


# Elucidating the Relationship Between Insomnia, Sex, and Cardiovascular Disease

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## Abstract

Sex differences in cardiovascular disease (CVD) mortality have been attributed to differences in pathophysiology between men and women and to disparities in CVD management that disproportionately affect women compared to men. Similarly, there has been investigation of differences in the prevalence and presentation of insomnia attributable to sex. Few studies have examined how sex and insomnia interact to influence CVD outcomes, however. In this review, we summarize the literature on sex-specific differences in the prevalence and presentation of insomnia as well as existing research regarding the relationship between insomnia and CVD outcomes as it pertains to sex. Research to date indicate that women are more likely to have insomnia than men, and there appear to be differential associations in the relation between insomnia and CVD by sex. We posit potential mechanisms of the relationship between sex, insomnia and CVD, discuss gaps in the existing literature, and provide commentary on future research needed in this area. Unraveling the complex relations between sex, insomnia, and CVD may help to explain sex-specific differences in CVD, and identify sex-specific strategies for promotion of cardiovascular health. Throughout this review, terms “men” and “women” are used as they are in the source literature, which does not differentiate between sex and gender. The implications of this are also discussed.

## Keywords

sex differences, female

## Introduction

Insomnia is a common disorder characterized by difficulty initiating or maintaining sleep.<sup>1</sup> It has a worldwide prevalence of up to 35%,<sup>2</sup> with up to half of cases having a chronic course.<sup>1</sup> There is not a strict definition of insomnia that necessitates a specific sleep amount, number of awakenings, or particular polysomnographic findings, as there is a nontrivial amount of overlap in these features between those with insomnia and those without insomnia. Because of this, patient self-report informs diagnosis of the condition rather than external, objective gauges.<sup>3</sup> Overall, insomnia is a psychiatric disorder based on patient reports of abnormal or distressing sleep patterns including difficulty falling asleep, awakening frequently, difficulty returning to sleep after each awakening, or early morning awakenings with subsequent inability to re-establish sleep. Diagnosis of insomnia requires 1) patient report of the aforementioned sleep disturbances; 2) abnormal sleep patterns despite sufficient opportunity for sleep; and 3) report of any one of a range of daytime impairments which may include

sleepiness, alteration of mood or attention, somatic symptoms due to lack of sleep, poor daytime social/school/work performance, or concerns about sleep.<sup>4</sup> Acute or short-term insomnia occurs for a period of less than 1 month and is considered the result of an acute psychologic or physiologic stressor, whereas

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persistent insomnia for a period of at least 3 months is considered chronic.<sup>5</sup>

Insomnia has been linked to a greater risk of cardiovascular disease (CVD) incidence and death.<sup>6</sup> Meanwhile, researchers have also demonstrated clear sex differences in CVD outcomes.<sup>7,8</sup> A recent review examined sex differences in the relationship between sleep duration (a separate phenomenon from insomnia) and CVD risk factors,<sup>9</sup> but few if any prior studies have examined the link between sex, insomnia and CVD. The purpose of this review is to summarize the literature on sex differences in insomnia prevalence, physiology and treatment; to review the relationship between insomnia and CVD as well as between sex and CVD; to elucidate how sex, insomnia and CVD interact; and finally to identify key gaps and directions for future research.

## Sex and Insomnia

Research has long shown that female sex is an important risk factor for the diagnosis of insomnia. One 2006 meta-analysis (29 studies; N = 1,265,015 observations; 57% women) found an increased risk of insomnia among women compared to men, which was even more pronounced when only high-quality studies (i.e., based on subject interviews, appropriateness of diagnostic criteria) were included in the analysis (n >5000) (relative risk [RR] = 1.64, 95% CI 1.48-1.81).<sup>10</sup> Additionally, studies done across populations in multiple countries have replicated the same sex-specific difference in risk-profile.<sup>11</sup> Experts have posited that anatomic, hormonal, and physiologic mechanisms may contribute to this phenomenon, as the increased rate of insomnia in women appears to arise after puberty.<sup>12</sup> In fact, women are more likely to suffer from insomnia than men throughout their lifetime,<sup>10</sup> and it is estimated that overall women have ~40% greater lifetime risk for insomnia compared to men.<sup>10,13,14</sup>

Sex differences in rates of insomnia may also be due in part to variations in circadian rhythm between men and women. Significant baseline differences in both circadian physiology and sleep homeostasis have been described between cis-gender (i.e., persons whose sense of personal identity and gender corresponds with their birth sex) men and women. Since circadian and homeostatic factors interact with each other to regulate the timing and quality of sleep,<sup>15,16</sup> sex differences in these factors likely have ramifications for the prevalence and features of insomnia in men and women. Women have been found to demonstrate a shorter circadian period (i.e., duration of the circadian cycle) than men by 6-18 minutes under highly controlled conditions, and a greater proportion of women than men have been found to have circadian periods shorter than 24.0 h (35% vs. 14%).<sup>16</sup> When this faster circadian clock cycling is studied in the context of an environmental light/dark cycle more pronounced advanced circadian timing in women has been found, with one study reporting dim light melatonin onset (a marker of the onset of the biological night) ~1.5 hours earlier in women compared to men.<sup>17</sup>

Genetic research supports the direction of this finding of faster circadian clock cycling, as circadian clock gene expression in the dorsolateral prefrontal cortex was found to peak earlier in woman than men.<sup>18</sup> In a recent laboratory-based study, it was observed that women had rhythms of sleep propensity and alertness that were phase advanced by about 2 hours compared to men, when measures were expressed relative to habitual wake time.<sup>19</sup> This suggests that women may be initiating sleep at a later biological time than men, and as a result, have a lower circadian drive to maintain sleep toward the end of the habitual sleep episode.<sup>19</sup> This observation may help explain the higher susceptibility that women show to insomnia, and in particular early morning awakenings. The shorter circadian period and phase advance of the biological clock in women compared to men suggests that women and men may demonstrate differences in chronotype, i.e. preferred timing of sleep during the 24-hour day. Indeed, survey-based research supports this, with reproductive-age women preferring to go to bed earlier and showing earlier chronotypes than men.<sup>20-22</sup> After age 40, women become later chronotypes relative to men, possibly due to hormonal modulation of the circadian system.<sup>23</sup>

Sex-specific chronotype differences may also have important non-physiologic causes. Women are particularly vulnerable to sleep problems during specific time periods of their lives including pregnancy, new motherhood, menopause, and post-menopause.<sup>24</sup> Research has indicated that the majority of family caregiving is carried out by women.<sup>25</sup> It is plausible that this social factor influences the previously mentioned sleep differences, increasing the likelihood that female caregivers initiate sleep when able based on children's sleep patterns. Fischer (2017) suggests that family-related factors may contribute to sleep disparities, noting that "typically- 'female' responsibilities such as household chores and childcare" may provide external cues that result in circadian rhythm modification. They posit that this external factor may influence internal/physiological circadian signaling and/or contribute to experienced light-dark exposure patterns.<sup>23</sup>

Despite these physiologic, environmental and social factors and the fact that women self-report shorter perceived sleep duration, lower sleep efficiency, and overall worse quality of sleep compared to men,<sup>26</sup> objective assessments often indicate that sleep quality of women is *better* than that of men. In studies making use of direct observation based on polysomnography, women have been found to have shorter sleep onset latency, less wake after sleep onset (WASO) time, less light (stage N1) sleep, and higher sleep efficiency,<sup>27-30</sup> all indicating better sleep quality. Reasons for this discrepancy between observed and reported quality of sleep are not definitively elucidated, but may include psychosocial factors, different rates of co-occurring major depression or generalized anxiety, and sex-specific differences in aspects of sleep that are considered important when self-reporting sleep quality.<sup>19,31,32</sup> In addition, men and women may differ in the homeostatic regulation of sleep. Levels of deep, slow wave sleep (stage N3) and electroencephalographic slow wave activity (SWA) – i.e. physiologic

markers of sleep homeostasis – are higher in women compared to men.<sup>28,33-35</sup> Sex differences in how the sleep homeostat responds to a sleep deprivation challenge has also been reported.<sup>36</sup> Specifically, women have an enhanced SWA response to a 40-hour sleep deprivation challenge, compared to men, suggesting that “sleep debt” may accumulate more strongly in women.<sup>12,36</sup> The greater “need for sleep” that is reported by women in survey studies,<sup>37</sup> may be reflective of this enhanced homeostatic sleep drive in women, and not sufficiently achieving this need may contribute to worsened sleep perceptions despite good quality sleep in women.

### **Sex and Insomnia Treatment**

For both acute and chronic insomnia, initial management involves identification and management of precipitating and perpetuating factors – e.g. identification of stressors, amelioration of poor sleep hygiene, etc. In the case of chronic insomnia, cognitive behavioral therapy for insomnia (CBT-I) is considered first-line therapy for most patients over medication by clinical practice guidelines of the American Academy of Sleep Medicine, the American College of Physicians, the European Sleep Research Society, and the British Association for Psychopharmacology endorse behavioral therapy.<sup>38-41</sup> However, constraints in time and resources often act as barriers that reduce patient access to CBT-I.<sup>42</sup> While men are often considered less likely than women to engage in behavioral therapies, research does not necessarily support that sex is a significant factor in CBT-I overall. In one American cohort (Stanford Sleep Disorders Clinic,  $n = 528$ ) gender was found not to be a significant predictor of CBT-I dropout.<sup>43</sup>

However, research has shown a significant sex-specific difference in prescription medication use for insomnia. Analysis of National Health and Nutrition Examination Survey data from 1999 through 2010 showed that female sex is a significant predictor of use of at least one medication commonly used for insomnia (adjusted odds ratio [AOR] = 1.32, 95% CI 1.08-1.61),<sup>44</sup> with nonbenzodiazepine benzodiazepine receptor agonists the most commonly used insomnia medication. Similar results were obtained in a 2011-2015 Korean prescription database study, which found more prescriptions for sedative/hypnotic medication among women compared to men. Zolpidem, in particular, was prescribed 1.6 times more frequently for women compared to men.<sup>45</sup> This is particularly relevant, as recent research revealed important sex-specific differences in the pharmacokinetic profile of this class of drugs. In fact, because slower drug metabolism among women could lead to outsized psychoactive effects compared to men at the same dose, the FDA has reduced the recommended dose of zolpidem by 50%.<sup>46</sup>

### **Sex and Insomnia: The Role of Age, Race/Ethnicity and Sexual/Gender Identity**

In addition to sex differences in prevalence, risk and treatment of insomnia, sex-specific disparities in insomnia prevalence

with regard to age and race/ethnicity have been described in the literature as well. One meta-analysis concluded that the excess risk of insomnia among women appears to be consistent and progressive across age, particularly in the elderly.<sup>10</sup> Specifically, the risk of insomnia among women compared to men increases from young adulthood to middle age to older age (RR = 1.28, 95% CI 1.13-1.43) among 15-30 year olds; RR = 1.46, 95% CI 1.29-1.63) among 31-64 year olds; RR = 1.73, 95% CI 1.65-1.83 among > 65 year olds).<sup>10</sup> Additionally, peri- and post-menopausal women experience increased sleep problems including insomnia, poor sleep quality and increased sleep disturbance, independent of what may be expected to occur with chronological aging.<sup>47</sup> It has been proposed that physiologic mechanisms—particularly physiologic transition periods (e.g. pubertal change, menstrual cycle, menopausal change) may contribute to this, though varying methodologies for measuring sleep quality and patterns,<sup>10,48</sup> preclude unequivocal conclusions.

With regard to race/ethnicity, while there is a large subset of sleep-related research that does not report/consider race and ethnicity, there are some examples of racial/ethnic disparities in sleep disturbances and insomnia severity, though the evidence is largely inconsistent.<sup>49</sup> Some comparative cross-sectional population-based have found no evidence of racial/ethnic disparities in prevalence of insomnia symptoms.<sup>49</sup> Yet other research supports that the trajectory of insomnia may also vary by race/ethnicity; among 22, 252 participants in the US Health and Retirement Study, insomnia severity was shown to increase with age to a greater extent among Hispanics compared to non-Hispanic whites after adjustment for multiple health conditions, BMI, and depression.<sup>50</sup> Related research into racial/ethnic differences in insomnia have found that exposure to racial/ethnic discrimination and other types of sociocultural stressors may be consistent and robust correlates of insomnia. For example, in a cross-sectional study of 40,038 United States women (35-74 years), there was an association between experiencing racial/ethnic discrimination and reporting difficulty initiating or maintaining sleep (prevalence ratio [PR] = 1.10, 95% CI 1.01–1.20).<sup>51</sup> Racial discrimination has also been shown to be a significant mediator of the relationship between race and insomnia symptom severity.<sup>52</sup> Another study found that among women, those who identify as Black/African American, Asian/Other, or Hispanic/Latino were significantly less likely than their white counterparts to have sleep complaints, while racial differences were not apparent among men; the authors posited that it may be that non-white women may be less likely to complain about their sleep.<sup>53</sup>

Compared to the quantity of literature on insomnia in general, however, there is much less on insomnia in LGBT populations and how nonbinary or non-cisgender status may affect the experience and consequences of insomnia. One study using data from the National Health Nutrition Examination Survey (2005-2014) found that bisexual women were more likely than heterosexual women to have ever told a health professional they had trouble sleeping (AOR 1.64 [95% CI = 1.15-2.34]).<sup>54</sup> There is also data that suggests that quality of sleep

is an important determinant of self-rated quality of life among both transgender men ( $\beta = -0.451$ ,  $p = 0.003$ ) and transgender women ( $\beta = -0.320$ ;  $p = 0.0029$ ).<sup>55</sup>

## Insomnia and CVD

Recent research suggests that insomnia increases the risk of CVD morbidity and mortality, including hypertension, coronary heart disease and heart failure.<sup>56</sup> Recent meta-analyses have shown that insomnia is associated with an increased risk of CVD events or death (RR = 1.45, 95% CI 1.29–1.62).<sup>6</sup> The China Kadoorie Biobank prospective study of 487,2000 adults found that individuals complaining of at least one insomnia symptom (self-reported difficulties in initiating or maintaining sleep, early morning awakening and/or daytime dysfunction) for at least 3 days per week had an increased risk of total incident CVD, while having all 3 insomnia symptoms conferred an 18%, 22% or 10% higher risk of total CVD, ischemic heart disease or ischemic stroke (not hemorrhagic stroke), respectively, compared to non-symptomatic patients.<sup>57</sup> One cohort of middle aged men, also found that baseline sleep disturbances were associated with an increased risk of heart failure (aHR = 1.52, 95% CI 1.16-1.99), particularly among overweight individuals (body mass index >25).<sup>58</sup>

Indeed, investigation from multiple countries supports the existence of a relationship between insomnia and subsequent CVD even adjusting for demographic characteristics and comorbidity. In a Taiwanese prospective cohort study of 44,080 adults, investigators found that presence of an insomnia diagnosis independently increased risk of subsequent myocardial infarction (adjusted HR 1.68, 95% CI 1.2102.16,  $p < 0.001$ ).<sup>59</sup> In a Finnish prospective cohort study, presence of self-reported frequent insomnia symptoms (>15 times/month) increased the odds of requiring anti-hypertensive medication (i.e. a hypertension diagnosis) (AOR = 1.47, 95% CI 1.14-1.91) and of receiving lipid-lowering medication (i.e., a dyslipidemia diagnosis) (AOR = 1.42, 95% CI 1.05-1.94) 5-7 years later, compared to no insomnia symptoms. Having occasional insomnia (symptoms 4-14 times/month) was also associated with both hypertension and dyslipidemia, though to a lesser degree than frequent symptoms, while rare insomnia symptoms (1-3 times/month) were not associated with risk, suggesting a dose response between insomnia frequency and CVD risk factors.<sup>60</sup> Overall, the preponderance of data suggests independent relationships between insomnia and development of hypertension, dyslipidemia, heart failure, acute coronary syndrome, and CVD death.<sup>6,61</sup>

The effects of insomnia on CVD appears to be potentiated by short sleep duration (a separate sleep construct outside the scope of this review). In one study, insomnia or poor sleep with objectively measured short sleep duration (<6 hours) conferred a 29% higher risk of incident CV events (i.e., first event of nonfatal or fatal myocardial infarction, angina pectoris, revascularization procedure, or stroke during follow up), while insomnia only and short sleep only were not associated with higher incident CVD.<sup>62</sup> In the Women's Health Initiative

(WHI), shorter sleep duration ( $\leq 5$  hours) was significantly associated with incident coronary heart disease and CVD among post-menopausal women, though this effect was entirely explained by comorbidities and behavioral risk factors (e.g., smoking) while severe insomnia (based on a 5-item WHI rating scale of bothersome symptoms related falling and staying asleep) appeared to be related to incident coronary heart disease and CVD among post-menopausal women even after adjusting for demographic, behavioral and medical risk factors.<sup>10</sup>

As for the mechanism of action for the relationship between insomnia and CVD, there is a large body of literature that suggests individuals with insomnia tend to be in a state of chronic physiologic hyperarousal characterized by multiple attributes including increased levels of circulating cortisol, increased sympathetic tone as evidenced by altered heart rate and contractility, increased metabolic rate, increased body temperature, decreased slow wave sleep, and increased number of arousals during REM sleep.<sup>2,56</sup> With regard to stress in particular, research has found associations between insomnia and both hormonal and behavioral responses to external stressors. It has been found that individuals with only family history of insomnia have both heightened self-reported reactivity to stressors co-occurring with a blunted cortisol response to stress (termed "abnormal stress regulation" by investigators).<sup>63</sup> Other research demonstrated that individuals with known insomnia had greater acute cortisol response, greater bedtime cortisol secretion, and increased pre-sleep cognitive arousal in response to stressors compared to good sleepers.<sup>64</sup> While it is quite plausible that stress reactivity is in some way related to the downstream effects of insomnia on CVD mortality, precise mechanisms by which hyperarousal may be related to CVD outcomes have not been definitively elucidated. Recent research in this area using a Mendelian randomization method (i.e., using genetic variants associated with an exposure to more robustly indicate whether the exposure causes an outcome) found that genetic predisposition to insomnia was associated with increased risk of coronary artery disease (AOR 1.10 95% CI 1.05-1.14,  $p < 0.001$ ) and heart failure (AOR 1.11 95% CI 1.05-1.18,  $p < 0.001$ ).<sup>65</sup>

## Sex and CVD

While insomnia appears to predict CVD mortality independent of sex, literature suggests that sex-specific disparities also exist for CVD mortality. Overall, men appear to have a greater absolute risk of CVD compared to women, with the magnitude of the difference varying by age, but women appear to have a higher relative risk.<sup>66</sup> While more men than women are living with and dying of coronary artery disease, the absolute number of women living with and dying of CVD and stroke exceed those of men, as does their number of hospital discharges for congestive heart failure and stroke.<sup>67,68</sup> In fact, despite being perceived as a "male disease," CVD remains the leading cause of death among women, with more than a quarter of a million women dying from heart disease in 2017 alone.<sup>69</sup> Specifically,

women have significantly higher rates of in-hospital death, heart failure,<sup>7</sup> and major bleeding as well as 3-year recurrent major adverse cardiac events (MACE).<sup>8</sup> Even 5-year post-ACS (particularly ST-segment–elevation MI (STEMI) and non-ST–segment elevation MI (NSTEMI)) all-cause mortality rates in women are nearly twice that of men.<sup>70</sup> In addition to in- and post-hospital mortality rates, sex is also an independent predictor of 30-day readmission for recurrent events, particularly among patients requiring percutaneous interventions.<sup>71,72</sup>

Several trials have suggested that sex differences in in-hospital mortality among post-ACS patients may be partially explained by long delays before admission, older age, as well as a higher clustering of CVD risk factors such as heart failure, metabolic syndrome, hyperlipidemia and diabetes; in fact diabetes is a stronger prognostic factor for survival after acute MI in women than men.<sup>7,72-78</sup> In addition, one meta-analysis found that after adjusting for age and baseline blood pressure, the risk of CVD per 10 mmHg SBP increment for women is 1.1 fold higher than for men ( $p < 0.01$ ; 95% CI 1.04-1.17).<sup>79</sup> Additionally, fewer women than men receive angiotensin-converting enzyme inhibitors (ACEI), aspirin, clopidogrel, beta blockers or statins<sup>80</sup> and undergo fewer invasive procedures including angiography, percutaneous coronary intervention (PCI) and reperfusion therapy.<sup>7,70,76-78,81-87</sup> This is despite the fact that some treatments like statins are associated with a greater reduction in recurrent major coronary events in women than men.<sup>88</sup> Additionally, fewer invasive procedures may be due to the fact that women are more likely to have non-obstructive coronaries despite symptoms and ischemia, suggesting lower diagnostic sensitivity and underdiagnosed microvascular disease.<sup>89,90</sup> Furthermore, women are 36% less likely to enroll in cardiac rehabilitation.<sup>81</sup> Even with improved quality of care/management<sup>68</sup> and after adjustment for clinical risk factors, however, sex differences in longer-term mortality remain, particularly among women <70 years and following STEMI.<sup>85</sup> Further, female sex remains a strong independent predictor for re-hospitalization for ACS and revascularization even after adjustment for prior revascularization, age, chronic disease, and other factors.<sup>91</sup>

## Sex, Insomnia, and CVD

### *Does Sex Moderate the Relationship Between Insomnia and CVD?*

While it is evident that both insomnia and sex independently and significantly predict CVD mortality, the literature on the interplay between sex and insomnia on CVD has been fairly inconsistent, with a paucity of studies examining modification by sex, which is more commonly included as a covariate.<sup>92</sup> Despite the greater burden of insomnia among women, some research does suggest that insomnia and CVD-related mortality may be more strongly related in men. In a 2002 study of 1870 Swedish adults, self-reported difficulty initiating sleep was associated with coronary artery disease death in men (RR = 3.1; 95% CI 1.5-6.3;  $P < 0.01$ ) but not women.<sup>93</sup> A 2018 study

of the Penn State Adult Cohort (a random general population sample of 1,741 American adults) demonstrated a significant interaction ( $p = 0.04$ ) between chronic insomnia and male sex. The investigators found that in men with chronic insomnia, risk of combined cardiovascular/cerebrovascular mortality was significantly increased by 2.9 fold, while there was a nonsignificant relationship among women.<sup>94</sup>

On the other hand, there is a mounting body of evidence that symptoms of poor sleep quality (e.g. Pittsburgh Sleep Quality Index (PSQI) score, problems falling asleep >2 night/week, >30 min to fall asleep) are more robustly associated with factors implicated in CVD progression in women than in men. These factors include psychosocial distress, higher fasting insulin, fibrinogen, and increased inflammatory biomarkers.<sup>95</sup> In one study, self-reported early morning awakening was significantly associated with 5-year increases in circulating IL-6 and fibrinogen in women despite adjustment for demographics, lifestyle/psychosocial factors, comorbid conditions, and medications; while no such association between sleep quality and IL-6 or fibrinogen was seen in men.<sup>96</sup> This type of association has been noted when making use of various inflammatory markers. For example, another study found that insomnia severity measured by the Insomnia Severity Index (ISI) was positively associated with amount of endothelial inflammation (as defined by nuclear factor kappa B level in harvested endothelial tissue) among women.<sup>97</sup>

In addition to physiological differences; pain level, social status and environmental, factors may also play a role. Insomnia and poor sleep quality are closely associated with pain and somatic symptoms. It is possible that insomnia may have a modulating effect on the sex differences in pain and somatic symptoms, especially in the adult population, as a shared genetic predisposition might underlie the associations of insomnia and sleep quality with pain and somatic symptoms.<sup>98</sup> With regard to employment, one study found that only men with manual occupations saw an increased risk of insomnia on CV events (myocardial infarction, stroke, or death due to ischemic heart disease), while women, regardless of socioeconomic status, had an increased risk of CV events attributed to insomnia; interestingly, combined insomnia and short sleep duration appeared to confer greater risk of CV events among men while, among women with insomnia, both short and long sleep duration appeared to increase the risk of CV events.<sup>10,99</sup> These studies suggest that the combined effects of socioeconomic status and sleep disturbance are needed to increase risk among men, while women may have other sociological or environmental factors that place them at increased risk. Investigators have suggested that the combination of insomnia and long-sleep duration may have been an epiphenomenon of comorbidity.<sup>10,99</sup>

Overall, the data regarding sex, insomnia, and CVD together are rather inconsistent. While there is evidence that the association between insomnia and CVD outcomes is more pronounced in men, there is also evidence for stronger associations between insomnia and behavioral and physiologic factors thought to increase CVD risk in women. Furthermore,

the latter inference has been replicated across various methodologies, including measurement of inflammatory factors in blood and tissue samples. Given this context, the data does not yet allow for definitive conclusions to be drawn.

### *Does Insomnia Help Explain the Relationship Between Sex and CVD?*

The frequency of reports of poor sleep quality among women and the previously discussed disparity in insomnia prevalence might lead some to posit that sleep disturbances may be one mechanism that contributes to sex-specific differences in in-hospital and post-discharge CVD morbidity and mortality. Research demonstrates that poor sleep quality after the first night of hospital admission is high compared to baseline sleep quality at home (50% vs. 18.8%,  $p < 0.001$  in one Thai sample; mean 5.5 versus 7.0 hours,  $p < 0.0001$  in a Canadian sample).<sup>100,101</sup> However, sub-analyses demonstrated that results did not differ by sex.<sup>101</sup> Women are also more likely than men to report post-discharge and post-ICU sleep disturbances.<sup>102,103</sup> However, to our knowledge, few if any prior studies have examined whether insomnia is an important mediator of the relationship between sex and CVD. Given sex differences in in-hospital and short-term CVD mortality,<sup>7</sup> poor sleep quality in hospital settings or post-discharge may be an additional unexplored mechanism.

There is also a bidirectional relationship between insomnia and psychopathology, with anxiety disorder preceding insomnia 73% of the time, and insomnia occurring first in 69% of comorbid depressive symptoms,<sup>104</sup> with some suggesting insomnia is a risk factor for developing depressive symptoms.<sup>105</sup> Depressive symptoms are more prevalent among women, are an important independent determinant of both quality of life and angiographic obstruction and ischemia,<sup>29</sup> and also appear to predict 1-year post-ACS mortality among women.<sup>106</sup> While research suggests that depression may have both direct and indirect effects (e.g., via hormonal/hypoestrogenism, dysmetabolic and inflammatory factors) on sex disparities in CVD,<sup>107</sup> it remains unknown whether insomnia, irrespective of depressive or anxiety symptoms, also accounts for a substantial portion of the sex differences in post-ACS outcomes.<sup>12</sup>

### *Does Obstructive Sleep Apnea Play a Role in Our Understanding of Sex, Insomnia, and CVD*

Insomnia overlaps with obstructive sleep apnea (OSA), a distinct sleep disorder that has also been identified in the literature as an important sleep-related risk factor for CVD. OSA is an objectively measured disorder of breathing specific to sleep characterized by repeated apneas (complete cessation of breathing) or hypopneas (reductions in breath amplitude) that cause arterial hypoxia and hypercapnia. Research has linked these apneas to both collapse of the upper airway (obstructive events) and reduced or entirely ceased brain stem respiratory signaling (central events) as well as to obesity.<sup>108</sup> In a review of

studies investigating the co-occurrence of these 2 disorders, Luyster (2010) found that 39%-59% of adults with OSA reported symptoms of insomnia and, conversely, 29%-67% of patients with insomnia were subsequently found to have an abnormal apnea-hypopnea index.<sup>109</sup> Research has shown that has OSA is associated with an increased risk of hypertension, congestive heart failure, coronary artery disease, and cardiac arrhythmias.<sup>110</sup> However, it remains unknown the extent to which insomnia and OSA independently predict CVD with investigators noting that the significant overlap in the diagnosis and management of OSA and insomnia poses challenges to this area of research.<sup>109</sup>

As for the role of sex, research suggests that OSA is more common in middle aged and older adults compared to young adults and among males compared to females.<sup>110</sup> However, women who report being diagnosed with OSA are more likely than diagnosed men to have the classical clinical features of the syndrome (obesity, loud snoring, and daytime sleepiness) and more likely to have respiratory disease, high cholesterol, and poor overall health.<sup>111</sup> There have been multiple explanations proposed to explain why research repeatedly demonstrates that OSA is more common in men than women, however. Posited mechanisms include differences in hormonal signaling as well as anatomic differences such as fat distribution and airway laxity. Additionally, it has been proposed that diagnostic bias may play a role, with men more likely to be diagnosed with OSA when they present with “classic” symptomatology,<sup>111</sup> as well as being more likely to be diagnosed with OSA as part of secondary CVD prevention. While men are more likely to report witnessed apneas or snoring, clinic-based patient samples indicate that women are more likely to complain of insomnia, depression, headaches, fatigue, nightmares, nighttime palpitations and hallucinations.<sup>111-116,117</sup>

Overall, few studies have examined whether sex influences the relationship between OSA and CVD,<sup>118</sup> though there is some data that suggests important differences. In a sample of 384 Saudi patients, women with OSA were more likely to be diagnosed with hypertension (61.8% F sample v. 32.6% M sample,  $p < 0.001$ ) and cardiac disease (26.2% F sample v. 17.6% M sample,  $p = 0.057$ ).<sup>119</sup> Further research is needed to elucidate the complex relationship between OSA, insomnia, sex and CVD, especially given the known sex-specific differences that also exist with respect to OSA. Given the nontrivial prevalence of OSA-insomnia co-occurrence, further investigation is needed to specifically determine the extent to which insomnia alone increases CVD risk, the extent to which OSA alone increases CVD risk, how these 2 disorders subsequently interact, and whether any interaction is also influenced by sex.

### **Gaps and Future Directions**

Overall, more deliberate definitions of sex and gender will be critical to research in this area. The literature referenced throughout this review rarely, if ever, defines these terms – tending to use them interchangeably – and appears to presume that individuals included in samples are cis-gender (or having a

personal gender identity that corresponds with assigned sex at birth). Inclusion of appropriate definitions of the terms sex and gender may help reduce the tendency for the sex variable to be dichotomized, increasing visibility of sample subjects that are neither cis-gender females nor cis-gender males and allowing for more frequent inclusion in statistical analyses. Using terms “gender” and “sex” interchangeably in medical and epidemiological research, implies that psychosocial and biological attributes tend to covary.<sup>66</sup> Increased specificity in these designations will also improve understanding of the mechanisms by which sex or gender interact with sleep and CVD. There is also growing consensus that while biological factors in males and females may affect behavior and vulnerability to chronic diseases like CVD and insomnia, the literature defines “gender” in contrast to the term “sex,” as a multidimensional, socially constructed roles for men and women that include biological/genetic, psychological, and social differences between individuals that influence behavior, emotions and attitudes.<sup>66</sup> In addition, research on the effect of sex on insomnia and CVD course would benefit from the use of intersectionality frameworks<sup>120</sup> to further conceptualize, measure, test, and interpret how gender intersects with other social identities (e.g., age, race/ethnicity, nativity status, sexual orientation, socioeconomic status) to confer adverse cardiovascular effects from insomnia, and in turn identify subpopulations at greatest risk.

Our review also supports recent calls for an increased number of women enrolled in clinical trials to better elucidate sex and CVD phenomena.<sup>121</sup> In addition to this, we propose that intentional enrollment of LGBT and otherwise nonbinary individuals would be useful, especially as the limited research that is available suggests sleep disturbance is an important determinant of quality of life in this population.

Additionally, advancing research in the area of sex, insomnia, and CVD would likely be facilitated by increasing uniformity in research methodologies that operationalize insomnia. Currently, variation in methods across different studies create differences in the exposure of interest from study to study, possibly contributing to the inconsistent nature of the data. For example, while some studies use a single self-reported sleep parameter (ex: difficulty falling asleep), others use standardized questionnaires like the ISI for insomnia or PSQI, while others rely on self-report of overall quality without the use of a validated survey tool. Additionally, some studies do not specify whether the insomnia is acute or chronic, and some combine insomnia with other measures like polysomnographic features, sleep duration, and comorbid disorders such as obstructive sleep apnea. However, sleep duration, for example, is a separate construct that also independently predicts CVD.<sup>122-126</sup> Disentangling these variables may allow for more systematic interpretation of results across different studies.

Another compelling future direction may be to investigate whether interventions aimed at alleviating insomnia (like CBT-I, sleep hygiene counseling, and others) also affect CVD outcomes or other physiologic measures / known risk factors related to CVD (e.g. blood pressure, inflammatory markers, cholesterol, etc). For example, one study noted that behavioral

intervention for insomnia resulted in reduction of participants’ blood pressure.<sup>127</sup> More research along these lines may help reveal mechanistic pathways between insomnia and CVD. Understanding the degree to which sex and gender moderate the effectiveness of these interventions will also be needed.

As alluded to in the previous sections, further research is needed to elucidate how sex influences the relationship between insomnia and CVD. Currently, a firm inference regarding sex-specific disparity between insomnia and CVD cannot be made with the existing data; nor can specific conclusions be drawn regarding mechanistic differences. Also, while they are outside the scope of our focus on insomnia, sleep apnea and sleep disordered breathing are other important CVD risk factors that clearly influence sleep quality, have differential prevalence by sex, and which warrant additional examination.<sup>128</sup>

## Conclusion

When the above body of literature is taken together, it can be concluded that insomnia and related indicators of poor sleep quality are more prevalent in women than men, and that there is an independent relationship between insomnia and CVD risk. However, there is a lack of consistency in the inferences drawn regarding the relationship between insomnia and CVD among men vs. women. The mechanisms of action in the relationship between insomnia and CVD may differ by sex and also warrant formal evaluation. Importantly, throughout the existing research “sex” tends not to be formally defined, and future research would benefit from improving on this and acknowledging differences between sex and gender. Finally, whether insomnia is a relevant mediator of the excess risk of CVD-related mortality seen in women has not been explored. Research will be needed to determine more specifically how these variables interact (e.g. additive, multiplicative, moderator vs. mediator) to further elucidate the role of sex in the relation between insomnia and CVD.

## Authors’ Note

Dr. Nathalie Moise and Dr. Rebecca Leeds had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Moise, Leeds; Acquisition of data: Usseglio, Leeds, Moise, Shechter, Aggarwal, Alcantara; Analysis and interpretation of data: Leeds, Moise; Drafting of the manuscript: Leeds, Moise, Shechter, Alcantara; Critical revision of manuscript for important intellectual content: Shechter, Alcantara, Aggarwal, Abdalla; Obtained funding: Moise; Study supervision: Moise.

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