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Restless legs syndrome and risk of incident cardiovascular disease in women and men: prospective cohort study

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ABSTRACT

Objectives—To evaluate the association between restless legs syndrome (RLS) and incident cardiovascular disease (CVD).

Design—Prospective cohort study.

Setting—Women's Health Study (WHS) and Physicians' Health Study (PHS), United States

Participants—29,756 female health professionals aged ≥45 years and 19,182 male physicians aged ≥40 years at baseline.

Main outcome measures—Main outcome was incidence of major cardiovascular disease; secondary outcome were first incidence of myocardial infarction, stroke, death due to CVD or coronary revascularization.

Results—3,487 (11.7%) women and 1,373 (7.2%) men met International Restless Legs Study Group criteria for RLS. In the WHS, 450 major CVD events occurred and 1,064 major CVD events were confirmed in the PHS. In both cohorts, RLS was not associated with increased risk of major CVD, stroke, myocardial infarction, CVD death, or coronary revascularization. After adjustment for major vascular risk factors, the hazard ratios (95% confidence interval) for major CVD were 1.15 (0.88 to 1.50) in women and 1.01 (0.81 to 1.25) in men. Highest multivariable-adjusted hazard ratios were 1.29 (0.91 to 1.82) for total stroke in women and 1.22 (0.87 to 1.70) for CVD death in men. Excluding participants with comorbidities potentially leading to RLS did not substantially change the effect estimates.

Conclusion—In these large prospective studies of female and male health professionals, RLS was not associated with an increased risk of any incident CVD event. Our data do not support the hypothesis that RLS is a marker of increased risk of vascular disease.

ARTICLE SUMMARY

Article focus

- The aim of this study is to evaluate the association between restless legs syndrome (RLS) and incident cardiovascular events in two large prospective cohort studies.

Key messages

- The results of our two large prospective cohorts do not suggest that either women or men suffering from RLS are at increased risk for any vascular disease event.
- RLS should not be considered a marker for increased cardiovascular disease risk.

Strengths and limitations

Strengths of this study include the large number of participants and outcome events, the prospective study design, the standardized assessment of RLS according to the four minimal diagnostic criteria, and confirmation of CVD cases by medical record review.

The following limitations should be considered: the information on RLS was self-reported and misclassification of cases is possible. No information on frequency, severity and duration of RLS symptoms was available and both cohorts consist of white health professionals which may limit the generalizability of the results to other populations.

INTRODUCTION

Restless legs syndrome (RLS) is a movement disorder characterized by an urge to move the legs, typically during rest, and is mostly accompanied by unpleasant leg sensations. This syndrome has been increasingly studied over the last years. According to results from population-based studies, RLS is a common disease with an estimated prevalence ranging from 4 to 29%.[1, 2] The prevalence of RLS increases with age and women are predominately affected. There is increasing evidence that dysfunction of the dopaminergic system is one underlying cause for the syndrome[3] although the precise mechanisms of this disease are still unknown. In addition, results from genetic studies indicate a genetic predisposition for the disorder.[4, 5]

Different comorbidities have been reported to be associated with RLS. Particularly, the relationship between RLS and prevalent cardiovascular disease (CVD), as suggested by several cross-sectional studies,[6-12] has gained attention due to the high prevalence of both conditions in the general population. In addition, one prospective study from the UK has reported an association between RLS and incident stroke, which was not found for ischemic heart disease.[13] As potential mechanisms for this relationship, an unfavorable CVD risk factor profile and an elevated activity of the sympathetic nervous system resulting in tachycardia and hypertension, have been proposed.[14][15] However, data on the association between RLS and vascular risk factors are inconsistent and studies evaluating the association between RLS and incident CVD are lacking.

Evaluating the association between RLS and CVD is of substantial public health importance because of the high prevalence of RLS. In addition, a relationship between these two diseases would have clinical implications for the management and treatment of patients and would further stimulate research to identify potential common pathophysiological mechanisms. The cross-sectional design of previous studies, however, does not allow determining the direction of association between RLS and CVD and prospective data are lacking. We therefore sought to evaluate the association between RLS and risk of incident CVD in two large prospective cohort studies, the Women's Health Study (WHS) and the Physicians' Health Study (PHS).

METHODS

Study Populations

The design and methods of both cohorts have been described in detail previously.[16-19] Briefly, the WHS was a randomized, placebo-controlled trial designed to test the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among apparently healthy women. A total of 39,876 US female health care professionals aged 45 years or older at study entry (1992-1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to receive active aspirin (100mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. After the termination of the trial in March 2004, the women who were still alive and willing to participate entered an observational follow-up. The return date of the 108-month questionnaire containing questions on RLS was defined as new baseline for this analysis. Of the 33,092 women in active follow-up at 108-months, we excluded 1,722 women with missing RLS information, 1,614 women who reported CVD events (myocardial infarction, stroke, CVD death, coronary revascularization) and angina prior to receiving the 108-months questionnaire, leaving a total of 29,756 women free of CVD or angina for this analysis.

The Physicians' Health Study I (PHS I) was a randomized, double blind, placebo-controlled trial to test the benefits and risks of low dose aspirin (325mg) and beta-carotene (50mg) in the primary prevention of CVD and cancer among 22,071 apparently healthy physicians aged 40 to 84 years at baseline in 1982. Baseline information was self-reported and collected by means of a mailed questionnaire that asked about many cardiovascular risk factors and life style variables. Every six months in the first year and yearly thereafter, follow-up questionnaires were sent to the participants. Since the trials' termination in 1995, observational follow-up is still ongoing. 7,641 PHS I participants were willing and eligible to enter the Physicians' Health Study II (PHS II).

The PHS II was launched in 1995. The PHS II is an ongoing randomized, double-blind, placebo-controlled trial to test the effects of vitamin C (500mg), vitamin E (400IU), beta-carotene (50mg), and a daily multivitamin (Centrum Silver) in the prevention of total and prostate cancer, CVD, and age-related eye disease among 14,641 US male physicians aged 55 years and older. Baseline information was self-reported and follow-up information was collected annually by mailed questionnaires. For the purpose of this analysis, we pooled data from the PHS I and PHS II, yielding a total of 29,071 participants. The return date of the questionnaire containing the RLS question (216-month questionnaire for PHS I participants and 12-month questionnaire for PHS II participants) was defined as new baseline for this analysis. At this time point, 24,505 men were still in active follow-up. We excluded 1,579 men with missing RLS questionnaire information and 3,744 men with CVD events and angina prior to the RLS assessment, leaving a total of 19,182 men free of angina and CVD at our defined baseline for our analysis.

All participants of the WHS and the PHS provided written informed consent, and the institutional review board of Brigham and Women's Hospital, Boston, MA, approved the studies as well as the analyses presented here.

Assessment of restless legs syndrome

Restless legs syndrome is diagnosed by presence of specific symptoms, and the diagnostic criteria have been established by the International Restless Legs Study Group (IRLSSG). We have implemented standardized questions in both cohorts addressing the four minimal diagnostic criteria of the IRLSSG. Participants were asked: "Do you have unpleasant leg sensations (like 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 of the three questions were defined as having RLS. This questionnaire has been established[20-22] and validated[23] in previous studies from Germany and Italy. Comparing the questionnaire based diagnosis of RLS with a physician's diagnosis as a gold standard showed good agreement (unweighted kappa=0.67, p<0.001).[23]

Outcome ascertainment

Participants of both cohorts were asked to report the occurrence of cardiovascular events including myocardial infarction and stroke during follow-up. In addition, information on coronary revascularization procedures (bypass surgery and percutaneous coronary angioplasty) was collected. Medical records were obtained for all cardiovascular events including coronary revascularization in the WHS and for all cardiovascular events, but not for coronary revascularization, in the PHS and were reviewed by an end points committee of physicians. The occurrence of myocardial infarction was confirmed if symptoms met the World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiograms. Non-fatal stroke was confirmed if the participant had a new focal neurological deficit of sudden onset and vascular origin that persisted for more than 24 hours. Stroke was classified into its major subtypes based on available clinical and diagnostic test information, including brain scans with excellent interrater agreement.[24, 25] Cardiovascular deaths were confirmed by reviews of autopsy reports, death certificates, medical records, and information obtained from next of kin or other family members. Major CVD was defined as a combined endpoint of non-fatal stroke, non-fatal myocardial infarction or death from CVD events.

Statistical analysis

We analyzed the association between RLS and incident CVD separately in both studies. Baseline characteristics were compared with respect to RLS status using t-test for continuous and chi-square test for categorical variables.

Person-time was calculated from the return of the questionnaire containing the RLS questions (baseline for this study) to the first incident CVD event, non-CVD death, last documented contact or end of the study, whatever occurred first. Information on cardiovascular risk factors and other covariates was updated from the start of the cohorts until the assessment of RLS.

Cox proportional hazards models were used to evaluate the association between RLS and the various CVD events. We calculated age- and multivariable-adjusted hazard ratios (HRs) and their corresponding 95% confidence intervals (95% CIs). The multivariable-adjusted models accounted for age, randomized aspirin assignments, history of hypertension,(yes/no) history of diabetes (yes/no), history of cholesterol level ≥ 240mg/dl (yes/no), parental history of myocardial infarction before the age of 60 years (yes/no), alcohol consumption (rarely/never, 1-3/month, 1-6/week, ≥ 1/day), smoking status (never, past, current), body mass index (BMI) (<25, 25-29.9, ≥30kg/m²), exercise (WHS: rarely/never, <1/week, 1-3/week, ≥4/week; PHS: rarely/never, ≤1/week, 2-4/week, 5-7/week), history of migraine (yes/no), and postmenopausal hormone use (WHS: never, past, current). Additional adjustment for race, geographic location, depression, iron-supplementation use, Parkinson's disease, snoring (PHS only), sleep duration (PHS only), fatigue (WHS only), number of pregnancies (WHS only), age at menarche (WHS only), postmenopausal status (WHS only), oral contraceptive use (WHS only) and analgesic use including aspirin, non-steroidal anti-inflammatory drugs, acetaminophen (WHS only) and aspirin containing drugs (WHS only) did not change the effect estimate of RLS on any CVD event by more than 10%.

A missing value indicator was incorporated in the outcome models for covariates if the number of participants with missing information was greater or equal to 100. We assigned participants with missing values to the covariate reference category if the number of missing information was less than 100. No covariate in the primary analysis had more than 4% missing.

We evaluated effect modification by age (<60, 60-<70, 70-<80, ≥80 years), iron supplementation use (yes/no), BMI (<25kg/m², 25-29·9kg/m², ≥30kg/m²), smoking status (never, past, current), history of hypertension (yes/no), fatigue (WHS only) and number of pregnancies (WHS only). Effect modification was tested by including an interaction term for RLS and the potential effect modifier to the outcome model.

The proportional hazards assumption was tested by including an interaction term for RLS status and logarithm of follow-up time for major CVD in age-adjusted models. We found no statistically significant violation.

We performed a sensitivity analysis by excluding participants with a history of polyneuropathy, kidney disease, liver disease, liver cirrhosis (PHS only), rheumatoid arthritis, intermittent claudication and participants who underwent peripheral artery disease surgery. The information on these covariates was updated from the start of the cohorts until assessment of the questionnaire addressing RLS.

For all analyses, we used SAS (version 9.1.3, SAS Institute Inc. Cary, NC). All p-values were 2-tailed and $p<0{\cdot}05$ was considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of participants according to RLS status are presented in Table 1 for the WHS and in Table 2 for the PHS. The prevalence for RLS was 11.7% among women and 7.2% among men. In contrast to the WHS, we observed an age-difference according to RLS status in the PHS. Men with RLS had a mean age of 67.8 years and were older than men without RLS. Compared to participants without RLS, both male and female RLS sufferers were more likely to report a history of hypertension, a history of diabetes, and a history of hypercholesterolemia. With regard to lifestyle factors, participants with RLS were more likely to have a BMI ≥30kg/m², to rarely/never drink, and to rarely/never exercise in both cohorts. In addition, both male and female RLS sufferers more frequently reported a history of depression and migraine.

Risk of CVD

WHS

A total of 450 first major CVD events, 176 myocardial infarctions, 245 strokes, 66 CVD deaths and 461 coronary revascularizations were confirmed during a mean follow-up of 6·0 years. Age- and multivariable-

adjusted HRs (95% CI) for the association between RLS and the various vascular events are presented in Table 3. Women with RLS had an increased age-adjusted HR of 1.42 (1.10 to 1.82) for coronary revascularization. The association was diminished and became insignificant after adjustment for vascular risk factors. RLS was not associated with a significantly increased risk for major CVD, myocardial infarction, stroke, or CVD death.

PHS

In Table 4, age- and multivariable-adjusted HRs (95% CI) for the association between RLS and vascular outcomes in the PHS are summarized. During a mean follow-up of 7·3 years, 1,064 major CVD events, 431 myocardial infarctions, 381 strokes and 389 CVD deaths were confirmed. In addition, 1,352 coronary revascularizations were reported. RLS at baseline was not associated with incident vascular events in age-adjusted or multivariable-adjusted models.

Sensitivity analyses

After excluding participants with comorbid conditions that have been associated with RLS, the lack of association between RLS and our outcome events remained robust, with the exception of stroke in the WHS. The multivariable-adjusted HR increased from 1.29 (0.91 to 1.82) to 1.42 (0.99 to 2.05).

In both cohorts, the effect estimates did not change by more than 5% when excluding a history of diabetes from the list of confounding factors in multivariable-adjusted models.

Effect modification

The associations between RLS and major CVD were not significantly modified by age (p for interaction in the WHS: 0.12, p for interaction in the PHS: 0.51), BMI (P for interaction in the WHS: 0.72, p for interaction in the PHS: 0.28), smoking status (P for interaction in the WHS: 0.71, p for interaction in the PHS: 0.43), iron supplementation use (P for interaction in the WHS: 0.75, p for interaction in the PHS: 0.35), history of hypertension (P for interaction in the WHS: 0.76, p for interaction in the PHS: 0.43), fatigue (p for interaction WHS: 0.91) or number of pregnancies (p for interaction WHS: 0.92).

DISCUSSION

In this study, evaluating data from two large, prospective cohort studies of women and men, RLS was not associated with an increased risk for incident vascular events including major CVD, myocardial infarction, stroke, coronary revascularization, and CVD death. Excluding participants with comorbidities that have been associated with RLS did not substantially change our results.

Comparison with other studies

In contrast to our results, findings from several cross-sectional studies have suggested a relationship between RLS and prevalent CVD.[6-12] Among the 3,422 participants of the Sleep Heart Health Study, those with RLS had multivariable-adjusted odds ratio (OR) (95% CIs) of 2.05 (1.38 to 3.04) for CVD and 2.07 (1.43 to 3.00) for coronary artery disease. Winkelman et al. additionally report an association between severity and frequency of RLS and CVD.[12] Compared to those without RLS, participants who reported a RLS frequency of 16-23/month had an OR of 3.53 (1.85 to 6.76) for CVD. Duration of disease was not related to CVD. In our cohorts, data on frequency and severity of symptoms was not available and we had no information about the duration of disease.

Two studies from Sweden, one analyzing a random sample of the female population of central Sweden aged 18-64 years and the other one evaluating a comparable random sample of men with the same age range, report an association between RLS and self-reported heart disease.[9, 10] As in our study, RLS was defined according to IRLSSG diagnostic criteria in these studies and the observed overall prevalences were comparable to those in our cohorts. The multivariable-adjusted OR for heart disease was 2.13 (1.18 to 3.86) in the female Swedish cohort and 2.5 (1.4 to 4.3) in the study evaluating the random sample of Swedish men.

In the Caerphilly cohort of 1,986 men, RLS was associated with incident stroke (multivariable-adjusted odds ratio of 1.67 (1.07 to 2.06)). In addition, the authors report an increased, but not significant OR of 1.24 (0.89 to 1.74) for incident ischemic heart disease events. While we do not find an association

between RLS and stroke in out main analysis, the sensitivity analysis suggest potential increased risk for stroke (RR 1.42 (0.99 to 2.05)). RLS was not defined according to IRLSSG diagnostic criteria and the associations were not adjusted for important vascular risk factors including hypertension and diabetes which are potential limitations of this study.[13]

One cross-sectional study using data from the Burden of Obstructive Lung Disease (BOLD) initiative in Iceland and Sweden is in line with our finding.[26] A random sample of adults aged 40 years and older was drawn from the national registries in both countries. Benediktsdottir et al. found a significant higher prevalence of RLS in Icelandic women compared to women from Sweden. In multivariable-adjusted models, RLS, defined according to IRLSSG criteria, was not associated with cardiovascular disease, assessed by a structured interview, in this study.

A high percentage of RLS patients report periodic limb movements during sleep (PLMS) and PLMS are considered as supportive clinical feature of RLS.[27] The association between periodic limb movements and incident cardiovascular disease has been recently evaluated among 2,911 men aged ≥ 65 years who participated in the Outcomes of Sleep Disorders in Older Men (MrOS) Sleep study.[28] Periodic limb movements were assessed by two indices, the Periodic limb movement index (PLMI) and the periodic limb movement arousal index (PLMAI). After 4.4 years of mean follow-up, men with a PLMAI ≥5 had a multivariable-adjusted HR of 1.26 (1.01 to 1.56) for all-cause cardiovascular disease compared to men with the lowest index category. The PLMI was not statistically significant associated with all-cause cardiovascular disease (HR: 1.25, 95% CI: 1.00 to 1.56) which was defined as a composite endpoint of coronary heart disease, cerebrovascular disease and peripheral artery disease. When evaluating the different endpoints separately, incident peripheral artery disease was the only cardiovascular disease event which was significantly associated with one of the indices in multivariable-adjusted models (HR: 2.00, 95%CI: 1.14 to 3.49). Although PLMS is frequently reported by RLS sufferers, it is not exclusively related to RLS and occurs in other sleep related disorders and medical conditions. Since the frequency of RLS sufferers could not be determined in the previous mentioned study, the results can not be translated to a RLS population and the comparability of these results to our study is limited.

RLS can be distinguished in idiopathic and secondary forms. A variety of disorders have been identified to be associated with secondary RLS including anemia, iron deficiency, rheumatoid arthritis, polyneuropathies and reduced renal function. La Manna et al. evaluated the association between RLS and incident CVD events among 100 end-stage kidney disease patients who were on dialysis three times a week.[29] After 18 months of follow-up patients with secondary RLS had an increased risk for cardiovascular disease events (myocardial infarction, stroke or peripheral artery occlusion), which however, did not reach statistical significance. In addition, patients with RLS had higher fibrinogen levels, albumin levels, white blood cell counts, and higher overall mortality suggesting that RLS status could be an indicator for poorer health status. Since the study analyzes a very distinct population, the comparability of these results with studies in healthier populations including ours is limited.

A possible explanation for the discrepancy between our results and those of previous studies is the prospective cohort design, which allows the assessment of incident CVD cases. Thus, while RLS does not seem to be a risk factor for subsequent CVD, it might be an indicator of a poor health status due to the presence of several, especially cardiovascular, comorbidities.

Strengths and limitations

Our study has several strengths including the large number of participants in both cohorts, large number of outcome events, prospective design, and standardized assessment of RLS according to the four minimal diagnostic criteria of the IRLSSG. Further, incident CVD events were confirmed by medical record review. In addition, information on many co-morbidities and lifestyle factors was available allowing us to adjust for potential confounders.

The following limitations should be considered when interpreting our results. First, information on RLS was self-reported and potential misclassification is possible. However, the questionnaire has been successfully used and validated in previous cohorts from Germany and Italy and the prevalences of RLS in both cohorts are similar to those reported in other population-based studies.[1] Furthermore, both

cohorts consist of health professionals and previous studies indicate that participants with a health profession accurately report information.[30] Moreover, we have excluded participants with comorbidities potentially mimicking RLS syndromes in sensitivity analysis and the results were largely unchanged. Second, we had no information on frequency, severity and duration of RLS symptoms. Third, residual and unmeasurable confounding remains possible as our study is observational. However, we are not aware of any factor that, if controlled for, would establish an association between RLS and CVD. Fourth, both of our cohorts consist of predominately white health professionals which may limit generalizability to other populations. However, we have no reason to believe that potential biological associations between RLS and CVD are different in our compared to other populations.

Clinical implications

Results of these two large prospective studies do not suggest that restless legs syndrome is a marker for increased risk of cardiovascular disease independent of other cardiovascular risk factors. However, our data also indicate that the prevalence of RLS increases with several comorbidities including traditional CVD risk factors like BMI, hypertension, and diabetes. Therefore, patients diagnosed with RLS should be carefully screened for relevant comorbidities and subsequently treated.

Unanswered questions and future research

RLS is a complex disease and the mechanisms underlying the disease have not been fully understood yet. Understanding the role of diverse comorbidities for the onset of RLS would be an important research target for the future in order to establish strategies to prevent the disease.

Table 1 Baseline characteristics according to RLS status in the WHS (n=29,756)

	No RLS	RLS	p-value
	n=26,269	n=3,487	
Demographic information			
Mean age, yrs (SD)	63.4 (6.9)	63.3 (6.8)	0.30
Ethnicity, n (%)			
White	24,786 (95.1)	3,376 (97.4)	<0.01
Geographic location, n (%)			<0.01
Northeast	5,168 (19.7)	605 (17.4)	
Southeast	5,985 (22.8)	825 (23.7)	
Midwest	9,362 (35.7)	1,312 (37.7)	
West	5,713 (21.8)	742 (21.3)	
CVD risk factors, n (%)			
History of hypertension	12,273 (46.7)	1,759 (50.4)	<0.01
History of diabetes	1,709 (6.5)	295 (8.5)	<0.01
History of cholesterol ≥ 240mg/dl	13,850 (52.8)	2,013 (57.8)	<0.01
BMI categories (kg/m²)			<0.01
<25	10,813 (41.8)	1,302 (37.8)	
25-29.9	8,866 (34.3)	1,195 (34.7)	
≥30	6,177 (23.9)	950 (27.6)	
Smoking status			<0.01
Never	13,484 (52.0)	1,619 (47.0)	
Past	10,352 (39.9)	1,504 (43.7)	
Current	2,083 (8.0)	321 (9.3)	
Alcohol consumption			0.05
Rarely/never	11,071 (42.4)	1,558 (44.9)	
1-3 drinks per month	3,044 (11.7)	394 (11.3)	

Table 1 cont.

1-6 drinks per week	8,969 (34.4)	1,138 (32.8)	
≥1 drink/day	2,936 (11.2)	314 (9.0)	
Exercise			<0.01
Rarely/never	9,875 (37.6)	1,380 (39.6)	
<1/week	5,224 (19.9)	728 (20.9)	
1-3 times/week	8,225 (31.3)	1,064 (30.5)	
≥ 4 times/week	2,939 (11.2)	314 (9.0)	
Parental history of myocardial infarction	4,391 (16.8)	646 (18.6)	<0.01
Postmenopausal status			0.13
Premenopausal	467 (1.8)	54 (1.6)	
Postmenopausal	23,368 (90.8)	3,082 (90.1)	
Biological uncertain	1,651 (6.4)	253 (7.4)	
Unclear/subject unsure	264 (1.0)	33 (0.96)	
Postmenopausal hormone use			<0.01
Never	5,626 (22.3)	636 (18.9)	
Past	6,347 (25.2)	836 (24.9)	
Current	13,225 (52.5)	1,891 (56.2)	
Other covariates, n (%)			
History of migraine during follow-up	5,509 (21.0)	909 (26.1)	<0.01
History of depression	3,132 (11.9)	707 (20.3)	<0.01
History of Parkinson's disease	105 (0.4)	21 (0.6)	0.08
Iron supplementation use	1,028 (4.0)	124 (3.6)	0.30
Being fatigued	9,101 (34.8)	1,776 (51.1)	<0.01

Percentages may not add up to 100% due to rounding or missing values.

Table 2 Baseline characteristics according to RLS status in the PHS (n=19,182)

	No RLS n=17,809	RLS n=1,373	p-value
Demographic information			
Mean age, yrs (SD)	66.6 (8.7)	67.8 (8.9)	<0.01
Ethnicity, n (%)			
White	16,091 (90.8)	1,288 (94.2)	<0.01
Geographic location, n (%)			0.16
Northeast	3,983 (22.4)	299 (21.8)	
Southeast	5,137 (28.8)	359 (26.2)	
Midwest	4,547 (25.5)	375 (27.3)	
West	4,031 (22.6)	329 (24.0)	
Other	111 (0.6)	11 (0.8)	
CVD risk factors, n (%)			
History of hypertension	8,596 (48.3)	703 (51.2)	0.04
History of diabetes	1,200 (6.7)	138 (10.1)	<0.01
History of cholesterol ≥ 240mg/dl	8,387 (47.1)	686 (50.0)	0.04
BMI categories (kg/m²)			<0.01
<25	7,550 (42.5)	519 (37.8)	
25-29.9	8,197 (46.1)	665 (48.5)	
≥30	2,038 (11.5)	189 (13.8)	
Smoking status			0.17
Never	9,763 (54.9)	719 (52.4)	
Past	7,543 (42.4)	617 (45.0)	
Current	495 (2.8)	37 (2.7)	
Alcohol consumption			<0.01
Rarely/never	3,120 (17.5)	292 (21.3)	

Table 2 cont.

1-3 times/month	2,171 (12.2)	157 (11.4)	
1-6 times/week	6,631 (37.3)	514 (37.4)	
≥1 times/day	5,862 (33.0)	410 (29.9)	
Exercise			<0.01
Rarely/never	6,174 (34.8)	536 (39.2)	
≤ 1/week	455 (2.6)	39 (2.9)	
2-4 times/week	7,917 (44.6)	594 (43.4)	
5-7 times/week	3,204 (18.1)	200 (14.6)	
Parental history of myocardial infarction	1,910 (10.7)	137 (10.0)	0.39
Other covariates, n (%)			
History of migraine during follow-up	2,157 (12.1)	202 (14.7)	<0.01
History of depression	1,709 (9.8)	219 (16.1)	<0.01
History of Parkinson's disease	207 (1.2)	20 (1.5)	0.33
Iron supplementation use	298 (1.9)	25 (2.1)	0.73
Sleep duration ≥ 8 hours	5,254 (32.7)	431 (34.9)	0.11
Snoring			0.24
Never	4,382 (26.9)	338 (27.0)	
A few nights	6,604 (40.6)	482 (38.5)	
Most nights	5,283 (32.5)	433 (34.6)	

Percentages may not add up to 100% due to rounding or missing values.

Table 3 Age- und multivariable-adjusted hazard ratios (HRs) for incident vascular events according to RLS status in the WHS

	Primary analysis (n=29,756)		Sensitivity analysis[†] (n=27,649)	
	No RLS history	Any history of RLS	No RLS history	Any history of RLS
	n=26,269	n=3,487	n=24,472	n=3,177
		HR (95% CI)		HR (95% CI)
Major cardiovascular event	n=386	n=64	n=338	n=56
Age-adjusted	1·00	1.25 (0.96 to 1.63)	1·00	1.27 (0.96 to 1.69)
Multivariable-adjusted*	1·00	1.15 (0.88 to 1.50)	1·00	1.18 (0.89 to 1.57)
Any stroke	n=207	n=38	n=178	n=35
Age-adjusted	1·00	1.39 (0.98 to 1.96)	1·00	1.51 (1.05 to 2.16)
Multivariable-adjusted*	1·00	1.29 (0.91 to 1.82)	1·00	1.42 (0.99 to 2.05)
Myocardial infarction	n=153	n=23	n=138	n=20
Age-adjusted	1·00	1.13 (0.73 to 1.75)	1·00	1.11 (0.69 to 1.77)
Multivariable-adjusted*	1·00	1.01 (0.65 to 1.57)	1·00	1.00 (0.62 to 1.59)
Coronary revascularization	n=388	n=73	n=346	n=59
Age-adjusted	1·00	1.42 (1.10 to 1.82)	1·00	1.30 (0.99 to 1.72)
Multivariable-adjusted*	1·00	1.24 (0.96 to 1.59)	1·00	1.14 (0.86 to 1.50)

Table 3 cont.

CVD death	n=57	n=9	n=52	n=6
Age-adjusted	1.00	1.21 (0.60 to 2.45)	1·00	0.90 (0.39 to 2.09)
Multivariable-adjusted*	1.00	1.11 (0.55 to 2.25)	1·00	0.85 (0.36 to 1.98)

*Adjusted for age, randomized treatment assignments, history of hypertension, history of diabetes, history of hypercholesterolemia, parental history of mi, history of migraine, alcohol consumption, BMI, smoking, exercise, and postmenopausal hormone use.

[T] 2,107 women with polyneuropathy, liver disease, kidney disease/failure, peripheral artery disease surgery, intermittent claudication, and rheumatoid arthritis were excluded from the analysis

Table 4 Age- and multivariable-adjusted hazard ratios (HRs) for incident vascular events according to RLS status in the PHS

	Primary analysis (n=19,182)		Sensitivity analysis[†] (n=15,625)	
	No RLS history	Any history of RLS	No RLS history	Any history of RLS
	n=17,809	n=1,373	n=14,578	n=1,047
		HR (95% CI)		HR (95% CI)
Major cardiovascular event	n=974	n=90	n=755	n=61
Age-adjusted	1·00	1.09 (0.88 to 1.35)	1·00	1.03 (0.79 to 1.33)
Multivariable-adjusted*	1·00	1.01 (0.81 to 1.25)	1·00	0.96 (0.74 to 1.25)
Any stroke	n=357	n=24	n=271	n=18
Age-adjusted	1·00	0.77 (0.51 to 1.17)	1·00	0.82 (0.51 to 1.33)
Multivariable-adjusted*	1·00	0.73 (0.48 to 1.11)	1·00	0.79 (0.49 to 1.28)
Myocardial infarction	n=392	n=39	n=315	n=25
Age-adjusted	1.00	1.23 (0.88 to1.71)	1·00	1.06 (0.70 to 1.59)
Multivariable-adjusted*	1.00	1.12 (0.80 to 1.55)	1·00	0.97 (0.64 to 1.45)
Coronary revascularization	n=1,239	n=113	n=976	n=87
Age-adjusted	1.00	1.15 (0.95 to 1.40)	1·00	1.22 (0.98 to 1.52)
Multivariable-adjusted*	1.00	1.06 (0.88 to 1.29)	1·00	1.12 (0.90 to 1.40)

Table 4 cont.

CVD death	n=350	n=39	n=260	n=25
Age-adjusted	1.00	1.27 (0.91 to 1.77)	1·00	1.17 (0.78 to 1.77)
Multivariable-adjusted*	1.00	1.22 (0.87 to 1.70)	1·00	1.13 (0.75 to 1.70)

*Adjusted for age, randomized treatment assignments, history of hypertension, history of diabetes, history of hypercholesterolemia, parental history of mi, history of migraine, alcohol consumption, BMI, smoking, and exercise.

[T] 3,557 men with a history of polyneuropathy, kidney disease, liver disease, liver cirrhosis, rheumatoid arthritis, intermittent claudication, and men who underwent peripheral artery disease surgery were excluded

Authors' contributions

Dr. Winter: Study design, data analysis, data interpretation, writing of a first draft of the manuscript

Dr. Schürks: Study design and conception, data interpretation, critical revisions of the manuscript draft for important intellectual content.

Dr. Glynn: Study design, data interpretation, critical revisions of the manuscript draft for important intellectual content.

Dr. Buring: Data interpretation, obtaining funding, critical revisions of the manuscript draft for important intellectual content.

Dr. Gaziano: Data interpretation, obtaining funding, critical revisions of the manuscript draft for important intellectual content.

Dr. Berger: Study design, data interpretation, critical revisions of the manuscript draft for important intellectual content.

Dr. Kurth: Study design and conception, data analysis, data interpretation, obtaining funding, critical revisions of the manuscript draft for important intellectual content.

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Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper.

Ethical approval

This study was approved by the Intuitional Review Board of Brigham and Women's Hospital, Boston (Protocol #: 2008-P-000613/3), MA, and all participants provided written informed consent.

Data sharing

No additional data available

Access to data

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

Conflict of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that this study has been funded by the National Institutes of Health, has no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work." Please see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests.

We report a full disclosure for the last 3 years for each author:

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Response to Reviewers' Comments

We appreciate the detailed and thorough comments of the associate editor and reviewers. We respond point-by-point and to the concerns raised by the reviewers. We have repeated the comments of the reviewers in italics before our response and indicate where we have made changes in the text of the paper, where appropriate.

Detailed comments from the BMJ meeting:

We thought this a well written and carefully analyzed study.
However, our main concern was that RLS is not sufficiently well known and the association with CVD not widely known about. As your paper reports a negative finding for a rare association that most readers will not know existed, overall we think it better suited to a specialty journal.

Response: Numerous cross-sectional studies have evaluated the association between RLS and CVD and reported positive association. Although the conclusions that can be drawn from cross-sectional studies are limited and a causal link between RLS and CVD cannot be established with this study design, these results have caused a lot of attention. Given the high prevalences of both RLS and CVD in the general population, a potential association would be relevant and have major public health consequences.

We think that the populations in these cohorts are probably not representative of patients who consult a doctor with the problem of RLS.

Response: While RLS may not appear to be an important issue in a general medicine practice, numerous population-based studies have shown that RLS is a very prevalent condition. Many patients with minor RLS symptoms do not seek medical care and only severe cases are treated by physicians. However, RLS is an important disease in the general population and evaluating risk factors and comorbidities of RLS on a more general population level have implications for the RLS populations seen by primary care physicians as well.

Our statistician had no major concerns about your paper except the handling of the missing data. You have used a missing value indicator method that has been shown in numerous studies to almost always result in biased estimates, so wonders why you did not opt for the multiple imputation method.

Response: While we understand the comment of the statistical editors, we believe that there are advantages and disadvantages to all methods dealing with missing data. We have carefully outweighed advantages and disadvantages of every single approach and decided to use the missing value indicator method for the following reasons. We have excluded missing information for our exposure and outcome of interest and have only used the missing value indicator approach for the covariate information. We have decided to choose this approach since a) with this approach we are only using real data and do not make any assumptions about the distributions of the covariates and the mechanisms led to the missing data (as In the multiple imputation method) b) the sample size/power/generalizability for the covariate with missing data and for the other covariates is at the maximum for the actually collected 'real' data. The effect estimate for the covariate could be biased if the reason that data are missing is related to the outcome and to the predictor. In addition, the effect estimates of other covariates may be biased. However, since we have chosen to include confounders based on a priori knowledge and not chosen any data driven selection algorithms, we consider this disadvantage of our missing data approach as negligible. Furthermore, the total number of missing covariate information in our cohort is fairly small (e.g. maximum of 4%). Thus, we believe that our approach is not biasing our analyses.

Reviewer Comments:

Reviewer: 1

1. Introduction: it is not clear how the hypotheses of sympathetic hyperactivity may rise from a clinical study. The statement is not clear (ref 15).

Response: Small clinical based studies have evaluated patients with periodic limb movement disorder (PLMS) and observed PLMS-related changes in heart rate and blood pressure. These changes were associated with EEG microarousals. Based on these observations it has been hypothesized that PLMS may be associated with sympathetic nerve hyperactivity. Since PLMS can occur in patients with RLS, it has been discussed that these transient elevations in heart rate and blood pressure occurring during the night may increase the risk for developing CVD events in patients with RLS. However, we believe that this information is too specific as introduction for this paper and we have simplified the section in the introduction.

2. Was the diagnosis of RLS validated within these cohorts? The MEMO study (ref 22 for validation) is a cross-sectional study in southern Germany where all subjects were examined neurologically and interviewed in person using standardized questions addressing the four minimal criteria for RLS. The WHS and PHS are based on mailed questionnaire. Is this relevant for the assessment? May the presence of neurological comorbidity be relevant?

Response: The issue on validation of RLS is not easy to answer. Based on the criteria established by the International Restless Legs Study Group (IRLSSG), RLS is defined by self reports and there is no diagnostic test confirming this disease. In two studies, self reported information has been validated against a physician's diagnosis (who is also referring to the criteria established by the IRLSSG). We have applied the identical 3-item RLS questionnaire which has been used and validated in the cited cohorts from Germany and Italy. In our methods paragraph outlining the RLS assessment (page 7), we cite two different RLS studies using data from the MEMO cohort. As mentioned by the reviewer, two trained physicians assessed RLS by using the 3-item standardized questionnaire in the study by Rothdach et al (reference 22). Along with references 20-21, we cite reference 22 in the context of studies that have used and established the 3-item questionnaire we have assessed our RLS cases with. In the second study using data of the MEMO cohort (reference 23), Berger et al. performed a validation of this questionnaire comparing the RLS classification based on the questionnaire against a RLS diagnosis of an examining neurologist, yielding a high degree of concordance (kappa=0.67). The statistical properties of the 3-item questionnaire were also very good with a sensitivity of 87.5% and a specificity of 95.6%. As our studies are very large, we obviously cannot validate the RLS self-reports against a physician diagnosis. However, the main aspect of a physician's diagnosis of RLS is to rule out other conditions that can mimic RLS symptoms, in particular diabetes and peripheral neuropathy. We have information available about a long list of potential co-morbid conditions that could result in RLS mimics and we have performed careful sensitivity analysis and reported the results (which are similar to our main findings). As both of our cohorts are composed of health professionals that have been shown to very accurately provide health related information, we believe that our sensitivity analyses sufficiently address potential misdiagnosis/categorization of RLS.

3. The lack of information on duration of the RLS may undermine some of the results of the study.

Response: Results of a previous study evaluating the association between RLS and CVD do not indicate an association between duration of RLS symptoms and CVD.[1] Thus, we believe that this is unlikely a major issue in our data.

4. The presentation as the results of sensitivity analyses with the statement "the association remained insignificant " with CI 0.99 to 2.05 is not convincing.

Response: When comparing the main effects, the results are not very different. Based on the a priori chosen alpha cutoff, the results are of the sensitivity analysis are not significant. However, we have removed that statement that the association remained insignificant.

5. No discussion on the results on stroke is present.
Our study shows no association between RLS and major CVD as well as the individual endpoints. There is a suggestion from out sensitivity analysis that the risk of total stroke may be increased (RR=1.42 (0.99 to 2.05)). We have now included brief statements about this fact when discussing the positive result of a Swedish study (on page 12). However, we believe that this finding is only a suggestion and we do not want to put a main focus on results of secondary analyses that do technically not reach the significance level.

Reviewer: 2
This analysis is of observational data from two trials.
The paper is of significance to clinicians as it clarifies the ambiguity surrounding the clinical importance of RLS, a frequently reported symptom. It makes a significant contribution to the debate on the association between restless legs syndrome (RLS) and vascular disease; adding to the single other longitudinal study reported to date.
The design of the studies is critical in providing longitudinal data. The studies are sufficiently large, have been rigorously conducted and appropriately analyzed.

It would be helpful for the authors to clarify in the PHS analysis, for the 7641 PHS II participants who also participated in PHS I, (presumably completing RLS questions in both) which were used in the analysis. That the follow-up period is slightly shorter and the population more healthy than the previous study are not significant objections to the author's interpretation of their findings.

Response: While participants in both PHS cohorts received the questionnaire containing the RLS questions approximately at the same time, the two cohorts differ somewhat in age and prevalent comorbidities. As we, however, have tested for effect modification by age and other variables and we have found no significant results, we do not believe that these differences have influenced our results.

The authors' interpretation of the findings is inconsistent. The findings are interpreted to show that RLS is not implicated in the causal pathway to vascular disease, but may be an indicator of poor health, including vascular health. This is entirely reasonable. However, their application is less clear. If RLS is a marker for vascular co-morbidities, then it is a marker for increased risk of vascular disease, contrary to the last sentence of the abstract. The solution is to make clear the distinction between a marker for disease risk and a determinant of disease risk. The double negative in the first sentence of the clinical implications section compounds this difficulty. This section should be re-written to state more clearly the authors' view.

Response: Based on the lack of clear biological concept why RLS should lead to CVD, we do not want to argue that RLS is a causal factor (i.e., risk factor). We thus have opted to call RLS a

marker of risk similar to other concepts (such as C - reactive protein being a marker of increased risk for CVD). We have edited the text to avoid confusion about this point.

This is an important paper as it clarifies the ambiguity surrounding the clinical significance of RLS.
I recommend its publication once clarifications have been made.
Note: There is a typo in page 7, paragraph 2 line 1 word 1.

Response: We have edited the text.

References

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STROBE statement checklist of items that should be included in reports of observational studies

Title of study: Restless legs syndrome and risk of incident cardiovascular disease in women and men: prospective cohort study

Corresponding author: Tobias Kurth

	Item No	Recommendation		Page in Manuscript
Title and abstract				
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	☒	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	☒	3
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	☒	5
Objectives	3	State specific objectives, including any prespecified hypotheses	☒	5
Methods				
Study design	4	Present key elements of study design early in the paper	☒	6ff
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☒	6ff
Participants	6	(*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. *Case-control study*? Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. *Cross sectional study*? Give the eligibility criteria, and the sources and methods of selection of participants	☒	6ff
		(*b*) *Cohort study*?For matched studies, give matching criteria and number of exposed and unexposed*Case-control study*?For matched studies, give matching criteria and the number of controls per case	☐	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	☒	8ff

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	☒	8ff
Bias	9	Describe any efforts to address potential sources of bias	☒	14ff
Study size	10	Explain how the study size was arrived at	☒	8ff
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	☒	8ff
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	☒	8ff
		(*b*) Describe any methods used to examine subgroups and interactions	☒	8ff
		(*c*) Explain how missing data were addressed	☒	8ff
		(*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed. *Case-control study*? If applicable, explain how matching of cases and controls was addressed. *Cross sectional study*? If applicable, describe analytical methods taking account of sampling strategy	☒	8ff
		(*e*) Describe any sensitivity analyses	☒	8ff
Results				
Participants	13*	(*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☒	10ff
		(*b*) Give reasons for non-participation at each stage	☐	n/a
		(*c*) Consider use of a flow diagram	☐	n/a
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	☒	10ff
		(*b*) Indicate number of participants with missing data for each variable of interest	☒	8ff
		(*c*) *Cohort study*? Summarise follow-up time (eg average and total amount)	☒	10ff
Outcome data	15*	*Cohort study*? Report numbers of outcome events or summary measures over time	☒	10ff
		Case-control study? Report numbers in each exposure category, or summary measures of	☐	n/a

		exposure		
		Cross sectional study? Report numbers of outcome events or summary measures	☐	n/a
Main results	16	(*a*) Report the numbers of individuals at each stage of the study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	☒	10ff
		(*b*) Give reasons for non-participation at each stage	☐	n/a
		(*c*) Consider use of a flow diagram	☐	n/a
Other analyses	17	Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses	☒	10ff
Discussion				
Key results	18	Summarise key results with reference to study objectives	☒	12ff
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	☒	14ff
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☒	15ff
Generalisability	21	Discuss the generalisability (external validity) of the study results	☒	14ff
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	☒	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross sectional studies.

This article and separate versions of the checklist for cohort, case-control, and cross sectional studies are available at www.strobe-statement.org.