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Restless legs syndrome and cardiovascular disease: A research roadmap

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Abstract

In this paper, we first critically appraise the epidemiologic literature examining the association of restless legs syndrome (RLS) with cardiovascular disease (CVD) and then consider whether lessons learned from the study of cardiovascular consequences of other sleep disorders might inform a research agenda to examine the potential mechanisms of cardiovascular morbidity of RLS. Cross-sectional and longitudinal studies are both mixed as to whether there is a meaningful association of RLS and CVD. On the other hand, numerous cross-sectional and longitudinal observational studies have shown a strong association of obstructive sleep apnea (OSA) with CVD risk. Each of the potential mediating mechanisms in OSA may also be assessed in RLS, including 1) neural mechanisms such as increased central sympathetic outflow, impaired baroreflex function, diminished heart rate and blood pressure variability, and increased chemoreflex sensitivity; 2) metabolic mechanisms such as glucose intolerance and reduced insulin sensitivity/diabetes as a result of sleep disturbance in RLS; 3) oxidative stress; 4) systemic or vascular inflammatory mechanisms; and 5) vascular mechanisms including impaired endothelial functioning, increased aortic stiffness, hypothalamic-pituitary axis activation or renin-angiotensin-aldosterone activation. Three known characteristics of RLS may contribute to these specific mechanisms of increased cardiovascular risk: 1) periodic limb movements of sleep, which are associated with large increases in heart rate and blood pressure; 2) sleep fragmentation and sleep deprivation, which are known to produce adverse consequences for neural, metabolic, oxidative, inflammatory, and vascular systems; and 3) iron deficiency, which is an emerging risk for cardiovascular disease. Future research priorities include additional epidemiologic studies which characterize multiple

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CVD risk factors, case-control studies which examine known markers of cardiovascular risk, and small clinical trials which assess the effects of RLS treatment on intermediate physiological markers such as sympathetic activity or baroreflex control, measures of vascular stiffness and reactivity, or measures of insulin sensitivity and glucose tolerance.

Keywords

restless legs syndrome; cardiovascular; epidemiology

1. Introduction

Restless legs syndrome (RLS) has been associated with cardiovascular disease (CVD) in both cross-sectional and prospective studies, although these are limited in number and yield conflicting results. In this paper, we first critically appraise the epidemiologic literature and then consider whether lessons learned from the study of cardiovascular consequences of other sleep disorders might inform a research agenda to examine the potential mechanisms of cardiovascular morbidity of RLS. The sleep disorder most extensively studied in relation to CVD is obstructive sleep apnea (OSA). While OSA is characterized by intermittent hypoxemia, a feature that is absent from RLS and often considered central to the cardiovascular consequences of OSA, there is evidence that hypoxemia is not the sole mediator of cardiovascular effects in OSA, with sleep disturbance also playing a role. Moreover, there is evidence from both naturalistic and experimental studies of sleep deprivation and sleep fragmentation that these disturbances in sleep patterns have cardiovascular and metabolic effects that may be relevant to the study of RLS: the majority of RLS patients report difficulties initiating and maintaining sleep. Further, the strong association of RLS with periodic limb movements during sleep (PLMS), and consequent sleep fragmentation and blood pressure increases, suggests another potential mechanism for RLS-related cardiovascular morbidity. Finally, it is possible that pathophysiologic features unique to RLS are contributors to cardiovascular risk.

2. Epidemiology of restless legs syndrome and cardiovascular disease

Both cross-sectional and longitudinal studies have examined the association between RLS and CVD (see Innes [1] for review), both providing evidence for and against such a relationship. Methodological issues most likely contribute to the variation in these outcomes. In particular, the number, age and sex of participants, the method of RLS diagnosis, RLS features, length of follow-up, control for confounders, method of outcome ascertainment, and type of outcome may all influence the results. In light of the absence of a pathognomonic RLS feature, it is not surprising that variation in RLS diagnostic features potentially contributes the most variation between studies, including requirements for frequency or duration of RLS symptoms, and primary versus secondary RLS.

1. Cross-sectional general population studies. Cross-sectional studies from multiple cohorts have examined the association of RLS and overall CVD. Swedish studies found an association of RLS with “heart problems” in both men (n=2 608, mean age=47, OR=2.5, 95% CI 1.4–4.3) and women (n=3 501, OR=2.1, 95% CI 1.2–

3.9) [2]. A multivariate analysis from the Wisconsin Sleep Cohort (n=2 821, mean age=55) found an association of RLS and CVD (OR=2.6, 95% CI 1.4–4.8) [3], though only in those with daily RLS symptoms. A similar multivariate analysis from the Sleep Heart Health Study (n=2 546, mean age=68) also found an association of RLS and CVD (OR=2.4, 95% CI 1.6–3.7), which again was only present in those with symptoms 16 days per month [4]. A study from Finland (n=995, mean age=57) using multivariate analysis found an OR=2.9 (95% CI 1.2–7.2) for RLS and coronary heart disease [5]. Two recent studies did not demonstrate associations of RLS and CVD using multivariate analysis: in the Physicians' Health Study (n=22,786 men, mean age=68), an OR=0.97 (95% CI 0.79–1.2) was reported for overall CVD, although stroke was positively associated with RLS (OR=1.4, 95% CI 1.1–1.9) and prevalent myocardial infarction (MI) was negatively associated with RLS (OR=0.73, 95% CI 0.55–0.97) [6]. In the Women's Health Study (n=30 262 women, mean age=64), there was no association of RLS with overall CVD (OR=0.98, 95% CI 0.74–1.3), although there were apparent differences by type of CVD: there was a significant positive association with coronary revascularization (OR=1.4, 95% CI 1.1–1.8), while neither MI (OR=1.3, 95% CI 0.93–1.9) nor stroke (0.68, 95% CI 0.44–1.1) were significantly related to RLS [7].

2. Longitudinal general population studies. Longitudinal studies are more useful than cross-sectional studies in assessing causal relationships; however, longitudinal studies have also provided mixed guidance on the relationship of RLS to CVD. In the Dortmund Health Study (n=1 312, age=52, mean follow up=2.1 years), RLS diagnosis was made in face-to-face interviews based on three standardized questions. Small numbers of incident cardiovascular events limited the strength of analyses [8]. A vascular comorbidity index was associated with a borderline significant increased risk of incident RLS (OR=1.3, 95% CI 1.0–1.7). The Study of Health in Pomerania, a cohort of middle-aged men and women, using the same method of RLS diagnosis, did not find that RLS (prevalence of 10.1%) predicted incident nor recurrent MI (OR=0.53, 95% CI 0.12–2.3) nor stroke (OR= 1.2, 95% CI 0.46–3.2) at 5-year follow-up, although the vascular comorbidity index again suggested “reverse” causality, being associated with a significant increased risk of incident RLS (OR=1.4, 95% CI 1.2–1.7) [9]. The high prevalence of RLS suggests that participants with a wide range of RLS severity were included in that group. Two large US studies also did not find that RLS was a risk factor for CVD. In the Women's Health Study, 11.7% of the nearly 30 000 participants met criteria for RLS based on a 3-question written survey. RLS was not a risk factor for incident total CVD events (OR=1.2, 95% CI 0.88–1.5) nor for stroke nor MI individually [9]. Exclusion of participants with a variety of causes of secondary RLS (e.g., end-stage renal disease [ESRD], polyneuropathy, rheumatoid arthritis) did not change the results. The RLS-CVD association was not presented for these secondary forms of RLS. In an analysis of the Physicians' Health Study performed by the same group, 7.2% of nearly 20 000 men were identified as having RLS using the same questions used by the Women's Health Study. Again, RLS was not a risk factor for overall incident

CVD events (OR= 1.0, 95% CI 0.81–1.3) or for stroke or MI individually, including sensitivity analyses excluding comorbidities as above [9].

In contrast to these negative studies, the Nurses' Health Study, with 70 694 female participants (mean age=67), used self-reported physician diagnosis to ascertain RLS status (2.1% prevalence). In addition, participants were asked the duration since RLS diagnosis. In this study, RLS was associated with a borderline significant increased risk of incident MI after a mean of 5.6 years of follow-up (OR=1.5, 95% CI 0.97–2.2); however, in those women who reported having received an RLS diagnosis more than 3 years previously, the risk for both incident MI (OR=1.8, 95% CI 1.1–3.0) and for fatal MI (OR=1.5, 95% CI, 0.55–4.0) were increased [10]. The risk of CVD was unchanged in sensitivity analyses that excluded patients with diabetes or ESRD.

Another large study, of enrollees in the Kaiser Permanente health system, used electronic health record searches to identify approximately 12 000 individuals with RLS, who were stratified into those with any of a large list of comorbid medical illnesses either before or following RLS diagnosis. These included both standard secondary associations of RLS (e.g., ESRD, iron deficiency) as well as some unusual ones (e.g., nocturnal myoclonus, leg cramps, claudication). In contrast to previous epidemiologic studies that found no apparent difference between "primary" RLS and "secondary" RLS or potential RLS mimics (e.g., peripheral neuropathy or diabetes mellitus as a proxy for neuropathy), the Kaiser study found a dramatic difference in RLS risk when stratified in this way. At a mean of 3.9 years of follow-up, in those individuals without a history of CVD, "primary" RLS was not a risk factor for overall CVD or coronary artery disease, but was a risk factor for hypertension (OR=1.2, 95% CI 1.1–1.3). On the other hand, those with "secondary" RLS had an elevated risk of overall CVD (OR=1.3, 95% CI 1.2–1.5) and of coronary artery disease (OR=1.4, 95% CI 1.3–1.6) [11]. One explanation is that the comorbidities used in the Kaiser analysis were much more inclusive than in the other studies, and included diagnoses often found in more severe RLS (nocturnal myoclonus, leg cramps), potentially biasing the secondary group to include sicker or more affected RLS cases. Further, the comorbidities defining "secondary" RLS either preceded or followed RLS diagnosis by one year, potentially including RLS cases with subclinical outcomes of interest in the "secondary" group.

A recent study from the Veterans Administration identified over 4 000 (predominantly male) individuals with a new diagnosis of RLS and matched for multiple comorbidities to the same number of veterans without RLS chosen from a pool of about 3.5 million individuals. Over a seven-year period, RLS was associated with increased risk for diagnosis of coronary heart disease (HR= 4.0, 95% CI 3.3–4.8) and stroke (HR= 3.9, 95% CI 3.1–4.9) [12]. From their data it was difficult to determine the chronological order of the RLS and other diagnoses, and given previous suggestions that CVD predisposes to RLS [8], better clarification of these results will be important, although this should not

affect the finding that incident RLS was associated with an increased mortality risk (HR 1.09, 95% CI 1.7–2.1).

3. Special risk populations. As an alternative to studying the general population, a Taiwanese study evaluated 1 089 patients with ESRD on hemodialysis who were followed for a mean of 3.7 years. ESRD with RLS was associated with an elevated risk of cardiovascular events (OR=2.8, 95% CI 2.0–4.1) compared to ESRD without RLS. RLS severity had a strong influence on this relationship, with OR=1.7 (95% CI 1.0–2.9), 2.8 (95% CI 1.6–4.7) and 2.9 (95% CI 2.0–4.5) for mild, moderate, and severe cases respectively [13]. Similar associations were observed for stroke. These relationships for cardiovascular events or stroke were materially unchanged when patients with polyneuropathy were excluded.

3. Obstructive sleep apnea and cardiovascular disease: an instructive model?

Numerous cross-sectional and longitudinal observational studies have shown a strong association of OSA with CVD risk. These observational studies are supported by animal models and human physiological studies exploring potential mechanisms underlying the OSA- cardiovascular disease relation. Although large clinical trials demonstrating a reduction in risk of major adverse cardiovascular and cerebrovascular events with treatment of OSA have not yet been completed, smaller trials focused on intermediate physiological measures and surrogate risk markers have repeatedly demonstrated improvement in blood pressure following treatment of OSA, with variable improvement in other indices of cardiovascular risk. There are multiple putative mechanisms linking OSA to CVD, including neural, metabolic, inflammatory, vascular, and oxidative stress mechanisms (Figure 1). While intermittent hypoxemia is often considered central to each of these mechanisms, it has been shown that while treatment of OSA, whether with continuous positive airway pressure (CPAP) or mandibular advancement devices, reduces blood pressure in OSA patients [14–17], control of hypoxemia with nocturnal supplemental oxygen does not. This suggests that other factors, such as sleep fragmentation, may also play an important role. The evidence supporting a role for these mechanisms in RLS is limited, but where available is discussed (Figure 2).

3.1. Neural mechanisms

By far the best-established mechanism linking OSA to CVD is increased sympathetic nervous system activity. Given the neural etiology of RLS, it is plausible that central nervous system regulatory abnormalities may also contribute to abnormalities in neural circulatory control in RLS, specifically in dysfunction of central autonomic vagal and sympathetic outflow. In general, a higher sympathetic drive and a lower vagal drive have been linked to increased cardiovascular risk. Neural circulatory dysfunction in RLS may have diverse manifestations, some of which are listed below.

1. Increased central sympathetic outflow. This can be measured through various methods including plasma catecholamines, urine catecholamines and metabolites, norepinephrine spillover and direct intraneural recordings of

sympathetic nerve activity. In patients with OSA, sympathetic nerve activity is markedly elevated because of chemoreflex-mediated responses to hypoxemia and hypercapnia [18]. Importantly, however, high sympathetic drive in OSA patients carries over into normoxic daytime wakefulness and has been implicated in the heightened prevalence of hypertension in OSA [19]. It is not known if sympathetic activity is similarly elevated in patients with RLS. Certainly, disturbed sleep and repeated arousals may trigger brief increases in sympathetic activity; furthermore, individual PLMS are clearly associated with large increases in heart rate and blood pressure. Whether these responses translate to heightened daytime sympathetic drive remains unknown.

2. Impaired baroreflex function. Baroreflex impairment has been linked to an increased risk of hypertension. Recent data from Bertisch et al. [20] suggest attenuated baroreflex gain in RLS patients off medications in comparison to normal control subjects. RLS patients also had attenuated limb blood flow and increased limb vascular resistance, conceivably suggesting the presence of increased sympathetic vasoconstrictor tone.
3. Cardiovascular variability. Patients with OSA have diminished heart rate variability and increased blood pressure variability compared to closely matched controls with similar BMI and blood pressure levels [21]. These variability characteristics are associated with an increased propensity to future hypertension and to end organ damage. Although detailed studies of cardiovascular variability have not been performed in RLS patients, there is evidence that they lack a normal physiologic heart rate variability response on tilt test [22].
4. Chemoreflex sensitivity. The chemoreflexes have a powerful influence on both sympathetic and vagal activity. In patients with OSA there is selective potentiation of the chemoreflex response to hypoxemia [23]. Administration of 100% oxygen during daytime wakefulness lowers both sympathetic drive and blood pressure, suggesting that in OSA, tonic chemoreflex activation even during normoxia contributes to increases in sympathetic outflow and blood pressure [24]. The baroreflexes serve as important inhibitors of chemoreflex gain. Therefore, impaired baroreflexes, as has been noted in patients with RLS, may contribute to increased chemoreflex sensitivity in RLS. Heightened chemoreflex gain in RLS patients would, like OSA, facilitate increased sympathetic vasoconstrictor tone and hence blood pressure. Whether chemoreflex sensitivity is increased in RLS is not known.

3.2. Metabolic mechanisms

Both cross-sectional and longitudinal observational studies show a strong association of OSA with glucose intolerance, reduced insulin sensitivity, and diabetes mellitus, after controlling for the shared risk factor of adiposity [25]. While multiple small treatment trials have provided conflicting evidence for improvement in metabolic function with CPAP treatment, there is a growing consensus that treatment of OSA can improve glucose metabolism, at least in patients who have not developed overt diabetes [26,27]. Animal data point to intermittent hypoxia as a possible mediator of the adverse metabolic effects of OSA

[28], although it should be noted that in animal models, intermittent hypoxemia also leads to sleep fragmentation. Over the last two decades there has been increased awareness that sleep disturbances independent of hypoxemia may play an important role in the pathogenesis of metabolic dysfunction. As insulin resistance and hyperglycemia elicit a repertoire of detrimental effects that favor the atherosclerotic process [29], metabolic dysfunction could thereby play a causal role linking RLS and cardiovascular disease.

1. Sleep deprivation. Insufficient sleep has been associated with reductions in insulin sensitivity, glucose intolerance, and increased risk for type 2 diabetes mellitus [30]. Laboratory-based studies have shown that sleep restriction in health subjects is associated with reduction of insulin sensitivity and impairments in glucose tolerance [31–34], impairments that appear to reverse with recovery sleep [35]. Putative mechanisms linking sleep restriction to metabolic impairments include increased sympathetic nervous system activity, alterations in corticotropic function, abnormalities in adipocyte function, and systemic inflammation [36–41]. Pooled data from epidemiological longitudinal studies support the notion that short sleep duration is associated with a higher risk for developing type 2 diabetes [42].
2. Sleep fragmentation. Disruption of sleep continuity is a hallmark of OSA, but is also seen in RLS, especially when accompanied by PLMS. In healthy volunteers, non-specific fragmentation of sleep for two nights decreases insulin sensitivity by 25% and is associated with a shift in sympathovagal balance towards heightened sympathetic nervous system activity [43]. Moreover, selective suppression of slow wave sleep can also lead to a similar level of decrease in insulin sensitivity [44].
3. Difficulty initiating and maintaining sleep. Prospective data from population-based research show that poor sleep quality increases the risk for incident diabetes independent of other well-established risk factors. A meta-analysis of the available literature has shown that difficulty initiating sleep and maintaining sleep are associated with relative risks of 1.5 and 1.9, respectively, for developing type 2 diabetes [45]. Mechanisms through which poor sleep quality may worsen metabolic function are not known.

3.3 Oxidative stress

Oxidative stress, which is increased in OSA [46], is well known to trigger precursors of vascular damage, including an increase in circulating cytokines, and predisposes to the development of cardiovascular disease [47]. More specifically, oxidative stress has been shown to activate several intermediate pathways that are relevant for the development of cardiovascular disease including the polyol and hexosamine pathway, protein kinase C pathway, NF- κ B-mediated vascular inflammation and formation of advanced glycation end-products [48,49]. These intermediate pathways can alter endothelial cell function including permeability, exacerbate systemic inflammation, and augment angiogenesis, cell growth and apoptosis [48,50]. While oxidative stress in OSA is most likely due to cyclic hypoxia and reoxygenation that is not relevant to RLS, hyperglycemia can alter endothelial nitric oxide availability and favor the accumulation of reactive oxygen species. Thus, RLS-related

impairments in sleep quality could, through effects on metabolic pathways, secondarily contribute to oxidative stress.

3.4. Inflammatory mechanisms

Systemic inflammation has been proposed as a mechanism linking OSA to CVD. A recent meta-analysis of published studies of inflammatory marker levels in OSA patients compared to non-OSA controls suggests increased levels of systemic markers of inflammation, including C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), intercellular adhesion molecule (ICAM), and interleukin-6 (IL-6), among others [51]. There is some evidence of publication bias, however, and a number of studies suggest that much of the association of OSA with systemic inflammation is explained by obesity [51,52]. Moreover, studies of the effect of OSA treatment on systemic markers of inflammation have yielded mixed results [53].

Other lines of investigation are more suggestive of an effect of OSA on vascular inflammation. Increased vascular endothelial cell production of cyclooxygenase-2 and inducible nitric oxide synthase, markers of vascular inflammation, has been demonstrated in patients with OSA compared to BMI-matched controls, and these levels are significantly decreased by treatment of OSA [54], and animal models also support such an association [53].

The putative mechanism underlying inflammation in OSA is intermittent hypoxemia, which has been shown to promote the expression of inflammatory gene pathways in cellular models of hypoxia [55]. There is limited evidence that sleep deprivation and fragmentation may also increase inflammation, although the magnitude of this effect in both observational studies and experimental sleep deprivation studies is modest [56]. Whether RLS is associated with increased systemic or vascular inflammation has been little studied. In a study of RLS prevalence in two Scandinavian countries, there was no apparent association of RLS with either CRP or IL-6 levels [57]. It is possible that PLMS may modify an association of RLS with inflammation, as suggested by a study that found frequent PLMS to be associated with elevated CRP in patients with RLS, although this should be interpreted with caution as no association was noted with TNF- α or IL-6 [58].

3.5. Vascular mechanisms

Impaired vascular function has been observed in OSA and may serve as both a marker and a mechanism of increased cardiovascular risk in OSA patients. Vascular manifestations of OSA include the following:

1. Impaired endothelial function. Endothelial dysfunction is an early marker of vascular abnormality and a strong predictor of incident CVD. This is most often measured in the macrovasculature by post-ischemic flow-mediated dilation of the brachial artery. Impaired endothelium-dependent vascular reactivity has been demonstrated in numerous observational studies of OSA patients and general community samples, and improvement in endothelium-dependent vascular reactivity with treatment of OSA has been well documented [59]. Decreased nitric oxide (NO) availability is mechanistically implicated, as evidenced by

impaired endothelium-dependent vascular reactivity, decreased circulating NO levels, and decreased endothelial NO synthase (eNOS) activity in endothelial cells of OSA patients. Endothelial inflammation and oxidative stress may also play a role. While intermittent hypoxia is a proposed common mediator of these pathways to endothelial dysfunction [60], sleep restriction of as little as 2 hours per night for 8 nights resulted in a large decrease in endothelium-dependent brachial artery dilation in healthy young adults [61], and in rats this effect has been shown to be independent of increased sympathetic nervous system activity [62]. Sleep fragmentation has also been shown to cause endothelial dysfunction in a mouse model [63]. Although there are few studies of endothelial function in RLS, compared to age- and sex-matched controls, RLS patients appear to have lower serum NO levels [64] and lower levels of flow-mediated brachial artery dilation [65].

2. Aortic stiffness. Aortic stiffness has recently been recognized as an important marker of CVD risk, and recent data suggest that this may precede and contribute to the development of hypertension. The most widely used measure of aortic stiffness is the carotid-femoral pulse wave velocity (CFPWV), a measure of distal aortic stiffness. Aortic stiffness has been identified in association with OSA, although causal mechanisms have not been elucidated [66,67]. While effects of hypoxemia or large changes in intrathoracic pressure have been suggested as mechanisms, a recent study found that a single night of total sleep deprivation was associated with increased aortic stiffness [68], suggesting a mechanism whereby RLS might contribute to aortic stiffness. It has also been recently demonstrated that PLMS are associated with increased arterial stiffness, as measured by a photoplethysmographic method, and that this effect is similar to that observed for OSA [69].
3. Hypothalamic-pituitary axis (HPA) activation. HPA activation has been inconsistently reported in association with OSA, with vasopressin implicated as a local paracrine mediator of increased blood pressure. Acute and subacute sleep restriction is also associated with increased evening cortisol levels [38], and limited evidence also suggests HPA axis activation, as evidenced by nocturnal cortisol levels, in RLS patients [70].
4. Renin-angiotensin-aldosterone system (RAAS) activation. Activation of the RAAS has been implicated in the increased blood pressure response to intermittent hypoxia in a rat model, although its importance in the hypertension resulting from OSA remains uncertain, with inconsistent findings from both observational studies and small clinical trials. Moreover, acute sleep deprivation in healthy young adults has been reported to cause a reduction in nighttime renin, angiotensin and aldosterone [71]. The relation of RLS to measures of RAAS activity has not been reported.

4. RLS-specific mechanisms with potential cardiovascular effects

Whether abnormalities in the dopaminergic pathways that characterize RLS may themselves have cardiovascular effects is uncertain; however, PLMS and iron deficiency, two known correlates of RLS, are plausible contributors to CVD.

1. Periodic limb movements of sleep. Frequent PLMS are present in the majority of individuals with RLS. Individual leg movements are associated with 10–20% increases in heart rate [72] and large elevations in blood pressure (10–15 mm diastolic and 25–30 mm systolic) [73] which begin at the time of leg movement onset and extend for 10–15 seconds afterwards. One study of elderly men found that a PLM index >30 significantly increased the risk for CVD at 4 years, particularly in those without prevalent hypertension (OR=1.9, 95% CI 1.1– 3.2) [74]. Whether PLMS convey risk for CVD through neural or vascular mechanisms, or some combination, is unknown. Although reduction in PLMS with the dopamine agonist rotigotine in patients with RLS reduced the number of sleep-related blood pressure “spikes” [75], it is not yet known whether this will have an influence on CVD risk in RLS.
2. Iron deficiency. Iron deficiency, a well-recognized cause of RLS, has been recently found to have increased prevalence in patients with coronary heart disease, and is associated with increased mortality in patients with coronary heart disease and type 2 diabetes mellitus [76]. In patients with heart failure and iron deficiency, intravenous iron therapy has been demonstrated to improve functional status and quality of life, and to reduce heart failure hospitalizations [77]. It is therefore possible that iron deficiency may play a role in the association of RLS with CVD.

5. Future research priorities

1. Epidemiology of RLS and CVD. While the data reviewed in this paper are suggestive of a relationship of RLS and CVD, the magnitude or the association, direction of causation (if any), and potential modification by factors including the etiology of RLS and presence of PLMS, have not been adequately studied. Incorporating RLS questions and measures of PLMS into ongoing cardiovascular epidemiology studies could provide an efficient approach to understanding the cardiovascular epidemiology of RLS, much as the incorporation of sleep questionnaires and sleep apnea testing into cardiovascular epidemiology studies have advanced the understanding of the cardiovascular epidemiology of OSA. These ongoing studies typically obtain measures of multiple CVD risk factors, and these can be used to elucidate potential mechanisms underlying any observed association of RLS with CVD. At the present time, standardized questionnaires for the assessment of RLS have been developed and should be used in epidemiologic studies. Identification of a simple, valid and reliable test for diagnosis of RLS would further facilitate epidemiologic research in this area.

2. Cross-sectional studies of CVD risk markers in RLS. Case-control studies in patients with RLS should be designed to explore the association of clinically diagnosed cases of RLS with markers of cardiovascular risk. Such studies are more conducive to detailed physiologic testing than are epidemiologic studies and should focus in particular on markers that may shed light on mechanisms relating RLS to CVD, with neural, metabolic, and vascular measures discussed above being of particular interest.
3. Small randomized clinical trials. At the present time there is insufficient justification for large clinical trials evaluating the impact of RLS treatment on cardiovascular morbidity and mortality. Small clinical trials that explore the effect of RLS treatment on intermediate physiological measures, such as sympathetic activity, baroreflex control, and other neural mechanisms; measures of vascular stiffness and reactivity; and measures of insulin sensitivity and glucose tolerance would all be appropriate and feasible. Such studies, if they demonstrated improvement in these physiologic intermediates with treatment of RLS, would provide a rationale for future large cardiovascular outcome studies.

References

1. Innes KE, Selfe TK, Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: a systematic review. *Sleep medicine reviews*. 2011; 16:309–39. [PubMed: 21733722]
2. Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Movement disorders : official journal of the Movement Disorder Society*. 2001; 16:1159–63. [PubMed: 11748753]
3. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep medicine*. 2006; 7:545–52. [PubMed: 16740407]
4. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology*. 2008; 70:35–42. [PubMed: 18166705]
5. Juuti AK, Laara E, Rajala U, Laakso M, Harkonen P, Keinanen-Kiukaanniemi S, et al. Prevalence and associated factors of restless legs in a 57-year-old urban population in northern Finland. *Acta neurologica Scandinavica*. 2009; 122:63–9. [PubMed: 19951275]
6. Winter AC, Berger K, Glynn RJ, Buring JE, Gaziano JM, Schurks M, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in men. *Am J Med*. 2013; 126:228–35. 35 e1–2. [PubMed: 23410563]
7. Winter AC, Schurks M, Glynn RJ, Buring JE, Gaziano JM, Berger K, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in women. *Am J Med*. 2013; 126:220–7. 7 e1–2. [PubMed: 23410562]
8. Szentkiralyi A, Volzke H, Hoffmann W, Happe S, Berger K. A time sequence analysis of the relationship between cardiovascular risk factors, vascular diseases and restless legs syndrome in the general population. *Journal of sleep research*. 2013; 22:434–42. [PubMed: 23374090]
9. Winter AC, Schurks M, Glynn RJ, Buring JE, Gaziano JM, Berger K, et al. Restless legs syndrome and risk of incident cardiovascular disease in women and men: prospective cohort study. *BMJ Open*. 2012; 2:e000866.
10. Li Y, Walters AS, Chiuev SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation*. 2012; 126:1689–94. [PubMed: 22967852]

11. Van Den Eeden SK, Albers KB, Davidson JE, Kushida CA, Leimpeter AD, Nelson LM, et al. Risk of Cardiovascular Disease Associated with a Restless Legs Syndrome Diagnosis in a Retrospective Cohort Study from Kaiser Permanente Northern California. *Sleep*. 2015; 38:1009–15. [PubMed: 26083613]
12. Molnar MZ, Lu JL, Kalantar-Zadeh K, Kovesdy CP. Association of incident restless legs syndrome with outcomes in a large cohort of US veterans. *J Sleep Res*. 2015 Sep 17. [Epub ahead of print]. doi: 10.1111/jsr.12335
13. Lin CH, Chen ML, Wu VC, Li WY, Sy HN, Wu SL, et al. Association of candidate genetic variants with restless legs syndrome in end stage renal disease: a multicenter case- control study in Taiwan. *European journal of neurology : the official journal of the European Federation of Neurological Societies*. 2014; 21:492–8.
14. Durán-Cantolla J, Aizpuru F, Montserrat JM, Ballester E, Terán-Santos J, Aguirregomoscorta JJ, Gonzalez M, Lloberes P, Masa JF, De La Peña M, Carrizo S, Mayos M, Barbé F; Spanish Sleep and Breathing Group. Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial. *BMJ*. 2010 Nov 24;341:c5991. [PubMed: 21106625]
15. Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristán L, Barbé F, Durán-Cantolla J, Aizpuru F, Mañas E, Barreiro B, Mosteiro M, Cebrián JJ, de la Peña M, García-Río F, Maimó A, Zapater J, Hernández C, Grau SanMarti N, Montserrat JM. Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA*. 2013 Dec 11; 310(22):2407– 15. [PubMed: 24327037]
16. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, Tracy RP, Rueschman M, Blumenthal RS, Lewis EF, Bhatt DL, Redline S. CPAP versus oxygen in obstructive sleep apnea. *N Engl J Med*. 2014 Jun 12; 370(24):2276–85. [PubMed: 24918372]
17. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *JAMA*. 2015 Dec 1; 314(21):2280–93. [PubMed: 26624827]
18. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995; 96:1897–1904. [PubMed: 7560081]
19. Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation*. 1998; 98:772–776. [PubMed: 9727547]
20. Bertisch SM, Muesan C, Schoerning L, Winkelman JW, Taylor A. Impact of restless legs syndrome on cardiovascular autonomic control. *Sleep*. 2015
21. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation*. 1998; 98:1071–1077. [PubMed: 9736593]
22. Izzi F, Placidi F, Romigi A, Lauretti B, Marfia GA, Mercuri NB, Marciani MG, Rocchi C. Is autonomic nervous system involved in restless legs syndrome during wakefulness? *Sleep Med*. 2014 Nov; 15(11):1392–7. [PubMed: 25266501]
23. Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation*. 1999; 99:1183–1189. [PubMed: 10069786]
24. Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. *Circulation*. 1998; 97:943–945. [PubMed: 9529260]
25. Ayas NT, Hirsch AA, Laher I, Bradley TD, Malhotra A, Polotsky VY, Tasali E. New frontiers in obstructive sleep apnoea. *Clin Sci (Lond)*. 2014 Aug; 127(4):209–16. [PubMed: 24780001]
26. Pamidi S, Wroblewski K, Stepien M, Sharif-Sidi K, Kilkus J, Whitmore H, Tasali E. Eight Hours of Nightly Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea Improves Glucose Metabolism in Patients with Prediabetes. A Randomized Controlled Trial. *Am J Respir Crit Care Med*. 2015 Jul 1; 192(1):96–105. [PubMed: 25897569]

27. Martínez-Ceron E, Fernández-Navarro I, Garcia-Rio F. Effects of continuous positive airway pressure treatment on glucose metabolism in patients with obstructive sleep apnea. *Sleep Med Rev.* 2016 Feb.25:121–30. [PubMed: 26146025]
28. Drager LF, Li J, Reinke C, Bevans-Fonti S, Jun JC, Polotsky VY. Intermittent hypoxia exacerbates metabolic effects of diet-induced obesity. *Obesity.* 2011; 19:2167–2174. [PubMed: 21799478]
29. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. *Cell Metab.* 2011; 14:575–85. [PubMed: 22055501]
30. Reutrakul S, Van CE. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. *Ann N Y Acad Sci.* 2014; 1311:151–73. [PubMed: 24628249]
31. Spiegel K, Leproult R, Van CE. Impact of sleep debt on metabolic and endocrine function. *Lancet.* 1999; 354:1435–39. [PubMed: 10543671]
32. Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metab.* 2009; 94:3242–50. [PubMed: 19567526]
33. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes.* 2010; 59:2126–33. [PubMed: 20585000]
34. van Leeuwen WM, Hublin C, Sallinen M, Harma M, Hirvonen A, Porkka-Heiskanen T. Prolonged sleep restriction affects glucose metabolism in healthy young men. *Int J Endocrinol.* 2010; 2010:108641. [PubMed: 20414467]
35. Broussard JL, Wroblewski K, Kilkus JM, Tasali E. Two Nights of Recovery Sleep Reverses the Effects of Short-term Sleep Restriction on Diabetes Risk. *Diabetes Care.* 2016
36. Irwin M, Thompson J, Miller C, Gillin JC, Ziegler M. Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. *J Clin Endocrinol Metab.* 1999; 84:1979–85. [PubMed: 10372697]
37. Reynolds AC, Dorrian J, Liu PY, et al. Impact of five nights of sleep restriction on glucose metabolism, leptin and testosterone in young adult men. *PLoS One.* 2012; 7:e41218. [PubMed: 22844441]
38. Leproult R, Copinschi G, Buxton O, Van CE. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep.* 1997; 20:865–70. [PubMed: 9415946]
39. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med.* 2006; 166:1756–62. [PubMed: 16983055]
40. van Leeuwen WM, Lehto M, Karisola P, et al. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. *PLoS One.* 2009; 4:e4589. [PubMed: 19240794]
41. Spiegel K, Tasali E, Penev P, Van CE. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* 2004; 141:846–50. [PubMed: 15583226]
42. Anothaisintawee T, Reutrakul S, Van CE, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta- analysis. *Sleep Med Rev.* 2015; 30:11–24. [PubMed: 26687279]
43. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest.* 2010; 137:95–101. [PubMed: 19542260]
44. Tasali E, Leproult R, Ehrmann DA, Van CE. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci U S A.* 2008; 105:1044–49. [PubMed: 18172212]
45. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care.* 2010; 33:414–20. [PubMed: 19910503]
46. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited-- the bad ugly and good: implications to the heart and brain. *Sleep Med Rev.* 2015 Apr.20:27–45. [PubMed: 25155182]
47. Taverne YJ, Bogers AJ, Duncker DJ, Merkus D. Reactive oxygen species and the cardiovascular system. *Oxid Med Cell Longev.* 2013; 2013:862423. [PubMed: 23738043]

48. Du XL, Edelstein D, Rossetti L, et al. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc Natl Acad Sci U S A*. 2000; 97:12222–26. [PubMed: 11050244]
49. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005; 54:1615–25. [PubMed: 15919781]
50. Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. *Cell Metab*. 2013; 17:20–33. [PubMed: 23312281]
51. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, Naseem J, Loomba R. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. *J Clin Sleep Med*. 2013 Oct 15; 9(10):1003–12. [PubMed: 24127144]
52. Chami HA, Fontes JD, Vasan RS, Keaney JF Jr, O'Connor GT, Larson MG, Benjamin EJ, Gottlieb DJ. Vascular inflammation and sleep disordered breathing in a community- based cohort. *Sleep*. 2013 May 1; 36(5):763–768. [PubMed: 23633759]
53. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. *Rev Endocr Metab Disord*. 2015 Mar; 16(1):25–34. [PubMed: 25502450]
54. Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, Colombo PC, Basner RC, Factor P, LeJemtel TH. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation*. 2008 Apr 29; 117(17):2270– 8. [PubMed: 18413499]
55. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation*. 2005 Oct 25; 112(17):2660–7. [PubMed: 16246965]
56. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry*. 2015 Jun 1. pii: S0006-3223(15)00437-0. [Epub ahead of print]. doi: 10.1016/j.biopsych.2015.05.014
57. Benediktsdottir B, Janson C, Lindberg E, Arnardóttir ES, Olafsson I, Cook E, Thorarinsdottir EH, Gislason T. Prevalence of restless legs syndrome among adults in Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep Med*. 2010 Dec; 11(10):1043–8. Epub 2010 Oct 18. DOI: 10.1016/j.sleep.2010.08.006 [PubMed: 20961808]
58. Trotti LM, Rye DB, De Staercke C, Hooper WC, Quyyumi A, Bliwise DL. Elevated C- reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. *Brain Behav Immun*. 2012 Nov; 26(8):1239–43. [PubMed: 22750520]
59. Hoyos CM, Melehan KL, Liu PY, Grunstein RR, Phillips CL. Does obstructive sleep apnea cause endothelial dysfunction? A critical review of the literature. *Sleep Med Rev*. 2015 Apr; 20:15–26. [PubMed: 25088969]
60. Atkeson A, Jelic S. Mechanisms of endothelial dysfunction in obstructive sleep apnea. *Vasc Health Risk Manag*. 2008; 4:1327–35. [PubMed: 19337546]
61. Calvin AD, Covassin N, Kremers WK, et al. Experimental sleep restriction causes endothelial dysfunction in healthy humans. *J Am Heart Assoc*. 2014; 3:e001143. [PubMed: 25424573]
62. Sauvet F, Florence G, Van Beers P, et al. Total sleep deprivation alters endothelial function in rats: a nonsympathetic mechanism. *Sleep*. 2014; 37:465–73. [PubMed: 24587568]
63. Carreras A, Zhang SX, Peris E, et al. Chronic sleep fragmentation induces endothelial dysfunction and structural vascular changes in mice. *Sleep*. 2014; 37:1817–24. [PubMed: 25364077]
64. Baskol G, Korkmaz S, Erdem F, Caniklioglu A, Kocyigit M, Aksu M. Assessment of nitric oxide, advanced oxidation protein products, malondialdehyde, and thiol levels in patients with restless legs syndrome. *Sleep Med*. 2012 Apr; 13(4):414–8. [PubMed: 22469072]
65. Koh SY, Kim MS, Lee SM, Hong JM, Yoon JH. Impaired vascular endothelial function in patients with restless legs syndrome: a new aspect of the vascular pathophysiology. *J Neurol Sci*. 2015 Dec 15; 359(1–2):207–10. [PubMed: 26671114]
66. Wang J, Yu W, Gao M, Zhang F, Gu C, Yu Y, Wei Y. Impact of Obstructive Sleep Apnea Syndrome on Endothelial Function, Arterial Stiffening, and Serum Inflammatory Markers: An Updated Meta-analysis and Metaregression of 18 Studies. *J Am Heart Assoc*. 2015 Nov 13; 4(11):e002454.

67. Chami, HA., Vasan, RS., Larson, MG., Benjamin, EJ., Mitchell, GF., Gottlieb, DJ. The association between sleep-disordered breathing and aortic stiffness in a community cohort. *Sleep Med.* 2015. [epub ahead of print] [dx.doi.org/10.1016/j.sleep.2015.11.009](https://doi.org/10.1016/j.sleep.2015.11.009)
68. Sunbul M, Kanar BG, Durmus E, Kivrak T, Sari I. Acute sleep deprivation is associated with increased arterial stiffness in healthy young adults. *Sleep Breath.* 2014; 18:215–20. [PubMed: 23852444]
69. Drakatos P, Higgins S, Pengo MF, Kent BD, Muza R, Karkoulas K, Leschziner G, Williams A. Derived Arterial Stiffness is Increased in Patients With Obstructive Sleep Apnea and Periodic Limb Movements During Sleep. *J Clin Sleep Med.* 2016; 12:195–202. [PubMed: 26414977]
70. Schilling C, Schredl M, Strobl P, Deuschle M. Restless legs syndrome: evidence for nocturnal hypothalamic-pituitary-adrenal system activation. *Mov Disord.* 2010; 25:1047– 52. [PubMed: 20535825]
71. Kamperis K, Hagstroem S, Radvanska E, Rittig S, Djurhuus JC. Excess diuresis and natriuresis during acute sleep deprivation in healthy adults. *Am J Physiol Renal Physiol.* 2010; 299:F404–11. [PubMed: 20519376]
72. Winkelman JW. The evoked heart rate response to periodic leg movements of sleep. *Sleep.* 1999 Aug 1; 22(5):575–80. [PubMed: 10450592]
73. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. *Neurology.* 2007 Apr 10; 68(15):1213–8. [PubMed: 17420405]
74. Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S. Osteoporotic Fractures in Men (MrOS) Study Group. Association of incident cardiovascular disease with periodic limb movements during sleep in older men: outcomes of sleep disorders in older men (MrOS) study. *Circulation.* 2011 Sep 13; 124(11):1223–31. [PubMed: 21859975]
75. Bauer A, Cassel W, Benes H, Kesper K, Rye D, Sica D, et al. Effects of rotigotine on the blood pressure elevations associated with periodic limb movements in restless legs syndrome. *Neurology.* in press.
76. von Haehling S, Jankowska EA, van Veldhuisen DJ, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. *Nat Rev Cardiol.* 2015 Nov; 12(11):659–69. [PubMed: 26194551]
77. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD. CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015 Mar 14; 36(11):657–68. [PubMed: 25176939]

Highlights

- Epidemiologic studies both support and refute an association between RLS and CVD
- Lessons learned from the OSA-CVD relationship may be helpful for RLS research
- Increased SNS activity is an established mechanism linking OSA to CVD
- Metabolic and vascular mechanisms may also contribute to CVD risk in OSA

Figure 1. Proposed mechanisms linking obstructive sleep apnea to cardiovascular disease
 While intermittent hypoxemia is unlikely to be relevant to RLS, there is evidence that sleep fragmentation and sleep deprivation may contribute to neural, metabolic, vascular, and inflammatory mechanisms. These pathways may therefore inform research in to the possible cardiovascular consequences of RLS.

Figure 2. Plausible mechanisms linking restless legs syndrome to cardiovascular disease
Those mechanisms for which there is some experimental evidence of an association with RLS or periodic limb movements are shown in solid boxes.

Table 1

Longitudinal studies of RLS and CVD

Cohort	N (RLS%)	Mean age, duration of follow-up	RLS information (duration, frequency, 1 ^o /2 ^o)	CVD outcomes
Study of Health in Pomerania [9]	4 308 (10.1%)	50.3 5 years	None; no change w/out DM cases	- MI -CVA
Women's Health Study [7]	29 756 (11.7%)	63.4 6 years	None; no change w/out ESRD/PVD	- first CVD event -MI -CVA
Physician's Health Study [6]	19 182 (7.2%)	66.6 7.3 years	None; no w/out ESRD/PVD	- first CVD event -MI -CVA
Nurse's Health Study [10]	70 977 (2.1%)	67 5.6 years	Duration > 3 years; no change w/out DM/ESRD	+(fatal) CHD +first MI event
Kaiser Permanente [11]	~12 000 with RLS	1 ^o =58; 2 ^o =65 3.9 years	Physician diagnosis; 2 ^o =many comorbidities	1 ^o :-CVD/MI/CVA 2 ^o :+CVD/MI/CVD
Veterans Administration [12]	7 392 (0.1%)	59.8 8.1 years	"Incident RLS"	+CHD/CVA

Abbreviations: "-", no relationship; "+", positive relationship with RLS; DM, diabetes mellitus; ESRD, end-stage renal disease; CHD, chronic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; CVA, cerebrovascular accident; 1^o, primary RLS; 2^o, secondary RLS.