Sleep Disturbances
Time to Join the Top 10 Potentially Modifiable Cardiovascular Risk Factors?

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“Sleep is that golden chain that ties health and our bodies together.”
—Thomas Dekker (1577–1632), Patient Grissel

Approximately 90% of the population-attributable risk for coronary artery disease has been estimated to relate to 9 potentially modifiable risk factors, including tobacco smoking, overweight, dyslipidemia, hypertension, physical inactivity, poor diet, and psychosocial factors. Accordingly, published guidelines for primary and secondary cardiovascular disease prevention support aggressive risk factor modification. Although sleep disturbances have not been identified as specific targets in current cardiovascular prevention guidelines, research over the last decade provides increasing evidence that poor sleep and sleep disorders significantly contribute to the development of heart disease. Furthermore, because of their prevalence, sleep disturbances ranging from sleep apnea to sleep curtailment may serve as important novel targets for cardiovascular disease risk reduction. This issue’s report by Laugsand and colleagues linking insomnia symptoms and subsequent risk of acute myocardial infarction (AMI) over an 11-year time period in a sample of >50,000 individuals from Nord Trondelag County, Norway, provides further evidence supporting the importance of sleep disorders in the pathogenesis of coronary artery disease. Use of a simple question, “Have you had difficulties falling asleep in the last month?” identified a group of individuals at a significantly increased relative risk of experiencing a subsequent AMI. Even after considering a comprehensive set of potential confounders such as age, depression, anxiety, and physical activity, the 3% of the sample who reported that this symptom occurred “almost every night” experienced a 40% to 50% increased multivariate adjusted hazard ratio for AMI. Further, there was a continuous graded relationship between increasing sleep disturbance and increased risk of AMI.

The pathophysiology of insomnia and its links to cardiovascular disease are not fully understood. Insomnia is considered to be a disorder of hyperarousal, with chronic activation of stress responses, which often is accompanied by increased metabolic rate, increased heart rate and decreased heart rate variability, and increased cortisol secretion. Thus, abnormalities in the autonomic nervous system and hypothalamic-pituitary axis may provide mechanistic bases linking insomnia and cardiovascular disease. A causal association linking insomnia to cardiovascular disease is supported by reports showing that experimental sleep deprivation or sleep disruption results in modest to high elevations in blood pressure and in levels of inflammatory mediators and in impaired glucose metabolism. Factors also implicated in atherogenesis. An association between curtailed sleep and atherogenesis is also supported by results from Coronary Artery Disease In Young Adults Study (CARDIA) that showed that the 5-year incidence rate of coronary artery calcium was inversely associated with sleep duration measured at an early time point.

The longitudinal design of Laugsand et al also supports a causal role for insomnia in the pathogenesis of coronary artery disease. However, because insomnia is commonly comorbid with both mood disorders and cardiopulmonary disease, establishing causality from observational data is difficult. It is possible that abnormalities in the autonomic nervous and neuroendocrine systems are common substrates for both insomnia and cardiovascular disease. Furthermore, numerous studies have identified that sleep disorders are associated with other indices of poor health, including low socioeconomic class, obesity, minority race, poor mental and physical health, and tobacco and alcohol use. Prior reports linking insomnia to cardiovascular disease have been criticized for failure to adequately control for depression and anxiety as well as for other confounders, limiting the ability to quantify the incremental effects of insomnia over and beyond the effects attributable to other cardiovascular risk factors. In the report by Laugsand et al, insomnia symptoms were, similar to previous reports, significantly more prevalent among older members of the cohort and in those with depressive and anxiety symptoms, diabetes mellitus, abnormal lipid levels, hypertension, smoking, and low physical activity levels. A major strength, however, of this report is the comprehensive series of statistical analyses, including sensitivity analyses, conducted to examine the consistency of associations across subgroups such as those defined by age, sex, use of hypnotic agents, and even the season studied. Recognizing the difficulty in constructing statistical models based on strong biological pathway data, alternative statistical models that included different sets of covariates that may operate as confounders, mediators, or moderators were pre-
sented. In aggregate, the consistency of the findings, especially in models adjusting for depression or anxiety, supported the validity of the results. In addition, noting that there was the possibility of reverse causation, analyses also were restricted to participants with more than 5 years of follow-up data, which again supported the overall study conclusions. Nonetheless, most confounders in these statistical models were derived from data using subjective reports, and the possibility of residual confounding cannot be excluded.

A systemic review estimated that symptoms of insomnia are associated with relative risks for cardiovascular disease ranging from 1.5 to 3.9. Thus, with a comprehensive adjustment for confounders, the multivariable adjusted hazard ratio of 1.45 by Laugsand et al is in the lower bounds of what has been previously reported. A limitation of the analyses reported by Laugsand et al is that exposure assessments were derived exclusively from data collected at a single baseline examination, without consideration of changes in sleep and other health factors over time. This report also did not distinguish between transient and chronic insomnia. Additionally, insomnia may precede the development of depression, and data on depressive symptoms occurring after the baseline examination were not evaluated. Finally, factors such as sedentary activity and dietary composition were not considered in analyses.

The focus of this article is insomnia, as identified by the classic insomnia symptoms: difficulties initiating sleep, problems maintaining sleep, and early morning awakenings. Although almost 9% of participants reported difficulty initiating sleep “often” or more, only 3.3% of the sample reported that this symptom occurred nightly—which was the threshold frequency level associated with the highest hazard ratio. A dose-response relationship, however, was observed between the number of insomnia symptoms and AMI, suggesting that the more disturbed sleep, the greater the cardiac risk. An advantage of using fairly simple questions to define a group at increased cardiovascular risk is the ability to incorporate such questions into routine clinical screening. The overall consistency of the associations across insomnia symptoms and for definitions that also qualified responses according to whether they caused work-related performance problems supports the validity of using a simple questionnaire-based approach for identifying high-risk groups which might benefit from targeted sleep disorder assessment. Nonetheless, it is important to recognize that insomnia symptoms do not equate with an insomnia disorder, which current definitions require to be identified on the basis of: (1) difficulty falling asleep, staying asleep, or nonrestorative sleep; (2) the difficulty is present despite adequate opportunities to sleep; (3) impaired sleep is associated with daytime impairment or distress; and (4) the sleep difficulty occurs at least 3 times per week and has been present for at least 1 month. Whereas approximately 30% of the population reports insomnia symptoms, 6% of adults meet the latter definition of insomnia. Data are not yet available to address how cardiovascular risk may differ between those who report insomnia symptoms compared with those who meet current definitions of insomnia disorder. Enhancing the recognition of sleep disorders within cardiology practice requires further consideration of which screening strategies, including defining the frequency and intensity of sleep disturbance symptoms, provide an optimal balance of sensitivity and specificity.

Insomnia also is only 1 of a number of sleep disorders that are associated with an increased risk of hypertension, cardiovascular disease, and cardiovascular-related mortality. Insomnia symptoms may occur with sleep apnea, periodic limb movement disorders, and shift work disorder, each of which is common and has been associated with an increased incidence of cardiovascular disease. Adverse cardiovascular effects of these myriad sleep disorders are thought to be mediated through their effects on sympathetic nervous system activation, alterations of the hypothalamic pituitary adrenal axis influencing secretion of cortisol and renin-angiotensin system activity, and by augmenting systemic levels of inflammation. These physiological perturbations may in turn contribute to renal dysfunction, endothelial changes, and atherosclerosis. It is possible that within the Norwegian cohort reported by Laugsand et al there was a subgroup of insomniacs with other primary sleep disorders, such as sleep apnea, which may have especially influenced the study findings. For the purposes of risk stratification, there is a need for further information on the co-occurrence of insomnia symptoms with other common sleep disorders occurring in cardiology practice.

Extreme values for average sleep duration—sleep durations of >5 to 6 hours or >9 to 10 hours per night—which may or may not be associated with insomnia symptoms—also have been associated with hypertension and cardiovascular disease. Insufficient sleep, perhaps partly through its effects on appetitive hormones, also is associated with an increased risk of obesity, a key target for traditional cardiovascular disease prevention. Although Langsand et al did not consider the influence of sleep duration on their results, prior research suggests that short sleep duration may adversely influence health outcomes independently or interactively with insomnia symptoms. For example, in the MONICA Ausberg study of nearly 7000 adults followed for a mean of 10 years, an almost 3-fold increased incidence of AMI was observed in women who reported sleeping ≤5 hours compared with those sleeping 8 hours per night. Although an association between the insomnia symptom, “sleep maintenance efficiency,” and AMI was observed, this association was attenuated in models that adjusted for other health attributes and behaviors. In a Pennsylvania community cohort, Vgontzas and colleagues performed a rigorous set of analyses attempting to dissect the influences of sleep duration from insomnia on hypertension.

In statistical models adjusted for multiple potential confounders, a 1-year history of insomnia and short sleep duration were each associated with hypertension. The highest risk of hypertension, however, was observed in a group with sleep duration of 6 hours; symptoms of poor sleep/insomnia were not associated with hypertension. Similarly, short sleep duration in the absence of sleep complaints was not associated with hypertension. Thus, further research is needed to dissect the effects of subjective sleep problems with objectively measured sleep duration.

Despite some study limitations, the study reported in this issue of Circulation, along with an abundance of other
observational data, strongly supports the importance of sleep health in influencing cardiovascular outcomes. This study identifies the robustness of relatively simple insomnia questions for identifying individuals from the general community at increased risk of AMI. Although it is not clear whether these questions would perform similarly in patients referred explicitly for primary or secondary cardiovascular disease risk reduction, the high prevalence of sleep disorders in the general population as well as in patients at risk of cardiovascular disease warrants consideration of systematic screening of such patient populations for treatable sleep conditions. Because asking about the frequency of insomnia symptoms may not provide information on sleep duration and other sleep disorders (eg, sleep apnea), there needs to be consideration of how to best choose sleep disorders screening questions with optimal predictive properties in targeted groups, such as those presenting with cardiovascular risk factors or established cardiovascular disease.

What are the implications to the cardiologist of this growing body of research linking sleep disorders and sleep behaviors to cardiovascular health? Although further research is needed to evaluate the influence of screening and treatment of sleep disorders on cardiovascular outcomes, the morbidities of insomnia, including its adverse influence on quality of life, cardiac function and health care utilization, may justify initiatives to identify sleep disturbances and improve sleep in patients with cardiovascular disease. These include encouraging patients to use principles of good sleep hygiene (avoiding alcohol and stimulants before bedtime, following regular bedtime routines, etc), use of medications that do not adversely affect sleep quality or duration, and identifying patients likely to benefit from a referral for a more comprehensive sleep disorders evaluation. Depression and anxiety are prevalent among patients with heart failure and those who have suffered a myocardial infarction, and their comorbidity with insomnia suggests the potential value of an integrated approach for addressing both mood and sleep disorders in selected groups of patients at high risk for these disorders. Additionally, the approach to promoting a healthy lifestyle, which traditionally has included encouragement of healthy eating patterns and physical activity, may be expanded to encompass behaviors across the entire 24-hour period, including sleep. There are close interrelationships among eating patterns, sleep, and stress, which share some common neurophysiological mechanisms. Health behaviors also are closely interrelated; specifically, insufficient sleep may alter energy levels and physical activity as well as alertness and adherence to medical regimens. As observational data, such as those reported by Laugsand et al, continue to mount, linking poor sleep to cardiovascular disease, clinical trials are needed to determine whether improving sleep, a health attribute integral to many physiological functions and behaviors, improves cardiovascular outcomes. Once demonstrated, poor sleep can take its place on the top 10 list of modifiable cardiovascular risk factors.

Disclosures

None.

References


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