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Vascular risk factors, cardiovascular disease and restless legs syndrome in women

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Abstract

Background—Previous studies evaluating the association between cardiovascular disease and vascular risk factors with restless legs syndrome showed inconsistent results, especially for the potential relation between various vascular risk factors and restless legs syndrome. We therefore aimed to analyze the relationship between vascular risk factors, prevalent cardiovascular disease and restless legs syndrome.

Methods—This is a cross-sectional study of 30,262 female health professionals participating in the Women's Health Study (WHS). Restless legs syndrome was defined according to diagnostic criteria of the International Restless Legs Study Group. Information on vascular risk factors (diabetes, hypertension, hypercholesterolemia, body mass index, alcohol, smoking, exercise, family history of myocardial infarction) was self-reported. Cardiovascular disease events (coronary revascularization, myocardial infarction, stroke) were confirmed by medical record review. Prevalent major cardiovascular disease was defined as non-fatal stroke or non-fatal myocardial infarction. Logistic regression models were used to evaluate the association between vascular risk factors, prevalent cardiovascular disease and restless legs syndrome.

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Results—Of the 30,262 participants (mean age: 63.6 years), 3,624 (12.0%) reported restless legs syndrome. In multivariable-adjusted models, body mass index (OR for BMI ≥35kg/m^2: 1.35, 95% CI: 1.17–1.56), diabetes (OR: 1.19, 95%CI: 1.04–1.35), hypercholesterolemia (OR: 1.17, 95% CI: 1.09–1.26), smoking status (OR for ≥15 cigarettes/day: 1.41, 95%CI: 1.19–1.66) and exercise (OR for exercise ≥ 4 times/week: 0.84, 95%CI: 0.74–0.95) were associated with restless legs syndrome prevalence. We found no association between prevalent cardiovascular disease (major cardiovascular disease, myocardial infarction, stroke) and restless legs syndrome prevalence. Women who underwent coronary revascularization had a multivariable-adjusted OR of 1.39 (1.10–1.77) for restless legs syndrome.

Conclusion—In this large cohort of female health professionals, various vascular risk factors are associated with restless legs syndrome prevalence. We could not confirm results of previous reports indicating an association between prevalent cardiovascular disease and restless legs syndrome.

Keywords

Vascular risk factors; cardiovascular disease; Restless legs syndrome; cohort study

Introduction

Restless legs syndrome is a neurological disorder characterized by an urge to move the legs usually accompanied by unpleasant leg sensations. The symptoms predominantly occur in the evening and at night. Inactivity and rest worsen the symptoms while patients experience relief by movement. The International Restless Legs Syndrome Study Group has published minimal diagnostic criteria to facilitate a standardized diagnosis of this disorder which is purely symptom based.[1, 2] According to results from population-based studies that have applied the minimal diagnostic criteria, the prevalence of restless legs syndrome ranges between 6–12 %, women being predominately affected.[3] The mechanisms causing restless legs syndrome are not fully understood. Research involving pharmacological, endocrinological and neuroimaging studies suggest a dysfunction of the dopaminergic system as an important pathophysiological concept.[4] In addition, studies have shown a genetic predisposition for restless legs syndrome.[5]

Restless legs syndrome is associated with many comorbidities and especially the potential relationship between cardiovascular diseases and restless legs syndrome has been evaluated in several studies suggesting an association between the two entities.[6–14] An unfavorable vascular risk factor profile among restless legs syndrome sufferers has been proposed as a potential mechanism linking cardiovascular disease and restless legs syndrome, but cross-sectional studies evaluating the association between various vascular risk factors and RLS have shown inconsistent results.[10, 12, 15–18] Potential explanations for these inconsistent results across studies include differences in study design and populations as well as varying definitions of restless legs syndrome and the various outcome variables.

We therefore aim to evaluate the association between vascular risk factors, prevalent cardiovascular disease, and restless legs syndrome in a cohort of women using data from the Women's Health Study (WHS).

Methods

Study Population

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 cardiovascular disease and

cancer among apparently healthy women. The design, methods and results have been described in detail previously.[19, 20] Briefly, a total of 39,876 US female health care professionals aged 45 years or older at study entry (1992–1995) without a history of cardiovascular disease, 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. All participants provided written informed consent, and the institutional review board of Brigham and Women's Hospital, Boston, MA, approved the WHS. Baseline information was self-reported and collected by a mailed questionnaire that asked about several 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.

Assessment of restless legs syndrome

A short questionnaire addressing the four minimal diagnostic criteria of the International Restless Legs Study Group[1] has been implemented in the 108-month follow-up questionnaire. Participants were asked to answer the following questions: “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?” For all questions, the response choices were “Yes”, “No”, or “I don't know”. Participants who answered yes to all of the three questions were defined as having restless legs syndrome. This questionnaire has been established and validated in previous studies from Germany and Italy.[15, 21–23]

Vascular risk factor ascertainment

Participants were asked to report information on cardiovascular disease risk factors at baseline and information was updated through follow-up. We included the most recent updated information on cardiovascular disease risk factors available with regard to time of restless legs syndrome assessment (108-month follow-up questionnaire). We distinguished the following cardiovascular disease risk factors: history of hypertension (yes/no), history of diabetes (yes/no), history of cholesterol ≥240mg/dl (yes/no), alcohol consumption (rarely/never, 1–3 drinks/months, 1–6 drinks/week, ≥1 drink/day), exercise (rarely/never, <1/week, 1–3 times/week, ≥4 times/week), body mass index (<23, 23–24.9, 25–29.9, 30–34.9, ≥35kg/m^2), smoking status (never, past, current <15 cigarettes/day, current ≥15 cigarettes/day), and parental history of myocardial infarction prior to age 60 (yes/no). Body mass index was calculated based on self-reported height and weight and we distinguished the following categories: <23, 23–24.9, 25–29.9, 30–34.9, ≥35kg/m^2. History of hypertension was defined as blood pressure ≥140 mmHg systolic or ≥ 90 mmHg diastolic or receiving antihypertensive treatment.

Assessment of cardiovascular disease events

Participants self-reported cardiovascular events and coronary revascularization. Medical records were obtained for all cardiovascular events and coronary revascularizations and reviewed by an end-points committee of physicians. Nonfatal stroke was confirmed if the participant had a new focal-neurological deficit of sudden onset that persisted for >24 hours and was classified into its major subtypes based on available clinical and diagnostic information with excellent interrater agreement.[24] The occurrence of myocardial infarction was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiogram results. Deaths were confirmed by review of autopsy reports, death certificates, medical records, or information obtained from next of kin or family members. Major cardiovascular disease was

defined as a combined end-point of any of these events: non-fatal myocardial infarction and non-fatal stroke.

For the purpose of this analysis, we included all confirmed prevalent cardiovascular events up to the 108-months follow-up questionnaire.

Statistical analysis

Of the 33,092 women in active follow-up at the 108-month questionnaire, we excluded 1,722 women with missing information for all three restless legs syndrome questions as well as women with missing information on body mass index (n=492), smoking status (n=441), alcohol consumption (n=188), exercise (n=12) and family history of myocardial infarction (n=141), leaving a total of 30,262 women for this analysis, taking into consideration missing information on multiple vascular risk factors for some women.

Baseline characteristics according to restless legs syndrome status were compared using chi-square-test for categorical and t-test for continuous variables. Age- and multivariable-adjusted logistic regression models were used to evaluate the association between the various vascular risk factors and restless legs syndrome with women with no history of restless legs syndrome as the reference group. We further evaluated the association between prevalent cardiovascular disease events and restless legs syndrome using age- and multivariable-adjusted logistic regression models and calculated odds ratios (ORs) and their corresponding 95% confidence intervals (CIs).

In the model evaluating the association between vascular risk factors and restless legs syndrome, restless legs syndrome case status was the dependent variable and independent variables were family history of myocardial infarction prior to age 60 years (yes/no), history of diabetes (yes/no), body mass index (23, 23–24.9, 25–29.9, 30–34.9, ≥35kg/m^2), smoking status (never, past, current <15 cigarettes/day, current ≥15 cigarettes/day, history of hypertension, exercise (rarely/never, <1/week, 1–3 times/week, ≥4 times/week), and alcohol consumption (rarely/never, 1–3 drinks/months, 1–6 drinks/week, ≥1 drink/day). This model was adjusted for age (continuous), randomized aspirin assignment (yes/no), postmenopausal status (premenopausal, postmenopausal, biologically uncertain, unclear/subject unsure), postmenopausal hormone use (never, past, current) and history of oral contraceptive use (no history, any history, unsure).

The multivariable-adjusted models evaluating the associations between prevalent cardiovascular disease events and restless legs syndrome status were adjusted for age, randomized aspirin assignment, history of depression, postmenopausal status, postmenopausal hormone use, history of oral contraceptive use, and all vascular risk factors as used in the first model.

Additional adjustment for race, geographic region, history of migraine, history of Parkinson's disease, being fatigued, iron supplementation use, number of pregnancies, age at menarche and analgesic use (nsaids,cox2 inhibitors, aspirin, aspirin containing drugs and acetaminophen) did not chance the effect estimates by more than 10% in multivariable-adjusted models evaluating vascular risk factors or prevalent cardiovascular disease events.

We evaluated effect modification of the association between prevalent cardiovascular disease events and restless legs syndrome prevalence by age (<60, 60–70, 70–80, ≥80 years), history of hypertension (yes/no), body mass index (<25kg/m^2, 25–29.9kg/m^2, ≥30kg/m^2), smoking status (never, past, current) and iron supplementation use (yes/no).

We performed a sensitivity analysis by excluding women with a history of polyneuropathy, kidney disease/kidney failure, liver disease, rheumatoid arthritis, intermittent claudication and those who underwent peripheral artery disease surgery. In a second sensitivity analysis approach, we only excluded women with diabetes as a confounder in the models evaluating the association between cardiovascular disease events and restless legs syndrome.

A missing value indicator was incorporated in the outcome models for covariates if the number of women with missing information was ≥100. We assigned women with missing values to the reference category if the number of missing information was <100.

For all analyses, we used SAS (version 9.1.3, SAS Institute Inc. Cary, NC). All p values were 2-tailed and $p < 0.05$ was considered statistically significant.

Results

Of the 30,262 participants, 3,624 (12.0%) met the minimal diagnostic criteria for restless legs syndrome.

Baseline characteristics according to presence of restless legs syndrome

Women with restless legs syndrome were more likely to have a history of hypertension, diabetes, hypercholesterolemia, and a parental history of myocardial infarction (Table 1). They were more likely to experience a myocardial infarction and to undergo a coronary revascularization procedure. With regard to lifestyle factors, women with restless legs syndrome were more likely to have a body mass index ≥30kg/m^2, to rarely/never drink, to rarely/never exercise, and to currently smoke. In addition, they were more likely to report a history of depression and migraine.

Vascular factors associated with restless legs syndrome

In examining the association between vascular risk factors and restless legs syndrome, hypercholesterolemia, diabetes, and body mass index showed increased odds for restless legs syndrome in age-adjusted models (Table 2). These associations attenuated, but stayed significant after further adjustment. In addition, we found a significant association between smoking status and restless legs syndrome which remained stable after adjustment for covariates. The observed association between history of hypertension, parental history of myocardial infarction and restless legs syndrome in age-adjusted models diminished after further adjustment. We found a decreasing odds for restless legs syndrome with increasing levels of exercise with only significant results for women who exercise ≥4 times/week.

Prevalent cardiovascular disease and restless legs syndrome

From baseline up to the 108-month follow-up, 467 major cardiovascular disease events, 234 myocardial infarctions, and 237 strokes were confirmed and 486 women underwent coronary revascularization procedures (Table 3). We found no statistically significant associations between major cardiovascular disease, myocardial infarction or stroke and restless legs syndrome prevalence in multivariable-adjusted models. Women who underwent coronary revascularization had an increased adjusted odds for restless legs syndrome compared with women with no intervention.

The associations between the various cardiovascular disease events and restless legs syndrome were not significantly modified by the presence of age or other vascular risk factors.

In sensitivity analyses excluding women with potential secondary causes for restless legs syndrome the association between cardiovascular disease risk factors and restless legs syndrome were very similar; however, the observed association for diabetes was no longer significant (data presented in appendix table 1). With respect to the association between cardiovascular disease events and restless legs syndrome, all associations further attenuated, especially the relationship between coronary revascularization and restless legs syndrome was no longer significant (appendix table 2).

Excluding diabetes as confounder did not substantially chance the associations (data not presented).

Discussion

In this large cross-sectional study of female health professionals aged 45 years and older at study entry, the cardiovascular disease risk factors history of diabetes, history of cholesterol ≥240mg/dl, smoking status, exercise, and body mass index were associated with restless legs syndrome prevalence. We found no association between prevalent major cardiovascular disease, myocardial infarction, or stroke and restless legs syndrome. Women who underwent coronary revascularization had a multivariable-adjusted OR of 1.39 (95% CI=1.10–1.77) for restless legs syndrome. However, after excluding women with potential secondary causes for restless legs syndrome, this association further attenuated and was no longer significant.

Several previous studies are in line with our finding of an association between cardiovascular risk factors including smoking,[10, 17, 25, 26] diabetes,[15, 17, 25] hypercholesterolemia,[18] exercise,[16] body mass index,[10, 16, 27] and restless legs syndrome prevalence. In contrast, other studies did not agree with our results.[9, 12, 22] In a recently published cross-sectional study among 65,544 female participants of the Nurses Health Study II, restless legs syndrome was associated with an adjusted OR of 1.20 (95% CI=1.10–1.30) for hypertension.[28] The association increased with increasing restless legs syndrome frequency. Women in the highest restless legs syndrome frequency category (≥15 times per month) had an OR of 1.41 (95% CI=1.24–1.61) for hypertension. In our study we had no information about restless legs syndrome frequency no allowing us to further study the association between restless legs syndrome frequency and hypertension.

The prevalence of restless legs syndrome varies by age and gender; hence, study results may differ depending on the age and gender distribution of the respective study populations. In the Study of Health in Pomerania, diabetes was only significantly associated with restless legs syndrome prevalence in older adults while smoking was only related to restless legs syndrome in younger participants after stratifying for age.[15] In addition, the association between body mass index, alcohol consumption, smoking status and restless legs syndrome varied by gender in a cross-sectional study from Korea.[16]

The mechanisms linking cardiovascular disease risk factors with restless legs syndrome are yet to be determined. One potential explanation includes common genetic predisposition and shared pathophysiological pathways. For example, studies suggest that both obesity and restless legs syndrome are associated with alterations of the central dopaminergic system.[4, 29] However, hypotheses involving pathophysiological pathways of restless legs syndrome should be drawn carefully since the underlying mechanisms of restless legs syndrome are not fully understood. The potential relationship between restless legs syndrome and obesity might also be mediated by sleep deprivation, a feature affecting most restless legs syndrome sufferers.[30] For example, studies indicate that sleep deprivation is associated with endocrine system alterations including reduced leptin levels, impaired glucose tolerance and elevated evening cortisol levels which can lead to obesity.[31, 32] A

third potential explanation for the association between restless legs syndrome and cardiovascular disease risk factors includes lifestyle habits, which may act as mediators. Two recently published case-control studies suggest that restless legs syndrome is associated with specific unfavorable lifestyle habits including nocturnal smoking and sleep related eating disorder.[33, 34] These findings raise the question whether restless legs syndrome results in a higher prevalence of lifestyle related comorbidities (e.g. obesity and smoking) or vice versa. However, the cross-sectional design of our study and previous reports does not allow drawing conclusions regarding direction and causality of the association.

In contrast to several other cross-sectional studies,[6, 9–14] results of our study do not suggest an association between prevalent cardiovascular disease including stroke and myocardial infarction and restless legs syndrome. Results from a population based study using data from Iceland and Sweden support our finding.[35] Women who underwent coronary revascularization procedures had an increased OR for restless legs syndrome in our cohort. However, after excluding women with potential secondary restless legs syndrome forms, the associations further attenuated supporting the notion that the association between cardiovascular disease and restless legs syndrome is mediated by comorbidities and might be limited to restless legs syndrome sufferers with secondary forms. The lack of association between restless legs syndrome and cardiovascular disease is further supported by a recent study showing that restless legs syndrome is not associated with the development of cardiovascular disease in men and women.[36]

Our approach to evaluate the association between prevalent cardiovascular disease and restless legs syndrome differs from other studies which might explain inconsistencies. The majority of studies reporting an association between cardiovascular disease and restless legs syndrome has included coronary revascularization procedures and/or angina in their cardiovascular disease definition[6, 9, 13, 14] or has chosen self-reported heart disease[10–12] while we have distinguished between coronary revascularization procedures, myocardial infarction, and stroke in addition to looking at major cardiovascular disease. Furthermore, assessment of cardiovascular disease was based on self-reported questionnaire data in most of the studies and not confirmed as in our study. However, the cross-sectional study design of our and previous studies does not allow a final answer the question whether RLS is associated with cardiovascular disease.

Study Strengths and Limitations

Our study has several strengths including the large size, the standardized assessment of restless legs syndrome according to the four minimal diagnostic criteria of the International Restless Legs Study Group and the detailed information on prevalent cardiovascular disease events which were confirmed by medical records. Furthermore, information on a variety of covariates was available allowing us to account for a number of potential confounders. The following limitations should be considered. First, information on restless legs syndrome was self-reported and misclassification is possible. However, our restless legs syndrome prevalence of 12.0% is similar to the prevalence reported in other studies.[3] Second, restless legs syndrome symptoms were self-reported and misclassification is possible. However, we used a questionnaire that has been validated before.[21] In addition, our cohort consists of female health professionals who are known to accurately report health information based on validation studies in our cohort and in other cohorts.[37, 38] Lastly, our cohort consists of female health professionals aged 45 and older at study entry which limits the generalizability of our results to other populations.

In summary, several cardiovascular disease risk factors including diabetes, hypercholesterolemia, body mass index, smoking status and exercise were associated with restless legs syndrome prevalence in our study, but we could not confirm results from

previous studies indicating an association between prevalent cardiovascular disease and restless legs syndrome.

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Conflict of interest We report a full disclosure for the last 3 years for each author: Dr. Winter has received an international postdoctoral research fellowship of the American Association of University Women and a research fellowship of the German Research Foundation.

Dr. Schürks has received an investigator-initiated research grant from the Migraine Research Foundation. He has received honoraria from L.E.K. Consulting for telephone surveys and from the American Academy of Neurology for educational material. Since August 2011 he is full-time employee of Bayer HealthCare Pharmaceuticals, Germany.

Dr. Glynn has received investigator-initiated research funding and support from the National Institutes of Health, AstraZeneca, and Novartis; and has received honoraria from Merck for lectures.

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Dr. Gaziano has received investigator-initiated research funding and support as Principal Investigator from National Institutes of Health, BASF, DSM Pharmaceuticals, Wyeth Pharmaceuticals, McNeil Consumer Products and Pliva; received honoraria from Bayer and Pfizer for speaking engagements, and is a consultant for Bayer, McNeil Consumer Products, Wyeth Pharmaceuticals, Merck, Nutraquest and GlaxoSmithKline.

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Appendix

Appendix Table 1

sensitivity analysis*. Age- and multivariable-adjusted† OR's (95% CI) for RLS according to vascular risk factors (n=28,015)

	No RLS	RLS	Age-adjusted	Multivariable-adjusted
	24,732	3,283	OR (95% CI)	OR (95% CI)
History of hypertension	11,569	1,652	1.16 (1.08, 1.25)	1.04 (0.96, 1.13)
History of diabetes	1,610	268	1.28 (1.12, 1.46)	1.13 (0.98, 1.30)
History of cholesterol ≥ 240mg/dl	13,106	1,908	1.24 (1.15, 1.33)	1.17 (1.08, 1.26)
BMI categories				

	No RLS	RLS	Age-adjusted	Multivariable-adjusted
	24,732	3,283	OR (95% CI)	OR (95% CI)
<23	5,864	679	1.00	1.00
23–24.9	4,524	559	1.07 (0.95, 1.20)	1.04 (0.93, 1.18)
25–29.9	8,480	1,148	1.17 (1.06, 1.29)	1.12 (1.01, 1.24)
30–34.9	3,856	558	1.25 (1.11, 1.41)	1.16 (1.02, 1.32)
≥35	2,008	339	1.46 (1.27, 1.69)	1.34 (1.15, 1.56)
Smoking Status				
Never	12,901	1,550	1.00	1.00
Past	9,868	1,441	1.22 (1.13, 1.31)	1.22 (1.13, 1.32)
Current < 15 cigarettes/day	985	139	1.17 (0.98, 1.41)	1.21 (1.00, 1.46)
Current ≥ 15 cigarettes/day	978	153	1.30 (1.09, 1.56)	1.31 (1.09, 1.57)
Alcohol consumption				
Rarely/never	10,397	1,449	1.00	1.00
1–3 drinks per month	2,883	384	0.96 (0.85, 1.08)	0.96 (0.85, 1.08)
1–6 drinks per week	8,553	1,087	0.91 (0.84, 0.99)	0.92 (0.84, 1.00)
≥1 drink/day	2,899	363	0.90 (0.80, 1.02)	0.90 (0.80, 1.03)
Exercise				
Rarely/never	9,258	1,285	1.00	1.00
<1/week	4,894	673	0.99 (0.90, 1.09)	1.01 (0.91, 1.12)
1–3 times/week	7,797	1,017	0.94 (0.86, 1.03)	0.98 (0.90, 1.07)
≥ 4 times/week	2,783	308	0.80 (0.70, 0.91)	0.85 (0.74, 0.97)
Parental history of myocardial infarction	4,207	625	1.15 (1.05, 1.26)	1.11 (1.01, 1.22)

*2,247 women with a history of polyneuropathy, kidney disease/kidney failure, liver disease, rheumatoid arthritis, intermittent claudication or who underwent peripheral artery disease surgery were excluded.

†Multivariable models include all vascular risk factors and were adjusted for age, randomized aspirin assignment, postmenopausal status, postmenopausal hormone use, oral contraceptive use.

Appendix Table 2

sensitivity analysis* Age- und multivariable-adjusted† OR's (95% CI) for RLS according to prevalent CVD events (n=28,015)

	No RLS history	Any history of RLS
	n=24,732	n=3,283
Major CVD event	n=349	n=47
Age-adjusted	1.00	1.02 (0.75, 1.38)
Multivariable-adjusted	1.00	0.91 (0.67, 1.24)
Coronary revascularization	n=329	n=60
Age-adjusted	1.00	1.39 (1.05, 1.83)
Multivariable-adjusted	1.00	1.20 (0.91, 1.60)
Myocardial infarction	n=163	n=27
Age-adjusted	1.00	1.25 (0.83, 1.89)
Multivariable-adjusted	1.00	1.10 (0.73, 1.66)

	No RLS history n=24,732	Any history of RLS n=3,283
Stroke	n=188	n=20
Age-adjusted	1.00	0.80 (0.50, 1.27)
Multivariable-adjusted	1.00	0.73 (0.46, 1.16)

*2,247 women with a history of polyneuropathy, kidney disease/kidney failure, liver disease, rheumatoid arthritis, intermittent claudication or who underwent peripheral artery disease surgery were excluded.

†Multivariable models were adjusted for age, randomized aspirin assignment, parental history of myocardial infarction, history of diabetes, body mass index, smoking status, alcohol consumption, history of hypertension, exercise, hypercholesterolemia, history of depression, postmenopausal hormone use, postmenopausal status, and oral contraceptive use

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Table 1

Baseline characteristics according to RLS status (n=30,262)

	No RLS	RLS	p-value
	n=26,638	n=3,624	
Demographic information			
Mean age, yrs (SD)	63.6 (6.9)	63.6 (6.9)	0.86
Ethnicity, %			
White	25,138 (95.1)	3,512 (97.5)	<0.01
Geographic location,%			
Northeast	5,216 (19.6)	623 (17.2)	
Southeast	6,093 (22.9)	859 (23.7)	<0.01
Midwest	9,553 (35.9)	1,359 (37.5)	
West	5,734 (21.6)	780 (21.5)	
Prevalent CVD events, %			
Major CVD	406 (1.5)	61 (1.7)	0.47
Coronary revascularization	398 (1.5)	88 (2.4)	<0.01
Myocardial infarction	194 (0.7)	40 (1.1)	0.02
Stroke	215 (0.8)	22 (0.6)	0.20
CVD risk factors, %			
History of hypertension	12,721 (47.8)	1,880 (51.9)	<0.01
History of diabetes	1,890 (7.1)	340 (9.4)	<0.01
History of cholesterol ≥ 240mg/dl	14,317 (53.8)	2,137 (59.0)	<0.01
BMI categories (kg/m^2)			
<23	6,250 (23.5)	735 (20.3)	
23–24.9	4,807 (18.1)	612 (16.9)	
25–29.9	9,120 (34.2)	1,249 (34.5)	<0.01
30–34.9	4,221 (15.9)	634 (17.5)	
≥35	2,240 (8.4)	394 (10.9)	
Smoking Status			
Never	13,800 (51.8)	1,694 (46.7)	
Past	10,673 (40.1)	1,589 (43.9)	<0.01
Current < 15 cigarettes/day	1,084 (4.1)	154 (4.3)	
Current ≥ 15 cigarettes/day	1,081 (4.1)	187 (5.2)	
Alcohol consumption			
Rarely/never	11,412 (42.8)	1,645 (45.4)	
1–3 drinks per month	3,096 (11.6)	411 (11.3)	0.03
1–6 drinks per week	9,065 (34.0)	1,170 (32.3)	
≥ 1 drink/day	3,065 (11.5)	398 (11.0)	
Exercise			
Rarely/never	10,066 (37.8)	1,439 (39.7)	
<1/week	5,287 (19.9)	753 (20.8)	<0.01
1–3 times/week	8,313 (31.2)	1,101 (30.4)	

	No RLS	RLS	p-value
≥ 4 times/week	2,972 (11.2)	331 (9.1)	
Parental history of myocardial infarction	4,571 (17.2)	692 (19.1)	<0.01
Other covariates, %			
History of migraine during follow-up	5,645 (21.2)	962 (26.6)	<0.01
History of depression	3,194 (12.0)	729 (20.1)	<0.01
History of Parkinson's disease	111 (0.4)	19 (0.5)	0.35
Iron supplementation use	1,049 (4.0)	126 (3.5)	0.17

Percentages may not add up to 100 because of missing values or rounding

Table 2

Age- and multivariable-adjusted* OR's (95% CI) for RLS according to vascular risk factors (n=30,262)

	No RLS	RLS	Age-adjusted	Multivariable-adjusted*	P for trend
	26,638	3,624	OR (95% CI)	OR (95% CI)	
History of hypertension	12,721	1,880	1.19 (1.11, 1.28)	1.06 (0.98, 1.15)	
History of diabetes	1,890	340	1.36 (1.20, 1.53)	1.19 (1.04, 1.35)	
History of cholesterol ≥ 240mg/dl	14,317	2,137	1.24 (1.16, 1.33)	1.17 (1.09, 1.26)	
BMI categories					<0.01
<23	6,250	735	1.00	1.00	
23–24.9	4,807	612	1.08 (0.97, 1.21)	1.06 (0.94, 1.19)	
25–29.9	9,120	1,249	1.17 (1.06, 1.28)	1.11 (1.00, 1.22)	
30–34.9	4,221	634	1.28 (1.14, 1.43)	1.18 (1.04, 1.33)	
>35	2,240	394	1.50 (1.32, 1.72)	1.35 (1.17, 1.56)	
Smoking Status					
Never	13,800	1,694	1.00	1.00	
Past	10,673	1,589	1.21 (1.13, 1.31)	1.22 (1.13, 1.31)	
Current < 15 cigarettes/day	1,084	154	1.16 (0.97, 1.38)	1.19 (1.00, 1.42)	
Current ≥ 15 cigarettes/day	1,081	187	1.41 (1.20, 1.66)	1.41 (1.19, 1.66)	
Alcohol consumption					
Rarely/never	11,412	1,645	1.00	1.00	
1–3 drinks per month	3,096	411	0.92 (0.82, 1.03)	0.93 (0.83, 1.04)	0.04
1–6 drinks per week	9,065	1,170	0.89 (0.83, 0.97)	0.92 (0.84, 1.00)	
≥ 1 drink/day	3,065	398	0.90 (0.80, 1.01)	0.92 (0.81, 1.04)	
Exercise					
Rarely/never	10,066	1,439	1.00	1.00	
<1/week	5,287	753	1.00 (0.91, 1.09)	1.02 (0.93, 1.12)	0.03
1–3 times/week	8,313	1,101	0.93 (0.85, 1.01)	0.98 (0.90, 1.06)	
≥ 4 times/week	2,972	331	0.78 (0.69, 0.88)	0.84 (0.74, 0.95)	
Parental history of myocardial infarction	4,571	692	1.14 (1.04, 1.25)	1.10 (1.00, 1.20)	

* Multivariable models include all vascular risk factors and were adjusted for age, randomized aspirin assignment, postmenopausal status, postmenopausal hormone use, oral contraceptive use

Table 3

Age- und multivariable-adjusted[a] OR's (95% CI) for RLS according to prevalent CVD events (n=30,262)

	No RLS history n=26,638	Any history of RLS n=3,624
Major CVD event	n=406	n=61
Age-adjusted	1.00	1.11 (0.85, 1.46)
Multivariable-adjusted	1.00	0.98 (0.74, 1.29)
Coronary revascularization	n=398	n=88
Age-adjusted	1.00	1.65 (1.31, 2.09)
Multivariable-adjusted	1.00	1.39 (1.10, 1.77)
Myocardial infarction	n=194	n=40
Age-adjusted	1.00	1.53 (1.09, 2.15)
Multivariable-adjusted	1.00	1.32(0.93, 1.87)
Stroke	n=215	n=22
Age-adjusted	1.00	0.75 (0.48, 1.17)
Multivariable-adjusted	1.00	0.68 (0.44, 1.06)

[a]Multivariable models were adjusted for age, randomized aspirin assignment, parental history of myocardial infarction, history of diabetes, BMI, smoking status, alcohol consumption, history of hypertension, exercise, hypercholesterolemia, history of depression, postmenopausal hormone use, postmenopausal status and oral contraceptive use