sleep, hypertension, and sex: role of sympathetic nervous system

Increases in sympathetic neural activity have been suggested as a potential contributor to the reported associations between sleep deprivation and hypertension, but until recently, direct evidence was lacking. This is perhaps the consequence of earlier work focused primarily on men. Specifically, Kato et al.[96] reported an increase in blood pressure and decrease in sympathetic nerve activity after 24 hours total sleep deprivation in six men and two women. Ogawa et al.[97] followed up with similar findings in six men, and attributed the increase in resting blood pressure to a resetting of the sympathetic arterial baroreflex. Thus, earlier work did not support the concept of sympathoexcitation as a contributing mechanism to the reported associations between short sleep and hypertension.

However, it is important to note that the epidemiological evidence suggests a stronger relationship between short sleep and hypertension in women than in men. Accordingly, two recent studies have shed new light on the relationship between experimental sleep deprivation and sympathetic neural activity. Carter et al.[98] reported that 24-hour total sleep deprivation elicited a similar pressor response in young healthy men and women. In contrast, peripheral sympathetic tone assessed *via* microneurography demonstrated that sympathetic nerve activity was significantly reduced in young men, a finding consistent with Kato et al.[96] and Ogawa et al.,[97] whereas sympathetic nerve activity tended to increase in young women.[98] Importantly, a more recent study has reported similar sex differences in postmenopausal women when compared with age-matched men.[99] Specifically, total sleep deprivation elicited a significant increase of sympathetic nerve activity in older women, but not in older men.[99] Taken together, these recent experimental total sleep deprivation studies demonstrate that although total sleep deprivation elicits a similar pressor response in men and women across the lifespan, the mechanisms (*i.e.*, sympathetic vs. alternative) may significantly differ.[98,99] Such differences could be pivotal when considering therapeutic strategies, particularly for older women who appear to have the strongest associations between short sleep and hypertension.[95]

Other sleep conditions associated with sleep deprivation

Other sleep disorders such as OSA and insomnia are also sympathoexcitatory. OSA elicits robust increases of sympathetic nerve activity during sleep, particularly during rapid eye movement sleep, and this sympathoexcitation appears to persist during wakefulness.[100,101] Continuous positive airway pressure, the primary treatment strategy for OSA, has been reported to reduce daytime resting sympathetic nerve activity in patients with OSA.[102] Despite well-characterized differences in sympathetic nerve activity between men and women, the relationship between sex, OSA, and sympathetic nerve activity remains unclear.

Only one study has assessed sympathetic neural activity in subjects with insomnia, and reported no group differences in resting sympathetic nerve activity.[103] However, subjects with insomnia demonstrated a significantly reduced sympathetic baroreflex sensitivity and a stronger sympathoexcitatory response to the cold pressor test than controls.[103] Unfortunately, the study population was not powered to assess potential sex differences.

Future work on sleep and hypertension

Given the health/sex disparity that exists with postmenopausal hypertension, there is a need to continue to examine any factors that might impact this condition. Evidence is accumulating to suggest that sleep deprivation may contribute to postmenopausal hypertension, and that the sympathetic nervous system may be a major contributing factor. However, studies to date have primarily focused on the total sleep deprivation model, which has limited ecological validity. Future work might aim to utilize sleep restriction, sleep extension, and other longer term interventions to better understand the complex relationships between sex, sleep, and sympathetic activity.

Conclusions

In summary, both sleep disturbances and CVD are common in women and associated with significant morbidity and mortality. Research suggests women may be particularly vulnerable to the negative effects of sleep disturbances at important stages of their life, including during pregnancy and after menopause. The proposed pathways linking sleep disturbances and adverse cardiovascular outcomes in women are numerous, and the complex interaction between them is not well understood. Future research focused on understanding the scope of sleep disorders in women, defining the underlying mechanisms, and testing interventions to improve sleep is critical for improving the cardiovascular health of all women.

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