Published in final edited form as:
Am J Med. 2013 March ; 126(3): 228–235.e2. doi:10.1016/j.amjmed.2012.06.039.

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

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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.

Dr. Buring has received investigator-initiated research funding and support from the National Institutes of Health and Dow Corning Corporation; research support for pills and/or packaging from Bayer Health Care and the Natural Source Vitamin E Association.

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.

Dr. Berger has received investigator-initiated research funding as principal or coordinating investigator in the areas of diabetes, depression and subclinical atherosclerosis, multimorbidity and health services research from the German Ministry of Research and Technology (BMBF). In addition, for the conduction of an ongoing study on the Course of Restless Legs Syndrome he has received unrestricted grants to the University of Muenster from the German Restless Legs Society and a consortium with equal shares formed by Boehringer Ingelheim Pharma, Mundipharma Research, Neurobiotec, UCB Germany and Switzerland, Vifor Pharma and Roche Pharma.

Dr. Kurth has received investigator-initiated research funding from the French National Research Agency, the US National Institutes of Health, Merck, the Migraine Research Foundation, and the Parkinson's disease Foundation. He is a consultant to World Health Information Science Consultants, LLC, and has received honoraria from the BMJ for editorial work, from the American Academy of Neurology and Merck for educational lectures and from MAP Pharmaceutical for contributing to a scientific advisory panel.

Authors' contributions

Dr. Winter: Study design, data analysis, data interpretation, writing manuscript

Dr. Berger: 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. Schürks: 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 All authors had full access to the data.

Abstract

Background—Prevalences of vascular risk factors, cardiovascular disease and restless legs syndrome increase with age. Prior studies analyzing the associations between vascular risk factors, cardiovascular disease, and restless legs syndrome found controversial results. We therefore aim to evaluate the association between prevalent vascular risk factors, prevalent cardiovascular disease and restless legs syndrome.

Methods—We conducted a cross-sectional study among 22,786 participants of the US Physicians' Health Studies I and II. Restless legs syndrome was classified according to the four minimal diagnostic criteria. Vascular risk factors and restless legs syndrome symptoms were self-reported. Prevalent cardiovascular disease events including major cardiovascular disease, stroke and myocardial infarction were confirmed by medical record review. Age- and multivariable-adjusted logistic regression models were used to evaluate the association between vascular risk factors, prevalent cardiovascular disease events and restless legs syndrome.

Results—The mean age of the cohort 67.8 years. Restless legs syndrome prevalence was 7.5% and increased significantly with age. Diabetes significantly increased the odds (OR: 1.41, 95%CI: 1.21–1.65), while frequent exercise (OR: 0.78, 95%CI: 0.67–0.91) and alcohol consumption of one or more drinks per day (OR: 0.80, 95%CI: 0.69–0.92) significantly reduced the odds of restless legs syndrome in multivariable-adjusted models. Prevalent stroke showed an increased multivariable-adjusted OR of 1.40 (1.05–1.86) while men with prevalent myocardial infarction had a decreased OR of 0.73 (0.55–0.97) for restless legs syndrome.

Conclusions—The restless legs syndrome prevalence among US male physicians is similar to men of the same age group in other western countries. A history of diabetes is the most consistent risk factor associated with restless legs syndrome. Prevalent stroke and myocardial infarction are related to restless legs syndrome prevalence.

Keywords

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

Introduction

Restless legs syndrome is a frequent, sleep related movement disorder causing a high disease burden. Women are twice as often affected as men, and the prevalence of the disorder has been shown to increase with age.[1] A large number of cross-sectional studies and surveys have been published, reporting on the prevalence of restless legs syndrome among different patient populations as well as the general population.[2] The prevalence of restless legs syndrome was observed to be higher in primary care populations compared to the general population. A possible reason for this is the higher prevalence of risk factors and the disease burden among primary care patients. Similar to the age-dependent prevalence of restless legs syndrome, risk factors for cardiovascular disease increase with age and are highly prevalent in the general population. Associations between cardiovascular disease risk factors and restless legs syndrome have been hypothesized and a potential link would have consequences for the development of cardiovascular disease among patients with restless legs syndrome, but would also offer opportunities for preventive strategies. However, prior studies found controversial results. Some report associations between restless legs syndrome and hypertension,[3, 4] diabetes and obesity,[4, 5] while others did not find an association with vascular risk factors.[6, 7] Variations in study design, definition of restless legs syndrome and risk factors may be one explanation for the inconsistency of results. Studies evaluating the association between restless legs syndrome, vascular risk factors, and cardiovascular disease events in the same study population are lacking.

We therefore aim to evaluate the association between prevalent vascular risk factors, prevalent cardiovascular disease events and restless legs syndrome in the Physicians' Health Study, a homogeneous and large longitudinal cohort study of US male physicians.

Methods

Study Population

The Physicians' Health Study I (PHS I) was a randomized trial to test the benefits and risks of low-dose aspirin (325mg) and beta-carotene (50mg) in the primary prevention of cardiovascular disease and cancer among 22, 071 apparently healthy physicians aged 40–84 years at baseline in 1982.[8, 9] Baseline information was self-reported and collected by means of a mailed questionnaire that asked about many vascular risk factors and lifestyle 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.

The PHS II[10] was launched in 1997 and 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, cardiovascular disease, and age-related eye disease among 14,641 US male physicians aged 55 years and older; 7,641 PHS I participants were willing and eligible to enter the PHS II. 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.

All participants provided written informed consent and the institutional review board of the Brigham and Women's Hospital approved the PHS and this study.

Vascular risk factor assessment

Cardiovascular disease risk factor information was assessed at PHS baseline and updated through follow-up. The most recently updated information available with regard to the questionnaire on which restless legs syndrome was ascertained during follow-up was used for this analysis. We distinguished the following risk factors: 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 (yes/no), alcohol consumption (rarely/never, <1–3 times/month, 1–6 times/week, or ≥1 times/day), smoking (never, past, current), exercise (rarely/never, ≤1 time/week, 2–4 times/week, 5–7 times/week) and body mass index. History of hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive treatment. Body mass index (weight in kilograms divided by height in meters squared (kg/m^2)), was calculated using self-reported height and weight information. We defined the following five body mass index levels: <23kg/m^2, 23–24.9kg/m^2, 25–29.9kg/m^2, 30–34.9kg/m^2, ≥35kg/m^2.

Cardiovascular disease ascertainment

Participants were asked to report the first occurrence of cardiovascular disease. Medical records were obtained for all cardiovascular disease events, but not for coronary revascularization, and were reviewed by an end-points committee of physicians. 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 >24h. Stroke was classified into its major subtypes with excellent interrater agreement.[11] 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 cardiovascular disease was defined as a combined end-point of nonfatal stroke and nonfatal MI. We included all confirmed cardiovascular disease events until the return date of the questionnaire containing the restless legs syndrome questions.

Assessment of restless legs syndrome

A short questionnaire addressing the four minimal diagnostic criteria of the International Restless Legs Study Group was implemented in the 216-month follow-up questionnaire (PHS I) and the 12-month follow-up questionnaire (PHS II), respectively. Participants were asked to answer the following questions: “Do you have unpleasant leg sensations (like crawling, paraesthesis 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 restless legs syndrome. This questionnaire has been used[1, 6, 7, 12] and validated.[13] Comparing the questionnaire based diagnosis of restless legs syndrome against a physician’s diagnosis as a gold standard showed good agreement (unweighted kappa=0.67, $p<0.001$) in the Memory and Morbidity in Augsburg Elderly study.[13]

Statistical analysis

Of the 25,357 participants in active follow-up at the time restless legs syndrome was assessed, we excluded 852 men who did not return the questionnaire containing the restless legs syndrome questions. We additionally excluded 1,579 men with missing information for all the three restless legs syndrome questions, as well as men with missing information for body mass index (n=33), smoking status (n=8), alcohol consumption (n=31) and exercise (n=69), leaving a total of 22,786 men for this analysis, taking into consideration missing information on multiple vascular risk factors for some men.

Baseline characteristics were compared with respect to restless legs syndrome status using chi-square test for categorical variables 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 and prevalent cardiovascular disease and restless legs syndrome. We 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 the various vascular risk factors. This model was adjusted for age (continuous) and randomized aspirin assignment (yes/no).

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

Additional adjustment for race, geographic location, snoring, sleep duration, migraine, iron supplementation use, Parkinson’s disease, analgesic use did not change the effect estimate >10%. We further considered a history of depression as an additional covariate in the models investigating the association between restless legs syndrome and vascular risk factors; however, this did not change the results.

We evaluated whether the association between prevalent cardiovascular disease and restless legs syndrome was modified by age (<60, 60–70, 70–80, ≥80 years), 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 4,619 men with potential secondary causes for restless legs syndrome including men with a history of polyneuropathy, kidney disease, liver disease, liver cirrhosis, rheumatoid arthritis, intermittent claudication and men who underwent peripheral artery disease surgery.

We further excluded men with a history of diabetes from the models evaluating the association between prevalent cardiovascular disease and restless legs syndrome which did not change the effect estimates by >5% (data not presented).

A missing value indicator was incorporated in the models for covariates if the number of men with missing information was ≥100. If the number of men with missing values was <100, we assigned these participants to the category indicating no event. 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

The overall prevalence of restless legs syndrome in this cohort of 22,786 US male physicians was 7.5%. The prevalence increased significantly with age from 6.2% in the age group <60 to 9.8% among those ≥80 years. It did not vary significantly by geographic location.

Baseline characteristics according to presence of restless legs syndrome

Men with restless legs syndrome were on average 1.4 years older than men without restless legs syndrome (Table 1). With regard to vascular risk factors, men with restless legs syndrome were more likely to have a history of hypertension, diabetes, and elevated cholesterol ≥240mg/dl. In addition, they were more likely to have increased relative body weight. A higher proportion of men with restless legs syndrome rarely or never consumed an alcoholic beverage. The percentage of physically inactive physicians was higher among restless legs syndrome cases. Cases were more likely to report coronary revascularization and stroke. When considering other potential comorbidities, restless legs syndrome cases were more likely to report a history of migraine, depression and Parkinson's disease.

Vascular factors associated with restless legs syndrome

A history of diabetes was significantly associated with restless legs syndrome (Table 2). The likelihood of having restless legs syndrome increased with increasing body mass index ($p_{trend}=0.01$). While the associations for the highest two categories were statistically significant in the age-adjusted model, they became insignificant when taking other vascular risk factors into account. Alcohol consumption and exercise were inversely related to restless legs syndrome. Men who consumed one or more drinks per day had a significantly 20% decreased odds of restless legs syndrome. Compared to inactive physicians, those who exercised 5 to 7 times per week had a 22% reduced odds of restless legs syndrome.

Prevalent cardiovascular disease and restless legs syndrome

We found significant associations between prevalent stroke and restless legs syndrome as well as between myocardial infarction and restless legs syndrome (Table 3). Men who

experienced a stroke had an increased odds while prevalent myocardial infarction was associated with a decreased odds for having restless legs syndrome.

The associations between vascular risk factors and restless legs syndrome were very similar, after excluding men with potential secondary causes for restless legs syndrome (appendix tables 1 and 2).

The associations between restless legs syndrome and cardiovascular disease events were not significantly modified by the presence of age or other vascular risk factors. The relationship between restless legs syndrome and prevalent stroke was significantly modified by smoking ($p_{interaction}$=0.04). Never smokers had increased odds of restless legs syndrome while there was no association ever smokers.

Discussion

In this large cohort of US male physicians we found an overall restless legs syndrome prevalence of 7.5%, which steadily increased with advancing age. Men who had a history of diabetes were more likely to have restless legs syndrome. Restless legs syndrome prevalence was reduced for participants who consumed one or more alcoholic drinks per day and for those who exercised regularly. Prevalent stroke and myocardial infarction were both associated with restless legs syndrome, but in opposite directions. While men with prevalent stroke had an increased OR for having restless legs syndrome, prevalent myocardial infarction was associated with a decreased risk for restless legs syndrome.

Our prevalence estimates are very similar to other population-based studies that used the minimal diagnostic criteria for restless legs syndrome. The results of three studies from Germany that used the same restless legs syndrome assessment method yielded prevalence estimates between 5.3% and 10.6% among male participants who were aged ≥50.[1, 7, 13] In addition, our data confirm that the prevalence of restless legs syndrome is increasing with age in men.

In several other cross-sectional studies that reported on the association between vascular risk factors and restless legs syndrome, diabetes is the most consistent factor.[14, 15] Some studies also report a relationship between obesity and restless legs syndrome.[15, 16] Our results are consistent with these findings, although the association between body mass index ≥30 and restless legs syndrome became insignificant after adjusting for covariates in our study.

The interrelationship between obesity, diabetes, and restless legs syndrome is complex. Obese individuals more often have diabetes and patients with long-term diabetes often have diabetic polyneuropathy, which may mimic restless legs syndrome symptoms. However, the current diagnostic criteria for restless legs syndrome allow for the co-occurrence of restless legs syndrome and polyneuropathy in the same individual. Thus, it is difficult to determine the role of diabetes in the onset of restless legs syndrome.

An association between restless legs syndrome and elevated cholesterol levels has been reported in a study from Israel.[5] Among 1,568 subjects attending a routine annual check-up, those who suffered from restless legs syndrome had a multivariable-adjusted OR of 1.60 (95% CI=1.05–2.44) for hypercholesterolemia compared to participants without restless legs syndrome. In our study, we observed only a small increase (OR=1.11, 95% CI=1.01–1.23). Other studies have reported that individuals with restless legs syndrome exercise less and consume less alcohol.[5, 14, 15] In our cohort, these associations were inverted, indicating that men who consumed less alcohol or who exercised less were at higher risk of having restless legs syndrome. Links between these two lifestyle habits and restless legs syndrome are difficult to interpret.

In line with our findings, is a study from the UK reported an association between restless legs syndrome and stroke. In the Caerphilly cohort of 1,986 men aged 55–69 years, men with restless legs syndrome had an OR of 1.67 (95% CI=1.07–2.60) for stroke.[17] Further, the association between restless legs syndrome and magnetic resonance imaging determined vascular brain lesions has been evaluated among 267 participants of the Memory and Morbidity in Augsburg Elderly Study.[18] In this population-based study, stroke was more frequently observed among restless legs syndrome cases, but the association was not significant (OR=2.46, 95% CI=0.97–6.28). However, owing to the design of existing studies current evidence does not allow determining the direction of association, specifically whether restless legs syndrome sufferers are at risk for developing stroke or restless legs syndrome is a consequence of stroke. As presented in a case report, restless legs syndrome symptoms occurred in a 48-year old woman a few days after experiencing a lacunar infarction.[19] In another case report, an acute ischemic stroke was associated with exacerbation of preexisting restless legs syndrome symptoms.[20]

Consistent with other studies, we found an association between prevalent myocardial infarction and restless legs syndrome. But contrary to previous reports, prevalent myocardial infarction was associated with a decreased risk of restless legs syndrome in our study. This may indicate that restless legs syndrome is a marker for increased prevalence of vascular risk factors but by itself not a risk factor for cardiovascular disease events. 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.[21]

A recent review discussed potential biologic mechanisms linking vascular risk factors and cardiovascular disease to restless legs syndrome.[22] Proposed pathophysiological mechanisms include sympathetic hyperactivity in individuals with restless legs syndrome and/or periodic limb movements in sleep causing nocturnal high blood pressure and hypertension. Further, sleep-related breathing disorders among patients with restless legs syndrome, causing apnea while asleep may lead to stroke and other cardiovascular disease events.

Study Strengths and Limitations

Our study has a number of strengths including its large size, the homogeneous group of participants, which limits confounding factors, the standardized assessment of restless legs syndrome using the minimal diagnostic criteria published by the International Restless Legs Study Group as well as detailed information on vascular risk factors and confirmed cardiovascular events during a long period of follow-up. In addition, the large amount of information on co-morbidities facilitated various sensitivity analyses.

The following limitations should be considered. First, restless legs syndrome was self-reported which can lead to misclassification. However, our classification of restless legs syndrome case status has been applied in other studies and been validated in detail.[1, 12, 13] Second, information on vascular risk factors and co-morbid conditions was also self-reported. However, it has been shown previously that self-reports of participants in the PHS, which are all physicians, as well as in other studies of health professionals are excellent and valid.[23–25] Third, restless legs syndrome case status was only assessed once. Thus, a temporal relationship between any of the conditions investigated and restless legs syndrome cannot be established. Fourth, as participants of our study were all physicians and most of them white, extrapolation of our results to other populations may be limited. Finally, as in all observational studies, residual confounding is possible.

In summary, in this large study of US physicians, the restless legs syndrome prevalence was comparable to that of men in other western countries. We do not find strong and consistent associations of restless legs syndrome with most vascular risk factors. The most consistent factor is diabetes. Prevalent stroke and myocardial infarction (inverse) were associated with restless legs syndrome. Further targeted research is warranted to disentangle the time of onset of restless legs syndrome in relation to vascular risk factors or cardiovascular disease events.

Acknowledgments

Financial sources:

This study was supported by a grant from the National Heart, Lung, and Blood Institute (HL-091880). The Physicians' Health Study is supported by grants from the National Cancer Institute (CA-34944, CA-40360 and CA-097193) and from the National Heart, Lung, and Blood Institute (HL-26490 and HL-34595).

We are indebted to the participants in the Physicians' Health Study for their outstanding commitment and cooperation, to the entire Physicians' Health Study staff for their expert and unfailing assistance.

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Table 1

Baseline characteristics according to RLS status (n=22,786)

	No RLS n=21,076	RLS n=1,710	p-value
Demographic information			
Mean age, yrs (SD)	67.7 (9.0)	69.1 (9.1)	<0.01
Ethnicity, %			
White	19,097 (91.1)	1,604 (94.1)	<0.01
Geographic location,%			0.17
Northeast	4,721 (22.4)	373 (21.8)	
Southeast	6,160 (29.2)	459 (26.8)	
Midwest	5,382 (25.5)	468 (27.4)	
West	4,687 (22.2)	398 (23.3)	
Other	126 (0.6)	12 (0.7)	
Prevalent CVD events, %			
Major CVD	1,113 (5.3)	107 (6.3)	0.08
Coronary revascularization	2,313 (11.0)	218 (12.8)	0.02
Myocardial infarction	736 (3.5)	54 (3.2)	0.47
Stroke	423 (2.0)	58 (3.4)	<0.01
Vascular risk factors, %			
History of hypertension	11,054 (52.5)	959 (56.1)	<0.01
History of diabetes	1,753 (8.3)	217 (12.7)	<0.01
History of cholesterol ≥ 240mg/dl	11,013 (52.3)	955 (55.9)	<0.01
BMI categories (kg/m^2)			<0.01
<23	3,883 (18.4)	312 (18.3)	
23–24.9	5,051 (24.0)	354 (20.7)	
25–29.9	9,701 (46.0)	806 (47.1)	
30–34.9	1,997 (9.5)	192 (11.2)	
Smoking status			0.36
Never	11,160 (53.0)	876 (51.2)	
Past	9,335 (44.3)	788 (46.1)	
Current	581 (2.8)	46 (2.7)	
Alcohol consumption			<0.01
Rarely/never	3,827 (18.2)	364 (21.3)	
1–3 times/month	2,550 (12.1)	214 (12.5)	
1–6 times/week	7,724 (36.7)	619 (36.2)	
≥1 times/day	6,975 (33.1)	513 (30.0)	
Exercise			<0.01
Rarely/never	7,461 (35.4)	679 (39.7)	
≤ 1/week	508 (2.4)	41 (2.4)	
2–4 times/week	9,242 (43.9)	734 (42.9)	
5–7 times/week	3,865 (18.3)	256 (15.0)	

	No RLS n=21,076	RLS n=1,710	p-value
Parental history of myocardial infarction	2,483 (11.8)	190 (11.1)	0.41
Other covariates, %			
History of migraine during follow-up	2,553 (12.1)	243 (14.2)	0.01
History of depression	2,106 (10.1)	278 (16.5)	<0.01
History of Parkinson's disease	282 (1.3)	34 (2.0)	0.03
Iron supplementation use	412 (2.2)	36 (2.4)	0.71
Sleep duration ≥ 8 hours	6,493 (34.3)	543 (36.1)	0.16
Snoring			0.25
Never	5,308 (27.7)	424 (27.8)	
A few nights	7,650 (40.0)	582 (38.1)	
Most nights	6,183 (32.3)	522 (34.2)	

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

Table 2

Age- and multivariable-adjusted OR's for RLS according to vascular risk factors (n=22,786)

	No RLS	RLS	Age-adjusted	Multivariable-adjusted[a]	P for trend
	21,076	1,710	OR (95% CI)	OR (95% CI)	
History of hypertension	11,054	959	1.06 (0.95, 1.17)	0.99 (0.89, 1.11)	
History of diabetes	1,753	217	1.53 (1.31, 1.78)	1.41 (1.21, 1.65)	
History of cholesterol ≥ 240mg/dl	11,013	955	1.13 (1.03, 1.25)	1.11 (1.01, 1.23)	
BMI categories					0.01
<23	3,883	312	1.00	1.00	
23–24.9	5,051	354	0.90 (0.77, 1.06)	0.90 (0.77, 1.05)	
25–29.9	9,701	806	1.09 (0.95, 1.25)	1.06 (0.92, 1.21)	
30–34.9	1,997	192	1.30 (1.07, 1.57)	1.20 (0.99, 1.45)	
≥35	444	46	1.42 (1.03, 1.97)	1.24 (0.89, 1.73)	
Smoking Status					
Never	11,160	876	1.00	1.00	
Past	9,335	788	1.02 (0.92, 1.13)	1.02 (0.92, 1.14)	
Current	581	46	1.00 (0.74, 1.36)	0.99 (0.72, 1.34)	
Alcohol consumption					<0.01
Rarely/never	3,827	364	1.00	1.00	
1–3 drinks per month	2,550	214	0.92 (0.77, 1.10)	0.92 (0.77, 1.09)	
1–6 drinks per week	7,724	619	0.88 (0.77, 1.00)	0.90 (0.78, 1.03)	
≥ 1 drink/day	6,975	513	0.77 (0.67, 0.89)	0.80 (0.69, 0.92)	
Exercise					0.01
Rarely/never	7,461	679	1.00	1.00	
≤ 1/week	508	41	0.97 (0.70, 1.35)	0.98 (0.70, 1.36)	
2–4 times/week	9,242	734	0.92 (0.83, 1.03)	0.96 (0.86, 1.08)	
5–7 times/week	3,865	256	0.75 (0.65, 0.87)	0.78(0.67, 0.91)	
Parental history of myocardial infarction	2,483	190	0.96 (0.82, 1.12)	0.95 (0.81, 1.12)	

[a]Multivariable models include all vascular risk factors and were adjusted for age, randomized aspirin assignments.

Table 3

Age- and multivariable-adjusted* OR's (95% CI) for RLS according to prevalent CVD events (n=22,786)

	No RLS history n=21,076	Any history of RLS n=1,710
Major CVD event	n=1,113	n=107
Age-adjusted	1.00	1.06 (0.86, 1.31)
Multivariable-adjusted	1.00	0.97 (0.79, 1.20)
Coronary revascularization	n=2,313	n=218
Age-adjusted	1.00	1.08 (0.93, 1.26)
Multivariable-adjusted	1.00	0.99 (0.85, 1.16)
Myocardial infarction	n=736	n=54
Age-adjusted	1.00	0.81 (0.61, 1.08)
Multivariable-adjusted	1.00	0.73 (0.55, 0.97)
Stroke	n=423	n=58
Age-adjusted	1.00	1.50 (1.13, 1.99)
Multivariable-adjusted	1.00	1.40 (1.05, 1.86)

* Multivariable models were adjusted for age, randomized aspirin assignments, parental history of myocardial infarction, history of hypertension, history of diabetes, history of hypercholesterolemia, alcohol consumption, BMI, exercise, smoking, and history of depression