Is Restless Legs Syndrome Associated with Cardiovascular Disease?

Restless legs syndrome is a common condition characterized by a strong urge to move the limbs that is usually worse during the evening and nighttime hours, that is worsened by rest, and that improves with activity. However, the prevalence has varied in different studies, primarily depending on the criteria chosen to define this disorder. Prior studies using the International Restless Legs Syndrome Study Group criteria have placed the prevalence between 3.9% and 14.3%. Restless legs syndrome is associated with diverse adverse consequences. Health-related quality of life is reduced in those with restless legs syndrome and is lower in those with more severe disease. Restless legs syndrome also can lead to an increased prevalence of insomnia, depression, and anxiety.

Several large epidemiologic studies have suggested a causal association between restless legs syndrome and cardiovascular disorders and hypertension after controlling for confounders such as age, witnessed apneas, and smoking. Furthermore, a recent study using prospectively obtained data from the Nurses’ Health Study found an increased risk of incident nonfatal myocardial infarction in those with a history of restless legs syndrome for 3 years or more (hazard ratio, 1.80; 95% confidence interval [CI], 1.07-3.01). The increased risk of coronary heart disease persisted after adjustment for blood pressure, diabetes duration, and use of diabetes medications. However, not all studies have observed an association between restless legs syndrome and cardiovascular disease. Conversely, frequent exercise and alcohol consumption of 1 or more drinks per day reduced the odds of restless legs syndrome. Of note, those with prevalent stroke had higher odds of a positive history of restless legs syndrome (odds ratio [OR], 1.41; CI, 1.05-1.86), whereas those with a history of myocardial infarction had lower odds of restless legs syndrome history (OR, 0.73; CI, 0.55-0.97).

The second study by Winter et al analyzed data from 30,262 female health professionals (mean age, 63.6 years) participating in the Women’s Health Study. The prevalence of restless legs syndrome was 12.0% and more likely with severe obesity and smoking. Exercise ≥4 times/week was associated with lower odds of restless legs syndrome (OR, 0.84; CI, 0.74-0.95). However, there was no association between restless legs syndrome and prevalent major cardiovascular disease defined as nonfatal myocardial infarction or stroke. Women who underwent coronary revascularization had increased odds (OR, 1.39; CI, 1.10-1.77) for restless legs syndrome compared with those with no intervention. However, this relationship also was no longer significant after excluding those with potential causes of restless legs syndrome.

To what extent do these new observations improve our understanding of restless legs syndrome? They certainly confirm the overall prevalence of restless legs syndrome and its increase with age in 2 large population samples. In addition, the prevalence in women appears to be higher than in men, although these rates are from different cohorts. Both studies showed a reduced risk of restless legs syndrome with frequent exercise, and diabetes was associated with a higher risk. These results are generally consistent with prior studies. However, unlike other investigations, a cross-sectional association with cardiovascular disease was not present or was inconsistent. Thus, the findings reported in this issue of the Journal are compatible with previous analyses using these cohorts published by the same authors in which they did not find an increased risk of incident major cardiovascular disease, stroke, myocardial infarction, cardiovascular disease death, or coronary revascularization in those with restless legs syndrome. The strength of these studies...
is the large number of participants. However, these studies have several limitations that may temper the conclusions.

One limitation was the use of questionnaires for diagnosis of restless legs syndrome. Although questionnaires are generally valid, they can still lead to identification of a significant number of false-positive participants with restless legs syndrome because other conditions can mimic the condition. However, to minimize the likelihood of false-positives, the authors performed sensitivity analyses excluding participants with potential secondary causes for restless legs syndrome, making this less of a concern. A more important limitation to these studies was that the history related to the duration of restless legs syndrome and the frequency and severity of restless legs syndrome were not available. In the Nurses’ Health Study, the hazard ratio for cardiovascular disease was increased only in those with a restless legs syndrome history for 3 years or more. Analysis of Wisconsin Sleep Cohort data demonstrated an increased risk of cardiovascular disease in those with daily symptoms of restless legs syndrome (OR, 2.58; 95% CI, 1.38-4.84), but not in those with less frequent symptoms. In the Sleep Heart Health Study, odds of cardiovascular disease were higher (OR, 2.07; CI, 1.43-3.00) for those with severe restless legs syndrome compared with those without restless legs syndrome. It is possible that any impact of restless legs syndrome on cardiovascular disease risk is apparent only in those with the greatest exposure. Furthermore, the age and racial makeup of the studies (older, primarily Caucasian participants) limit the generalizability of the results. Finally, apart from methodological issues, some of the variability in studies assessing the relationship between restless legs syndrome and cardiovascular disease may be related to the presence and severity of periodic limb movements during sleep, which is frequently seen in association with restless legs syndrome, and whether these periodic limb movements are associated with arousals and increased sympathetic activity. Absence of polysomnography in the current studies makes it impossible to make a determination regarding the presence of periodic limb movements or arousals.

The relation between restless legs syndrome and cardiovascular disease continues to be nebulous. Prospectively designed studies controlling for major confounders need to be conducted to better elucidate this relationship. Furthermore, future studies should consider better diagnostic modalities, be it more specific questionnaires or requiring physicians or trained professionals to diagnose restless legs syndrome. Documentation of frequency and severity, as well as duration of symptoms, and the presence of periodic leg movements will help our understanding of the relationship between restless legs syndrome and cardiovascular disease, and the pathophysiology thereof.

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References


