REVIEW

Incident Cardiovascular Events and Death in Individuals With Restless Legs Syndrome or Periodic Limb Movements in Sleep: A Systematic Review

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Study Objectives: To systematically review the current evidence examining restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS) as prognostic factors for all-cause mortality and incident cardiovascular events (CVE) in longitudinal studies published in the adult population.

Methods: All English language studies (from 1947 to 2016) found through Medline and Embase, as well as bibliographies of identified articles, were considered eligible. Quality was evaluated using published guidelines.

Results: Among 18 cohorts (reported in 13 manuscripts), 15 evaluated the association between RLS and incident CVE and/or all-cause mortality and 3 between PLMS and CVE and mortality. The follow-up periods ranged from 2 to 20 years. A significant relationship between RLS and CVE was reported in four cohorts with a greater risk suggested for severe RLS with longer duration and secondary forms of RLS. Although a significant association between RLS and all-cause mortality was reported in three cohorts, a meta-analysis we conducted of the four studies of highest quality found no association (pooled hazard ratio = 1.09, 95% confidence interval: 0.80–1.78). A positive association between PLMS and CVE and/or mortality was demonstrated in all included studies with a greater risk attributed to PLMS with arousals.

Conclusions: The available evidence on RLS as a prognostic factor for incident CVE and all-cause mortality was limited and inconclusive; RLS duration, severity, and secondary manifestations may be important in understanding a possible relationship. Although very limited, the current evidence suggests that PLMS may be a prognostic factor for incident CVE and mortality.

Keywords: systematic review, cardiovascular diseases, mortality, RLS, PLMS.

Statement of Significance

Although several mechanisms may modulate a higher risk of cardiovascular events (CVE) in individuals with restless legs syndrome (RLS) and/or periodic limb movements in sleep (PLMS), the evidence remains mixed in the longitudinal studies published to date. Despite some studies suggesting a possible association, the available evidence on RLS as a prognostic factor for incident CVE and mortality was limited and inconclusive. Duration, severity, and secondary versus primary RLS may be important features in understanding this relationship. Although limited, the current evidence on PLMS as a prognostic factor suggests a significant association. Future large population-based studies with a sufficient number of outcome events, a broad range of population demographic characteristics, and standardized definitions used to define PLMS/RLS are needed.

INTRODUCTION

Restless legs syndrome (RLS) is a common but under-recognized chronic sensorimotor disorder characterized by a strong, nearly irresistible urge to move the limbs which is usually worse at rest, occurs in the evening or night time, and is relieved with movement.[1–3] RLS symptoms may range from being minimally annoying to severely disruptive of life. The prevalence of RLS in the general population has been reported to be between 5% and 10%[4–7] and is estimated to be 2.7% for those with moderately or severely distressing symptoms.[4]

Periodic limb movements in sleep (PLMS) are characterized by periodic episodes of repetitive limb movements during sleep, which most often occur in the lower extremities and may be associated with arousals from sleep. PLMS are seen in about 80–90% of patients with RLS, but are also commonly observed with increasing age and in other disorders, and are not specific for RLS.[8] The overall prevalence of PLMS in the general population (defined as a periodic limb movement index > 15/hour) has been reported to be between 4.3% and 9.3%.[9]

Despite sharing some common underlying pathophysiological mechanisms with sleep-disordered breathing, which has been shown to be closely associated with cardiovascular (CV) consequences,[10] the prognostic implications of RLS and PLMS have been relatively underexplored in the context of CV and cerebrovascular disease. Multiple mechanisms may modulate an association between RLS/PLMS and CV and cerebrovascular disease including inflammation,[11] oxidative stress,[12,13] sympathetic activation,[14] metabolic dysregulation,[15] hypothalamic-pituitary-adrenal system activation,[16] sleep disturbance, and sleep deprivation.[17]

Cross-sectional studies suggest a link between RLS and diabetes, hypertension, obesity, and CV risk and between PLMS and hypertension, CV, and cerebrovascular risk.[15,18,19] Table 1 lists the cross-sectional studies conducted in the general population that have examined the relationship between RLS and CV disease. Although several nonmutually exclusive mechanisms may modulate a higher CV risk in patients with RLS/PLMS, the evidence remains mixed in the longitudinal studies published to date.

Accordingly, the objective of our study was to systematically review the current evidence examining RLS and PLMS as prognostic factors for all-cause mortality and incident cardiovascular events (CVE) in longitudinal studies published in the adult population.

METHODS

Protocol and Registration

We conducted and reported this review in accordance with the Preferred Reporting Items for Systematic Reviews and

Table 1—The Cross-sectional Studies Conducted in the General Population That Have Examined the Relationship Between RLS and Cardiovascular Disease[a]: Summary of Study Characteristics and Findings.

#	Authors, year, country, cohort	Exposure	Outcome	Findings
1.	Ulfberg et al., 2001,[7] Sweden Register of all Dalarna County residents	RLS: IRLSSG criteria	"Heart problems"	Positive[b]
2.	Ohayon et al., 2002,[20] United Kingdom, Germany, Spain, Portugal, Italy Noninstitutionalized residents from five countries	ICSD criteria (1990) for RLS and PLMS	Heart disease	Positive
3.	Berger et al, 2004.,[5] Germany Study of Health in Pomerania	RLS: IRLSSG criteria	MI	Positive
4.	Foley et al, 2004.,[21] United States Community-dwelling adults	RLS: Self-reported unpleasant feelings in legs or ever told by doctor	Heart disease	Positive
5.	Lee et al, 2006.,[22] United States Baltimore Health and Mental Health Study	RLS: IRLSSG criteria	Heart disease	Negative
6.	Phillips et al, 2006.,[23] United States Community-dwelling adults	RLS: IRLSSG criteria	Heart disease	Positive
7.	Winkelman et al, 2006.,[24] United States Wisconsin Sleep Cohort	RLS: "repeated urge to move your legs" and "strange and uncomfortable feelings in the legs," "when sitting or lying down" which occur at least weekly, "get better when you get up and start walking" and "disrupt your sleep".	Heart attack, CAD, coronary bypass, angioplasty, or pacemaker	Positive
8.	Alattar et al, 2007.,[25] United States North Carolina Family Practice Research Network study	RLS: "tingling, creeping, or restless feelings in the legs while trying to sleep"	Heart disease, stroke	Positive
9.	Mallon et al, 2008.,[26] Sweden Population registry of Dalarna and Gavleborg Counties	RLS: "creeping sensations in your legs when trying to fall asleep?"	Heart disease	Positive
10.	Wesstrom et al, 2008.,[27] Sweden General population of Dalarna County	RLS: IRLSSG criteria	"Heart problems"	Positive
11.	Winkelman et al, 2008.,[28] United States Sleep Heart Health Study	RLS: IRLSSG criteria	Stroke, heart failure, or CAD	Positive
12.	Benediktsdottir et al, 2010,[29] Iceland and Sweden, National Registries of Iceland and Sweden	RLS: IRLSSG criteria	CVD	Negative
13.	Chen et al, 2010.,[30] Taiwan Taiwanese residents	RLS: IRLSSG criteria	Cardiovascular disease	Positive
14.	Juuti et al, 2010.,[31] Finland National Population Registry of Finland	RLS: IRLSSG criteria	CHD	Positive
15.	Möller et al, 2010.,[32] Germany Primary care practices in Germany	RLS: IRLSSG criteria	Heart disease	Positive
16.	Cosentino et al, 2012.,[33] Italy Clinical cohort	RLS: IRLSSG criteria	Heart diseases	Negative
17.	Winter et al, 2013.,[34] United States Women's Health Study	RLS: IRLSSG criteria	Coronary revascularization, myocardial infarction, stroke	Negative
18.	Winter et al, 2013.,[35] United States US Physicians' Health Studies	RLS: IRLSSG criteria	Major cardiovascular disease, stroke, and MI	Positive

Table 1—*Continued*

#	Authors, year, country, cohort	Exposure	Outcome	Findings
19.	Shi et al, 2015.,[36] China Community of Shanyang town, Jinshan district, Shanghai, China	RLS: IRLSSG criteria	Cardiovascular disease	Negative
20.	Safak et al, 2016.,[37] Turkey Community-dwelling elderly living in an urban area	RLS: IRLSSG criteria	Coronary heart disease and cerebrovascular disease	Negative

CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular disease; ICSD = International Classification of Sleep Disorders; IRLS = International RLS Study Group Rating Scale; IRLSSG = International Restless Legs Syndrome Study Group; MI = myocardial infraction; ; PLMS = periodic limb movements in sleep; RLS = restless legs syndrome.

[a]Fourteen cross-sectional studies from the systematic review conducted by Innes et al.[15] were included in this table.

[b]Positive: any significant relationship; negative: no significant relationship.

Meta-Analyses (PRISMA) guidelines.[38] The PRISMA guidelines provide an evidence-based minimum set of items when reporting systematic reviews and meta-analyses and are highly recommended to be used when conducting such studies. Before starting this study, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on December 14, 2015 (registration number CRD42015032241). The protocol is available from: http://www.crd.york.ac.uk/PROSPERO.

Information Sources and Data Searches

All peer-reviewed studies published in the English language from 1947 to July 2016 that used a longitudinal study design and collected data in either a prospective or retrospective manner were eligible. Articles were identified using Medline and EMBASE, and the bibliographies of identified articles and reviews were also reviewed. We developed a comprehensive search strategy to identify prognostic studies of RLS/PLMS that examined the outcomes of CVE and mortality.[39] The medical subject headings (MeSH) used for our literature search to identify the exposures of interest were "Restless Legs Syndrome" and "Nocturnal Myoclonus Syndrome."[40] The keywords were: "restless legs syndrome," "Ekbom syndrome," "Willis-Ekbom disease," "periodic limb movement disorder," "PLMD," "sleep-related movement disorder(s)," "leg motor activity," "myoclonic hyperkinesias," "nocturnal myoclonus syndrome," "RLS," "periodic leg movement(s)," "periodic limb movement(s)," "sleep leg movement(s)," and "PLM,"[40] The full search strategy for MEDLINE is available in a data supplement (Supplementary Table S1). The search terms were adapted for use with other bibliographic databases. The initial searches were rerun just before the final analyses to retrieve further studies for inclusion.

Inclusion and Exclusion Criteria

We included studies that met the following criteria: (1) Evaluated adults (ie, patients ≥18 years of age); (2) PLMS were detected using polysomnography (PSG), and/or RLS was diagnosed using any recognized diagnostic criteria at baseline; (3) included only primary or both primary and secondary forms of RLS; (4) reported the proportion of participants without RLS/PLMS; and (5) followed patients for at least 1 year. We excluded studies that (1) evaluated adolescents or children (ie, patients < 18 years of age), (2) only reported on secondary forms of RLS, and those that (3) examined PLMS that were associated with a particular disease (eg, heart failure or renal disease). Although there is no sufficient evidence to support well-defined subtypes of RLS, we referred to "primary" forms of RLS when the cause was not definitively known and to "secondary" RLS when the condition occurred in association with a particular disease known to be strongly associated with RLS (eg, iron deficiency, pregnancy, or chronic renal failure).[3,41] We excluded studies that examined only secondary forms of RLS because such presentations may be a manifestation of an underlying condition and reflect its severity and may also have a different pathogenesis compared to primary RLS and require different management strategies. For the same reasons, we excluded PLMS that were associated with a particular disease.

Our predictors were the presence and severity (if available) of RLS or PLMS. The adverse outcomes evaluated (either objectively documented or self-reported) were (1) CVE (nonfatal and fatal) and (2) all-cause mortality. CVE included coronary artery disease (eg, angina, myocardial infarction, and coronary revascularization procedures), stroke, congestive heart failure, and arrhythmias.

Data Extraction: Selection and Coding

Two reviewers (TK, MK) independently screened study titles and/or abstracts and read the full texts of manuscripts that appeared to fulfill the inclusion criteria. Discrepancies in opinion were resolved through discussion with a third reviewer (MIB).

A previously developed standardized form[10] was used to assess study quality and synthesize study results from the included articles. Extracted information included the following: (1) study design (eg, prospective or retrospective); (2) study setting (eg, clinical vs. community-based study); (3) demographics of the study population and baseline characteristics; (4) details of the definition(s) of RLS/PLMS; (5) recruitment and study completion/attrition rates; (6) definition of outcomes and timing of measurements; (7) the analytic approach used; (8) variables included in the statistical model (if applicable); and (9) information for the assessment of the risk of bias. The primary author (TK) extracted the data independently, and the second author (MK) reviewed the quality of data extraction.

Discrepancies were resolved through discussions with the other authors (MIB and BJM).

Risk of Bias (Quality) Assessment

Study quality was evaluated independently by two reviewers (TK and MK) using the Quality in Prognosis Studies (QUIPS) tool to assess risk of bias in studies of prognostic factors.[42,43] The appraisal consisted of two steps: the first step involved assessment of six potential sources of bias (i.e., study participation, study attrition, prognostic factor and outcome measurements, study confounding, and statistical analysis and reporting); the second step involved grading the presence of potential biases as "Yes," "Partly," "No," or "Unsure". A similar approach to the Scottish Intercollegiate Guidelines Network (SIGN) methodology (available from: http://www.sign.ac.uk/methodology/checklists.html) was applied to summarize the overall level of potential bias for each study: (1) "++" when all or most of the quality criteria proposed by Hayden et al. were fulfilled (allowing one "Partly" while appraising all potential sources of bias); (2) "+" when some of the criteria were fulfilled; (3) "–" when few or no criteria were fulfilled (ie, at least one "Yes" for a potential form of bias). In addition, as proposed by SIGN, studies with a retrospective study design did not receive a "++" rating, as this study design is weaker than a prospective approach. In this manuscript, we refer to studies receiving an overall assessment of "++" as "high quality studies" and studies receiving an overall assessment of "+"as "moderate quality studies", as was used in a previously published prognostic review.[10] Details are presented in a data supplement (Supplementary Table S2).

Data Synthesis

The included studies were synthesized through tabulation and qualitative description. We anticipated that there would be limited scope for meta-analysis due to the high heterogeneity between studies. However, where studies used the same definition for RLS/PLMS, with the same outcome measure, we planned to pool adjusted hazard ratios (aHRs) with their 95% confidence intervals (CIs) extracted from each article using a random-effects (DerSimonian–Laird estimator for the amount of heterogeneity) meta-analysis in R, version 3.1.0 (www.r-project.org) using the "metafor" package. Heterogeneity was assessed using the Cochran's Q-test of (residual) heterogeneity; a p-value of less than .10 was considered to represent evidence of heterogeneity.[44] To quantify inconsistency, we used an I^2 statistic estimate (percent), which assesses how much of the total variability in the effect size estimates can be attributed to heterogeneity between studies.[45] We considered an I^2 value greater than 50% to be indicative of substantial heterogeneity.[46]

If the necessary data were available, we planned to present the results separately for individuals with RLS and PLMS, as well as stratify separately for our outcomes of CVE and all-cause mortality.

RESULTS

Study Selection and Quality Assessment

Of the 52 manuscripts we identified, 13 articles were included[26,47–58] (Figure 1): ten assessed the association between RLS and CV events and/or mortality, and three assessed the association between PLMS and our outcomes of interest. Reasons for the exclusion of the 39 studies are presented in a data supplement (Supplementary Table S3). In total, 18 cohort studies were appraised for quality, since three manuscripts used data from more than one cohort study. Specifically, four prospective cohorts, the Dortmund Health Study (DHS), Study of Health in Pomerania (SHIP), Women's Health Study (WHS), and Physicians' Health Study (PHS) were used in multiple studies to address different outcomes: Szentkirályi et al.[50], used data from all four cohort studies (outcome was mortality), Winter et al.[51], from two cohort studies (WHS, PHS; CVE outcome), and Szentkirályi et al.[53] from two cohort studies (DHS, SHIP; CVE outcome).[36] Of the 18 cohort studies (Table 2), 17 were assessed as having "Partly" or "No" on all bias criteria. Eight of these cohorts, published in five manuscripts, were identified as being of high quality.[26,50–52,56]

Study Characteristics

Summaries of the included studies are presented in Table 3. Of the 18 cohorts evaluated, eight (six with a prospective design) investigated the association between RLS and CV events, eight (seven with a prospective design) examined the link between RLS and all-cause mortality, and three (one with a prospective design) studied the association between PLMS and CV events or all-cause mortality.

The eight cohort studies that evaluated RLS as a prognostic factor for CV disease[48,49,51,53–55] examined diverse middle-aged populations including community cohorts, health administrative data, registered nurses, physicians, and other health care professionals; the smallest sample size among these cohort studies was 1312 subjects. Two studies assessed only men[48,51] and another two studies examined only women.[49,51] Only two studies used the International Restless Legs Syndrome Study Group (IRLSSG) criteria to define RLS.[51,53] The follow-up assessments ranged from 2.1 to 10 years and from 47 to 1064 CVE occurred including ischemic heart disease and stroke (both fatal and nonfatal) as defined using ICD-9 and ICD-10 codes, medical records, mailed questionnaires, and face-to-face interviews.

Eight cohort studies examined RLS as a prognostic factor for all-cause mortality.[26,47,50,52,55] All but one study examined middle-aged populations using health administrative data, population-based cohorts, and cohorts of health professionals; of these cohort studies, the smallest number of subjects included was 1299. Two cohorts evaluated only men[50,52] and one study examined only women.[50] Five of the eight cohorts used the IRLSSG criteria to define RLS. The follow-up period ranged from 3.5 to 20 years, and across all studies from 55 to 2765 individuals died.

Three studies focused on PLMS, assessed by in-laboratory or in-home PSG, as a prognostic factor for CVE and/or all-cause mortality.[56–58] These studies were based on middle-aged or elderly populations; the smallest number of subjects included among these studies was 584. One study was based on only men; two studies defined PLMS based on full PSG. During the median follow-up that ranged from 2.8 to 5.7 years, 90 to 1172 events occurred. CVE and mortality were defined based on ICD-9 and ICD-10 codes, patient medical records and

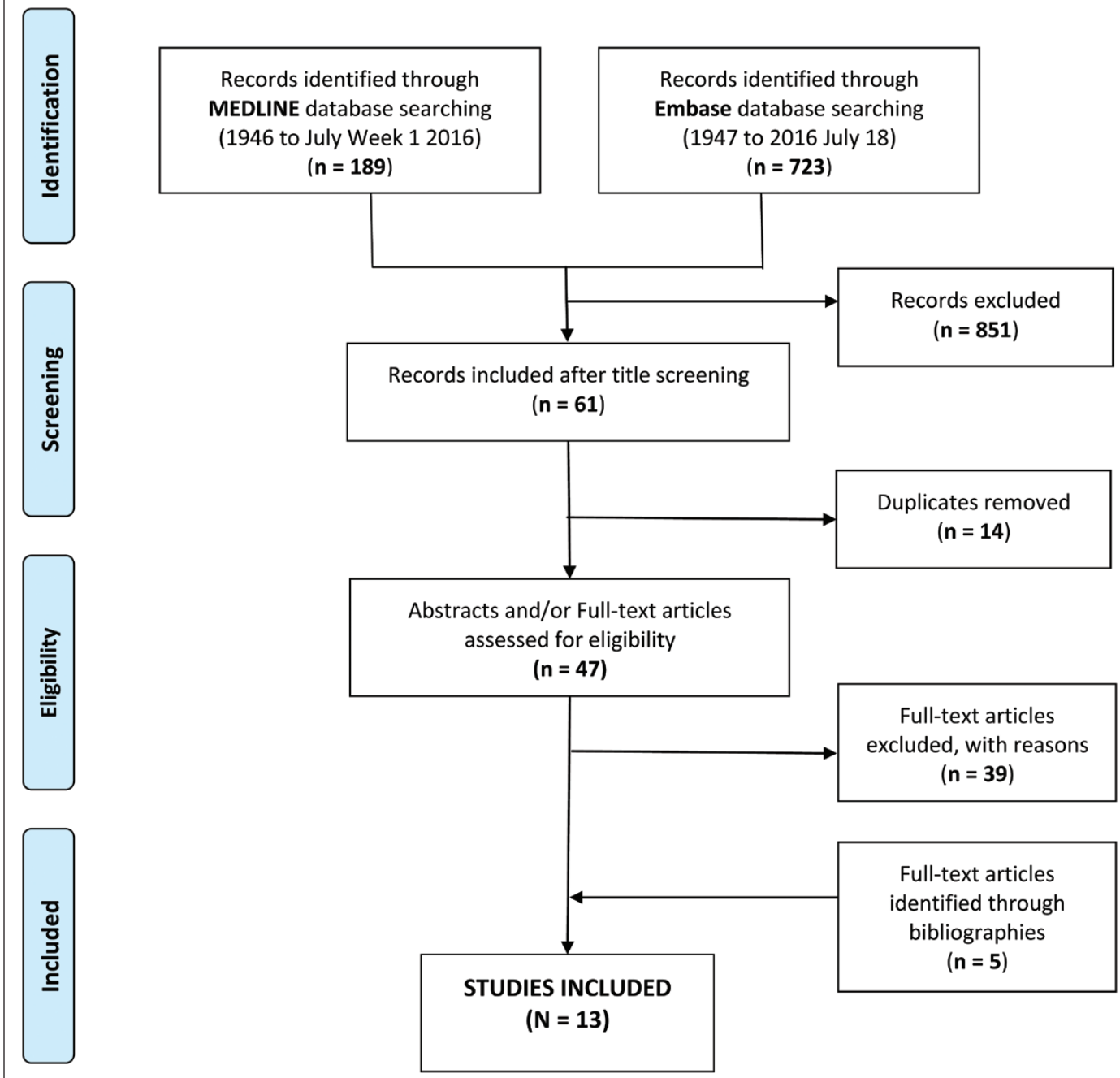

Figure 1—Flow diagram for identification of relevant studies. Reasons for exclusion of the 39 studies were: Secondary RLS only (*n* = 11), abstract only (*n* = 10), outcome did not match our inclusion criteria (*n* = 8), cross-sectional study (*n* = 7), and published as an editorial/letter only (*n* = 3). RLS = restless legs syndrome.

supporting documentation, interviews with participants and next of kin, and death certificates.

Synthesis of Results

The evidence for an association between RLS and CVE was mixed and was based on eight study cohorts, two of high quality (published in one paper)[51] and six of moderate quality.[48,49,53–55] Four study cohorts supported a positive association, while another four did not support a significant relationship. Neither of the high quality study cohorts reported on by Winter et al.[51] found a significant association between RLS as defined by IRLSSG criteria and CV disease in either men or women (Table 3). Two of three cohort studies of moderate quality found an association between RLS and stroke.[48,55] With regards to other CV outcomes, a positive association was only found for individuals who reported chronic RLS symptoms (≥3 years)[49] or secondary RLS[54] and in one study based on health administrative data.[55]

The evidence for an association between RLS and all-cause mortality was based on eight study cohorts, five of high quality[26,50,52] and three of moderate quality.[47,50,55] Only three of the eight study cohorts demonstrated a significant relationship

Table 2—Quality Assessment of Included Studies.

	Study		Study participation	Study attrition	Prognostic factor	Outcome	Confounding measurement and account	Analysis	Overall assessment of the study
RLS as a Prognostic Factor for CVD									
1.	Elwood et al., 2006, UK		No	No	Partly	No	Partly	Partly	+
2.	Li et al., 2012, USA		No	Unsure	Partly	No	Partly	No	+
3.	Winter et al., 2012, USA	WHS	No	No	No	No	Partly	No	++
4		PHS	No	No	No	No	Partly	No	++
5.	Szentkirályi et al., 2013, Germany	DHS	Partly	No	No	Partly	Partly	No	+
6.		SHIP	Partly	No	No	Partly	Partly	No	+
7.	Van Den Eeden et al., 2015, USA		No	No	Partly	No	Partly	No	+ retrospective design also
8.	Molnar et al., 2016, USA[a]		No	No	Partly	No	No	No	+ retrospective design also
RLS as a prognostic factor for all-cause mortality									
1.	Pollak et al., 1990, USA		No	No	Partly	No	Partly	No	
2.	Mallon et al., 2008, Sweden		No	No	Partly	No	No	No	++
3.	Szentkirályi et al., 2012, Germany and USA	DHS	Partly	No	No	No	Partly	No	+
4.		SHIP	No	No	No	No	Partly	No	++
5.		WHS	No	No	No	No	Partly	No	++
6.		PHS	No	No	No	No	Partly	No	++
7.	Li et al., 2013, USA		No	No	Partly	No	No	No	++
8.	Molnar et al., 2016, USA[a]		No	No	Partly	No	No	No	+ retrospective design also
PLMS as a prognostic factor for CVD or/and all-cause mortality									
1.	Koo et al., 2011, USA		No	No	No	Partly	No	No	++
2.	Mirza et al., 2013, USA		No	No	No	No	Yes	Partly	− retrospective design also
3.	Kendzerska et al., 2014, Canada		No	No	No	No	Partly	No	+ retrospective design also

CVD = cardiovascular disease; DHS = The Dortmund Health Study; PHS = Physicians' Health Study; RLS = restless legs syndrome; SHIP = Study of Health in Pomerania; WHS = Women's Health Study.
[a]Both CVD and all-cause mortality were studied as outcomes in the Molnar et al. (2016) cohort.

between RLS and all-cause mortality. We conducted a meta-analysis on the four cohorts of high quality that used the IRLSSG criteria to define RLS[50,52] and also found that the association between RLS and all-cause mortality was not significant (pooled aHR = 1.09, 95% CI: 0.80–1.78, $I^2 = 0\%$, p-value for the test for heterogeneity = .89) (Figure 2). In the one study of high quality which did not use the IRLSSG criteria, RLS was found to be a significant predictor only in women with daytime sleepiness.[26]

The evidence for an association between PLMS and CVE and mortality was based on one study of moderate[58] and one study of high quality[56]; both studies demonstrated a significant association between PLMS and our outcomes of interest. After adjusting for confounders, an increase in the frequency of PLMS in sleep, with or without related arousals, was associated with a 5–26% increased hazard for the composite CV outcome[56,58] and a 5% increased risk of all-cause mortality.[58] The effect of a periodic limb movement arousal index ≥5 was comparable with that of a PLM index ≥30.[56]

DISCUSSION

We conducted a systematic review to investigate the relationship between RLS and PLMS with incident CVE and all-cause mortality. Of the 18 cohorts evaluated (reported in 13 manuscripts), 14 (78%) study cohorts used a prospective study design and eight (44%) were of high quality. Most of the included study cohorts investigated the association between RLS and CV events and/or all-cause mortality.

Overall, the evidence supporting RLS as a prognostic factor for incident CVE was mixed with neither of the two high quality study cohorts revealing a significant link. Individuals with secondary (but not primary) forms of RLS and longer term exposure to

Table 3—Included Study Cohort Characteristics (*n* = 13).

	Authors, year, country, cohort	Study participation	Study attrition	Prognostic factor	Outcomes	Confounding measurement and account	Analysis and results
RLS as a prognostic factor for CVD							
1.	Elwood et al., 2006, United Kingdom. The Caerphilly cohort Prospective community-based cohort	1874 men Age: 55–69 years Excluded: prior IHD or stroke	F/u: 10 years (initial response rate: 89%; rate for the current study not reported)	Restless legs (SR): experiencing "restless legs or bothersome twitches" once or twice a week or more (yes/no)	ICD-10; hospital and general practitioner notes Incident IHD (fatal and nonfatal) (*n* = 213); ischemic strokes (*n* = 107)	Age, social class, smoking, alcohol consumption, BMI, and neck circumference	Logistic regression Stroke 1.67 (1.07–2.60)* IHD 1.24 (0.89–1.74)
2.	Li et al., 2012, United States. The nurses' health study Prospective cohort of female registered nurses	70,977 women Mean age: 67 years Excluded: prior CHD or stroke	F/u: 5.6 years (attrition not reported)	Restless legs (SR):- had ever received a physician-based diagnosis of RLS (yes/no) - duration of RLS symptoms (in years)	Medical records Nonfatal MI and fatal CHD (*n* = 698)	Age, BMI, ethnicity, smoking and menopausal status, hormone use, alcohol intake, physical activity, treatment (antidepressant, aspirin, antihypertensive, antiarrhythmic, iron, and vitamins supplements), comorbidities (diabetes, arthritis, HTN, cancer, ↑cholesterol, renal failure, or Parkinson's disease), sleep duration, and snoring frequency. At baseline and time-varying variables.	Cox regression CHD RLS vs. No: 1.46 (0.97–2.18) RLS < 3 years vs. No: 0.98 (0.44–2.19) RLS ≥3 years vs. No: 1.72 (1.09–2.73)* Nonfatal MI RLS vs. No: 1.47 (0.93–2.33) RLS < 3 years vs. No 0.87 (0.32–2.33) RLS ≥3 years vs. No 1.80 (1.07–3.01)* Fatal CHD RLS ≥3 years vs. No: 1.49 (0.55–4.04)
3.	Winter et al., 2012, United States. Two prospective cohort studies: The Women's Health Study (WHS) and the Physicians' Health Study (PHS)	29,756 women ≥45 years 19,182 men ≥40 years Excluded: CVD events or angina at baseline	F/u: 6.0 years <4% missing in the primary analyses.	IRLSSG criteria for RLS (SR) (yes/no)[a] - version of IRLSSG criteria used was not stated	Medical records Incident CVD (MI, stroke, death due to CVD, or coronary revascularization) (*n* = 450 in the WHS, *n* = 1064 in the PHS)	Age, BMI, alcohol intake, smoking status, exercise, comorbidities (HTN, diabetes, migraine, ↑cholesterol), family history of MI, postmenopausal hormone, and aspirin use.	Cox regression CVD women: 1.15 (0.88–1.50), men: 1.01 (0.81–1.25) Stroke women: 1.29 (0.91–1.82) CVD death men: 1.22 (0.87–1.70)
4.	Szentkirályi et al., 2013, Germany Two prospective cohort studies: The Dortmund Health Study (DHS) and the Study of Health in Pomerania (SHIP)	DHS: *n* = 1312 SHIP: *n* = 4308 Mean ages: 50–52 years 47–49% men	Median f/u: DHS: 2.1 years SHIP: 5.0 years	The 1995 IRLSSG criteria (SR) (yes/no)[a]	DHS: a mailed questionnaire SHIP: a face-to-face interview Incident MI (*n* = 37 + 11) and stroke (*n* = 35 + 12)	Age, gender, education, alcohol consumption, smoking, physical activity, hemoglobin, glomerular filtration rate, cholesterol level, and cardiovascular diseases	Logistic regression, MI, DHS: SHIP: 0.53 (0.12–2.27) Stroke DHS: 1.59 (0.17–15.16) SHIP: 1.20 (0.46–3.17)

Table 3—*Continued*

	Authors, year, country, cohort	Study participation	Study attrition	Prognostic factor	Outcomes	Confounding measurement and account	Analysis and results
5.	Van Den Eeden et al., 2015, United States. Retrospective cohort study within Kaiser Permanente Northern California	7621 primary RLS 4507 secondary RLS (anemia, pregnancy, or chronic renal failure) Mean age > 58 years 31% men Excluded: CAD, CVD, stroke, or HTN	Mean f/u: 3.9 years	Electronic clinical databases Computerized algorithm that incorporated longitudinal clinical records related to the diagnosis and treatment of RLS and comorbidities (yes/no)	ICD-9; electronic clinical databases Incident CAD (angina, MI, coronary revascularizations, CAD death) (primary + secondary RLS cases: *n* = 310 + 338) Incident CVD (CAD and stroke) (*n* = 478 + 451)	Matched each RLS case with up to 50 individuals with no clinical record of RLS by age, sex, race/ethnicity, zip code, and membership duration; did not control for other sleep disorders	Cox regression CVD Primary: 0.95 (0.86–1.04) Secondary: 1.33 (1.21–1.46)* CAD Primary: 0.99 (0.89–1.13) Secondary: 1.40 (1.25–1.56)*
6.	Molnar et al., 2016, USA. Nationally representative cohort of US veterans	A propensity-matched cohort of 7392 patients 93% men Mean age: 60 years Included: normal kidney function and no prior RLS diagnosis Excluded: CHD and stroke at baseline	Median f/u: 8.1 years	The VA inpatient and outpatient Medical SAS data sets using the ICD-9-CM diagnostic code for RLS	Incident CHD: an ICD-9-CM or CPT code for acute MI, coronary artery bypass grafting or percutaneous angioplasty (*n* = 582) Incident stroke: an ICD-9-CM code for ischemic stroke (*n* = 397)	Propensity score: age, gender, race/ethnicity, income, marital status, baseline eGFR, comorbidities at baseline (diabetes, HTN, CVD, heart failure, cerebrovascular disease, PVD, lung disease, dementia, rheumatic disease, malignancy, HIV/ AIDS, depression, OSA, and PLMS and BMI). Adjusted for insomnia in the sensitivity analysis.	Cox regression CHD: 3.97 (3.26–4.84)* Stroke: 3.89 (3.07–4.94)*
RLS as a prognostic factor for all-cause mortality							
1.	Pollak et al., 1990, USA. Community elderly cohort Prospective cohort study	Total of 1855 (39.7% men) 65–98 years (mean 75.4 years)	F/u: 3.5 years	Restless legs (SR): Had "jerked or kicked" their legs during sleep during the last 6 months or felt "pins and needles or restlessness" in their legs while trying to sleep (yes/no)	All-cause mortality *n* = 309	Age, problems with ADL, self-assessed health, income, cognitive impairment, depression, and living alone Preliminary models: number of medical conditions, religion, self-assessed health, perceived control over health, and educational background	Cox regression Women: 1.36 (0.94–1.96) Men: 0.92 (0.60–1.42)
2.	Mallon et al., 2008, Sweden. Prospective population-based cohort of middle-aged Swedish individuals	Total of 3496 with complete questionnaire data Age: 30–65 years 50% men	F/u: 20 years	"Yes": Scores 3–5 Restless legs: "How often are you bothered by creeping sensations in your legs when trying to fall asleep?" (1–5). DS: "How much of a problem do you have with daytime sleepiness?" (1–5)	Death certificates from the National Cause of Death Register in Sweden (*n* total = 657: 379 men and 278 women)	Age, short sleep time, living alone, smoking, habitual snoring, BMI, HTN, heart disease, diabetes, asthma, and depression	Cox regression Women RLS with DS: 1.85 (1.20–2.85)* RLS without DS: 0.91 (0.63–1.32) Men RLS with DS: 0.81 (0.51–1.28) RLS without DS: 1.25 (0.88–1.78)

Table 3—*Continued*

	Authors, year, country, cohort	Study participation	Study attrition	Prognostic factor	Outcomes	Confounding measurement and account	Analysis and results
3.	Szentkirályi et al., 2012, Germany and United States. Four prospective cohort studies: DHS, SHIP, WHS, and PHS	DHS: *n* = 1299 SHIP: *n* = 4291 WHS: *n* = 31,370 women PHS: *n* = 22,926 men Mean ages: 50.3–67.8 years	F/u: 6–11 years	The 1995 IRLSSG criteria (SR) (yes/no)#	German cohorts: municipal registries US cohorts: relatives, postal authorities, National Death Index, review of death certificates and medical records. DHS: *n* = 55 SHIP: *n* = 540 WHS: *n* = 2287 PHS: *n* = 542	Age, gender, BMI, smoking, physical activity and histories of diabetes, hypertension, MI, stroke, and cancer	Cox regression DHS: 0.21 (0.03–1.53) SHIP: 0.99 (0.76–1.29) WHS: 0.93 (0.71–1.21) PHS: 1.07 (0.93–1.23)
4.	Li et al., 2013, United States. The Health Professionals Follow-up Study Prospective cohort study of male US health professionals	18,425 men 40–75 years Excluded: diabetes, arthritis, and renal failure through the f/u	F/u: 8 years	2003 IRLSSG criteria[b]: No RLS, RLS with symptoms 5–14 times/month, and RLS with symptoms 15+ times/month	State vital statistics records, the National Death Index, family reports, and the postal system (*n* = 2765)	Age, BMI, physical activity, ethnicity, smoking, alcohol consumption, iron, and vitamin supplements, dietary iron intake, use of medications and history of major chronic diseases, snoring, sleep duration, and presence of insomnia with daytime sleepiness.	Cox regression RLS vs. No 1.30 (1.11–1.52)* RLS 5–14 vs. No 1.32 (1.07–1.63)* RLS 15+ vs. No 1.28 (1.02–1.60)*
5.	Molnar et al., 2016, United States. Nationally representative cohort of US veterans (VA)	A propensity-matched cohort of 7392 patients 93% male Mean age: 59.8 years Inclusion criteria: normal kidney function and without RLS diagnosis	Median f/u: 8.1 years	The VA inpatient and outpatient medical SAS data sets using the ICD-9-CM diagnostic code for RLS	The VA vital status files (*n* = 1635)	Propensity score: age, gender, race/ethnicity, income, marital status, baseline eGFR, comorbidities at baseline (please see details above). Adjusted for insomnia in the sensitivity analysis.	Cox regression 1.88 (1.70–2.08)*
PLMS as a prognostic factor for CVD and all-cause mortality							
1.	Koo et al., 2011, United States. The Outcomes of Sleep Disorders in Older Men Community Study (MrOS Sleep Study); an ancillary study of the Osteoporotic Fractures in Men Study (MrOS) Prospective observational study	2911 men Mean age: 76.4 ± 5.5 years Excluded: treated for OSA or snoring using positive pressure therapy, a dental appliance, or oxygen	F/u: 4.4 ± 0.8 years >99% response rate	In-home PSG: PLMI: <5, 5 to < 30, ≥30 PLMAI: <1, 1 to < 5, ≥5.	Combined sources: participants, medical records, death certificates; interviews with next of kin. Incident CVD (CHD, PAD, and CBD) CHD: 345 CBD: 117 PAD: 98 Composite: 500	Age, clinic site, BMI, race, depression, diabetes, hypertension, smoking, alcohol use, physical activity, use of antidepressants, and benzodiazepines, AHI	Cox regression PLMI 30+ vs. <5 CHD: 1.26 (0.97–1.65) CBD: 0.89 (0.56–1.40) PAD: 2.00 (1.14–3.49)* cCVD: 1.25 (1.00–1.56)* PLMAI 5+ vs. <1 CHD: 1.23 (0.95–1.61) CBD: 1.12 (0.71–1.79) PAD: 1.50 (0.92–2.46) cCVD: 1.26 (1.01–1.57)* Men without HTN: PLMI 30+ vs. < 5 1.89 (1.11–3.22)* PLMAI 5+ vs. < 1 1.74 (1.04–2.93)*

Table 3—*Continued*

	Authors, year, country, cohort	Study participation	Study attrition	Prognostic factor	Outcomes	Confounding measurement and account	Analysis and results
2.	Mirza et al., 2013, United States. Mayo Clinic Clinically-based retrospective study	*n* = 584 Median age: 65 years 51% men RLS patients referred for PSG with baseline cardiac ECHO Excluded: ESRN, severe neuropathy, Parkinson's disease, and heart failure	Median f/u: 2.8 years	Full PSG:- PLMS-related arousals/ hour of total sleep time - PLMI > 35/hour vs. ≤35/hour	Patient records Incident heart failure (*n* = 185), recurrent (≥2) cardiac hospitalization (*n* = 142) (heart failure, dysrhythmia, and myocardial ischemia or infarction), and death (*n* = 90)	Univariate only	Kaplan–Meier Logistic regression Heart failure: 1.62 (1.14–2.30)* Mortality: 1.77 (1.12–2.79)*
3.	Kendzerska et al., 2014, Canada. Clinically based retrospective study	10,149 patients Mean age: 50 years 62% men	Median f/u: 5.7 years	Full overnight PSG; PLMI as a continuous variable	ICD-9, ICD-10 codes CV composite (*n* = 1172) All-cause death (*n* = 762) AMI (*n* = 145) Stroke (*n* = 100) CHF (*n* = 414)	Sex, age, smoking status, daytime sleepiness, PSG variables, and baseline comorbidities	Cox regression PLMI: 13.4 vs. 0 CV composite 1.05 (1.03–1.07)* All-cause death 1.05 (1.02–1.07)* AMI: 0.98 (0.91–1.05) Stroke: 1.01 (0.94–1.09) CHF: 1.05 (1.02–1.09)*

ADL = activities of daily living; AIDS = acquired immune deficiency syndrome; AMI = acute myocardial infarction; BMI = body mass index; CAD = coronary artery disease; CBD = cerebrovascular disease event (stroke or transient ischemic attack); cCVD = all-cause cardiovascular disease (ie, CHD + CBD + PAD); CHD = coronary heart disease; CHF = congestive heart failure; DHS = the Dortmund Health Study; DS = daytime sleepiness; IHD = ischemic heart disease; IRLSSG = International Restless Legs Syndrome Study Group; HIV = human immunodeficiency virus; HTN = hypertension; MI = myocardial infarction; OSA = obstructive sleep apnea; PAD = peripheral arterial disease; PHS = Physicians' Health Study; PLMI = periodic limb movement index; PLMAI = periodic limb movement arousal index; PSG = polysomnography; PVD = peripheral vascular disease; RLS = restless legs syndrome; SHIP = Study of Health in Pomerania; SR = self-reported; WHS = Women's Health Study.

[a]Participants were asked four diagnostic criteria of the IRLSSG: "Do you have unpleasant leg sensations (such as crawling, paraesthesias, or pain) combined with a motor restlessness and an urge to move?", "Do these symptoms occur only at rest and does moving improve them?", "Are these symptoms worse in the evening or at night compared with the morning?" Participants who answered yes to all the three questions were defined as having RLS.

[b]A participant who had symptoms ≥5 times per month and answered yes to the subsequent questions was considered to have RLS; others (including men with symptoms 1–4 times per month) were classified as no RLS.

*$p < .05$.

RLS appeared to be at higher risk of incident CVE. The association between RLS and all-cause mortality was not significant, as assessed by a meta-analysis we performed on the four studies of high quality that used the IRLSSG criteria to define RLS.[50,52] Finally, the evidence supporting the role of PLMS as a prognostic factor for incident CVE and all-cause mortality was very limited[56,58]; however, the collective literature to date suggests a significant association, potentially stronger for PLMS associated with arousals.

Potential mechanisms that link RLS and CVE include sympathetic overactivity, hypoxia, and vascular risk factors (VRFs) frequently associated with RLS (eg, diabetes, hyperlipidemia, and obesity[15]); however, given that the exact time of the incident CVE is unknown, CVE could alternatively lead to RLS via vascular pathology in the central nervous system or the periphery.[28,59,60]

The inconsistent results among the studies evaluating RLS as a predictor for CVE and mortality are likely explained by several factors, including variability in the definitions and methods used to ascertain a diagnosis of RLS (as well as RLS severity), the absence of information on primary versus secondary forms of RLS in some studies, lack of information on the presence of PLMS at baseline and treatment of RLS in follow-up, variability in the demographic characteristics of the participants evaluated, differences in study attrition rates and follow-up times, and the relatively small number of events per outcome in some studies. The inconsistent and limited available evidence on the association between RLS and individual CV outcomes could mean there are few true relationships. The variety of definitions used for the components of the composite CV outcomes and the relatively small numbers of events per separate

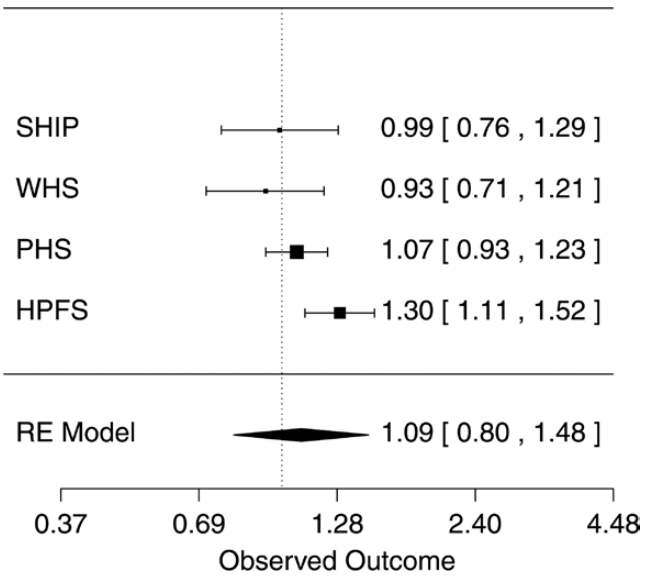

Figure 2—Adjusted association between RLS defined using the IRLSSG criteria and all-cause mortality in high quality studies. Forest plots showing the adjusted association between RLS and all-cause mortality. Boxes represent adjusted hazard ratios (HRs) and lines are 95% confidence intervals (CIs). The vertical dotted line represents no difference in all-cause mortality between individuals with RLS and without. Values to the right of the dotted line indicate increase hazard. Pooled HR and 95% CIs are represented by the diamond shape. HPFS = the Health Professionals Follow-up Study; IRLSSG = International Restless Legs Syndrome Study Group; PHS = the Physicians' Health Study; RE = random-effects; RLS = restless legs syndrome; SHIP = the Study of Health in Pomerania; WHS = the Women's Health Study.

component in some studies limits the conclusions that we can draw. Furthermore, as has been observed in the sleep apnea literature, in older populations,[47,49,56,57] the relationship with CVE was observed to be weaker; this was likely because of the presence of various comorbid conditions that likely weakened any significant association seen with RLS.

Because some studies relied on self-report of symptoms via questionnaires, the possibility of having incorrectly categorized patients with RLS (rather than with a condition that mimics RLS symptoms) is a potential issue; prior work has demonstrated that the four core diagnostic criteria for RLS cannot exclude RLS from conditions that may present with similar sensory symptoms (eg, leg cramps, peripheral neuropathy, radiculopathy, arthritis, positional discomfort and so on).[61] Hence, some studies may have included patients with "RLS mimics" and contaminated the results. On the other hand, usage of "physician-diagnosed RLS" on questionnaires in other studies may have underestimated the true prevalence of this condition because physicians may underdiagnose RLS[4]; in addition, use of "physician-diagnosed RLS" may have led to a selective identification of individuals with severe RLS.[49] Ideally, the presence of RLS would be determined via diagnostic interviews with participants conducted by physicians or other trained personnel; however, use of such a method would be impractical or costly for large studies. Most studies also used self-report measures of baseline comorbidities, which may be more vulnerable to misclassification as well.

The finding that secondary, but not primary, forms of RLS were linked with incident CVE[54] may be an important finding explained by the complex and incompletely understood pathogenesis of RLS. Important interactions between genetic factors and comorbid medical conditions may contribute to the pathogenesis of RLS.[62] One limitation of most of the epidemiological studies reviewed in the present manuscript is that they did not distinguish between primary and secondary forms of RLS. As proposed by Wong et al.,[63] an explanation for the mixed results in the present literature could be that study cohorts negative for a significant relationship may have been enriched with primary RLS cases, while study cohorts demonstrating a positive link may have been enriched in secondary RLS cases. Secondary forms of RLS may have contributed to a greater risk for CVE through the RLS-associated conditions that gave rise to the RLS symptoms (eg, renal disease, iron deficiency, anemia, etc.).[63] The finding that women with RLS for at least 3 years had a higher risk of incident CVE suggested that longer term exposure to RLS-associated conditions may have contributed to the origin of vascular disease.[49]

As recently proposed by Trenkwalder et al.,[62] the traditional dichotomy between primary and secondary forms of RLS may be misleading. Rather, it has been suggested to view RLS as the complex interaction of genetic and environmental factors: the more genetic factors contribute to the manifestation of RLS, the fewer comorbid medical conditions are needed to develop the phenotype of RLS.[62] Although speculative and beyond the data presented in our review, primarily genetic manifestations of RLS may not be significant contributors to incident CVE, while manifestations of RLS mostly associated with comorbid conditions may be potentially important contributors to CVE, with more severe and longer duration exposures portending poorer outcomes.

Because observational studies cannot determine the direction of the relationship between RLS and CVE, the observed data are limited by unaddressed potentially confounding factors; there is also a possibility that the cerebrovascular and CVE themselves, or various VRFs, gave rise to the phenotype of RLS. It is well established that stroke can give rise to both RLS and PLMS.[59] In addition, RLS has been demonstrated to be linked with peripheral hypoxia,[64] and so it is conceivable that a CVE that impairs systemic perfusion may contribute to the development of RLS. Moreover, in the time sequence analysis reported by Szentkirályi et al.,[53] VRFs such as obesity were found to be independently associated with incident RLS; however, when the analyses were conducted with reversed sequential order, RLS at baseline was not associated with incident CVE or with any VRF. Another (less likely) possibility is that positive associations reported in the literature between RLS and CVE may be due to older RLS-related treatment such as low-dose pergolide, which has been reported to give rise to valvular heart disease[65]; of note, most studies did not report on RLS-related treatments such as dopamine agonists. Furthermore, most studies reviewed did not objectively measure markers of iron deficiency.

Consistent with its complex pathogenesis, it has been proposed that RLS may be divided into three discrete components: PLMS, subjective sensorimotor symptoms, and sleep disturbance[66]; it is

plausible that each component may contribute differently to vascular risk. Although PLMS occur frequently in RLS, they are not exclusively related to RLS and occur in a host of other sleep disorders and medical conditions.[8] We propose that, among patients with secondary forms of RLS, PLMS may serve as the physiological link to increased vascular risk. Numerous mechanisms may link PLMS with vascular disease. For example, PLMS are associated with surges of nocturnal sympathetic hyperactivity which manifest as transient elevations in night-time heart rate and blood pressure (BP).[14,67] Recurrent surges in BP every night for many years or decades may cause repeated mechanical stress on the vasculature, leading to vascular remodeling; in addition, variability of blood flow caused by BP oscillations is thought to induce sheer stress, platelet activation, leading to atherosclerosis and a potentially hypercoagulable state.[68] Another mechanism that may link RLS with vascular disease is inflammation. In a study of patients with RLS, those with elevated PLM indices (≥45 PLMS per hour of sleep) had more than a 3-fold chance of having an elevated C-reactive protein (CRP), a marker of systemic inflammation, compared to RLS patients with lower PLM indices. In that study, the presence of RLS by itself was not reported to be associated with increased levels of serum CRP, suggesting that PLMS were the main modulator of the elevated CRP levels.[69] Indeed, prior work has suggested that RLS itself is not associated with elevated levels of inflammatory markers.[29,70] These findings underscore the potential importance of PLMS,[71] rather than a diagnosis of RLS alone, in mediating inflammation as a possible linking mechanism.

Several limitations were present in the studies that investigated the prognostic value of PLMS, including the fact that these studies were limited by a lack of information about the presence of RLS at baseline and did not report on treatments for RLS/PLMS. Furthermore, arbitrary thresholds for PLMS severity do not have clear clinical significance or predictive value. Finally, a single measurement of PLMS at baseline does not account for the night-to-night variability and changes in PLMS seen over time.[72,73]

The inclusion of only peer-reviewed studies in our systematic review may have introduced a bias associated with exaggerating the estimate of the actual effect.[74] However, to mitigate the impact of a possible publication bias, we included studies published in open-access journals, which are presumably associated with less editorial bias against negative study results.

Future large population-based studies with long follow-up periods, a sufficient number of outcome events, a broad range of population demographic characteristics, and standardized definitions used to define PLMS/RLS (including primary vs. secondary forms, duration, and severity) are needed to explore further the potential prognostic role of RLS/PLMS in CVE development. Following this, randomized controlled trials would be needed to assess the impact of treating RLS/PLMS on vascular outcomes, with a particular emphasis on examining the potential role of severity and frequency of PLMS/RLS symptoms.

CONCLUSIONS

The available evidence on RLS as a prognostic factor for incident CVE and all-cause mortality was limited and inconclusive. Significant heterogeneity in study populations, outcomes, and other methodological aspects introduced significant inconsistencies between studies. Duration, severity, and secondary versus primary RLS may be important features in understanding a possible relationship with CV disease and mortality. Although limited, the evidence on PLMS as a prognostic factor for incident CV diseases and mortality suggests a significant association.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *SLEEP* online.

FUNDING

None.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2016
Submitted in final revised form December, 2016
Accepted for publication January, 2017
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DISCLOSURE STATEMENT

All authors declare that they have no known conflicts of interest.