Vascular Risk Factors, Cardiovascular Disease, and Restless Legs Syndrome in Women

Anke C. Winter, MD, MSc,[a] Markus Schürks, MD, MSc,[a,d] Robert J. Glynn, PhD, ScD,[a] Julie E. Buring, ScD,[a] J. Michael Gaziano, MD, MPH,[a,b] Klaus Berger, MD, MPH,[c] Tobias Kurth, MD, ScD[a,e,f]

[a]Division of Preventive Medicine and [b]Division of Aging, Department of Medicine, Brigham and Women's Hospital, Boston, Mass; [c]Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany; [d]Department of Neurology, University Hospital of Essen, Essen, Germany; [e]INSERM Unit 708–Neuroepidemiology, Bordeaux, France; [f]University of Bordeaux, Bordeaux, France.

ABSTRACT

BACKGROUND: Previous studies evaluating the association of 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 relationships 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 [BMI], alcohol, smoking, exercise, and family history of myocardial infarction) was self-reported. Cardiovascular disease events (coronary revascularization, myocardial infarction, and stroke) were confirmed by medical record review. Prevalent major cardiovascular disease was defined as nonfatal stroke or nonfatal myocardial infarction. Logistic regression models were used to evaluate the association between vascular risk factors, prevalent cardiovascular disease, and restless legs syndrome.

RESULTS: Of the 30,262 participants (mean age: 63.6 years), 3624 (12.0%) reported restless legs syndrome. In multivariable-adjusted models, BMI (odds ratio [OR] for BMI $\geq$ 35 kg/m^2, 1.35; 95% confidence interval [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 $\geq$ 15 cigarettes/day, 1.41; 95% CI, 1.19-1.66), and exercise (OR for exercise $\geq$ 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, and 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.

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

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KEYWORDS: Cardiovascular disease; Cohort study; Restless legs syndrome; Vascular risk factors

Restless legs syndrome is a neurologic disorder characterized by an urge to move the legs and usually accompanied by unpleasant leg sensations. The symptoms predominantly occur in the evening and at night. Inactivity and rest worsen the symptoms, whereas patients experience relief by movement. The International Restless Legs Syndrome Study

Conflict of Interest: See last page of article.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Requests for reprints should be addressed to Tobias Kurth, MD, ScD, INSERM U708–Neuroepidemiology, Université Bordeaux Segalen, 146 rue Léo Saignat, Case 11, 33076 Bordeaux Cedex, France.

E-mail address: tobias.kurth@univ-bordeaux.fr

Group has published minimal diagnostic criteria to facilitate a standardized diagnosis of this disorder that 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 from 6% to 12%, women being predominately affected.[3] The mechanisms causing restless legs syndrome are not fully understood. Research involving pharmacologic, endocrinologic, and neuroimaging studies suggest a dysfunction of the dopaminergic system as an important pathophysiologic 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 2 entities.[6-14] An unfavorable vascular risk factor profile among those with restless legs syndrome 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 restless legs syndrome have shown inconsistent results.[10,12,15-18] Potential explanations for these inconsistent results across studies include differences in study design and populations and varying definitions of restless legs syndrome and the various outcome variables.

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

MATERIALS AND 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.[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 assigned randomly to receive active aspirin (100 mg 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, Mass) 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.

CLINICAL SIGNIFICANCE

- Several vascular risk factors, including diabetes, hypercholesterolemia, body mass index, smoking status, and exercise, were associated with the prevalence of restless legs syndrome in this cohort of female health professionals.

- Our data do not suggest a relationship between prevalent cardiovascular disease and restless legs syndrome.

Assessment of Restless Legs Syndrome

A short questionnaire addressing the 4 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 (eg, 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 3 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 ≥ 240 mg/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 (BMI) (<23, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m^2), smoking status (never, past, current <15 cigarettes/day, current ≥ 15 cigarettes/day), and parental history of myocardial infarction before age 60 (yes/no). BMI was calculated on the basis of self-reported height and weight, and we distinguished the following categories: <23, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m^2. History of hypertension was defined as blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg 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-neurologic deficit of sudden onset that persisted for > 24 hours and was classified into its major subtypes on the basis of 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 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: nonfatal myocardial infarction and nonfatal stroke. For the purpose of this analysis, we included all confirmed prevalent cardiovascular events up to the 108-month follow-up questionnaire.

Statistical Analysis

Of the 33,092 women in active follow-up at the 108-month questionnaire, we excluded 1722 women with missing information for all 3 restless legs syndrome questions and women with missing information on BMI (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 the chi-square test for categoric variables and the t test for continuous variables. Age- and multivariable-adjusted logistic regression models were used to evaluate the association between 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 before age 60 (yes/no), history of diabetes (yes/no), BMI (23, 23-24.9, 25-29.9, 30-34.9, ≥35 kg/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), postmeno-

pausal 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 (nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, aspirin, aspirin-containing drugs, and acetaminophen) did not change 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), BMI (<25, 25-29.9, ≥30 kg/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, or intermittent claudication, and those who underwent peripheral artery disease surgery. In a second sensitivity analysis approach, we excluded only 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 (v 9.1.3, SAS Institute Inc, Cary, NC). All P values were 2 tailed, and P < .05 was considered statistically significant.

RESULTS

Of the 30,262 participants, 3624 (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, and 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 BMI ≥ 30 kg/m^2, to rarely/never drink, to rarely/never exercise, and to

Table 1 Baseline Characteristics According to Restless Legs Syndrome Status (n = 30,262)

	No RLS n = 26,638	RLS n = 3624	P Value
Demographic Information			
Mean age, y (SD)	63.6 (6.9)	63.6 (6.9)	.86
Ethnicity, n (%)			
White	25,138 (95.1)	3512 (97.5)	<.01
Geographic Location, n (%)			
Northeast	5216 (19.6)	623 (17.2)	
Southeast	6093 (22.9)	859 (23.7)	<.01
Midwest	9553 (35.9)	1359 (37.5)	
West	5734 (21.6)	780 (21.5)	
Prevalent CVD Events, n (%)			
Major CVD	406 (1.5)	61 (1.7)	.47
Coronary revascularization	398 (1.5)	88 (2.4)	<.01
Myocardial infarction	194 (0.7)	40 (1.1)	.02
Stroke	215 (0.8)	22 (0.6)	.20
CVD Risk Factors, n (%)			
History of hypertension	12,721 (47.8)	1880 (51.9)	<.01
History of diabetes	1890 (7.1)	340 (9.4)	<.01
History of cholesterol ≥ 240 mg/dL	14,317 (53.8)	2137 (59.0)	<.01
BMI Categories, n (%)			
<23 kg/m^2	6250 (23.5)	735 (20.3)	
23-24.9 kg/m^2	4807 (18.1)	612 (16.9)	
25-29.9 kg/m^2	9120 (34.2)	1249 (34.5)	<.01
30-34.9 kg/m^2	4221 (15.9)	634 (17.5)	
≥35 kg/m^2	2240 (8.4)	394 (10.9)	
Smoking Status, n (%)			
Never	13,800 (51.8)	1694 (46.7)	
Past	10,673 (40.1)	1589 (43.9)	<.01
Current < 15 cigarettes/d	1084 (4.1)	154 (4.3)	
Current ≥ 15 cigarettes/d	1081 (4.1)	187 (5.2)	
Alcohol consumption, n (%)			
Rarely/never	11,412 (42.8)	1645 (45.4)	
1-3 drinks/mo	3096 (11.6)	411 (11.3)	.03
1-6 drinks/wk	9065 (34.0)	1170 (32.3)	
≥ 1 drink/d	3065 (11.5)	398 (11.0)	
Exercise, n (%)			
Rarely/never	10,066 (37.8)	1439 (39.7)	
<1/wk	5287 (19.9)	753 (20.8)	<.01
1-3 times/wk	8313 (31.2)	1101 (30.4)	
≥ 4 times/wk	2972 (11.2)	331 (9.1)	
Parental history of myocardial infarction	4571 (17.2)	692 (19.1)	<.01
Other Covariates, n (%)			
History of migraine	5645 (21.2)	962 (26.6)	<.01
History of depression	3194 (12.0)	729 (20.1)	<.01
History of Parkinson's disease	111 (0.4)	19 (0.5)	.35
Iron supplementation use	1049 (4.0)	126 (3.5)	.17

BMI = body mass index; CVD = cardiovascular disease; RLS = restless legs syndrome.
Percentages may not add up to 100 because of missing values or rounding.

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 BMI 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 that remained stable after adjustment for covariates. The observed association among history of hypertension, parental history of myocar-

Table 2 Age- and Multivariable-adjusted* Odds Ratios (95% Confidence Interval) for Restless Legs Syndrome According to Vascular Risk Factors (n = 30,262)

	No RLS 26,638	RLS 3624	Age Adjusted OR (95% CI)	Multivariable Adjusted* OR (95% CI)	P for Trend
History of hypertension	12,721	1880	1.19 (1.11-1.28)	1.06 (0.98-1.15)	
History of diabetes	1890	340	1.36 (1.20-1.53)	1.19 (1.04-1.35)	
History of cholesterol ≥ 240 mg/dL	14,317	2137	1.24 (1.16-1.33)	1.17 (1.09-1.26)	
BMI Categories					<.01
<23	6250	735	1.00	1.00	
23-24.9	4807	612	1.08 (0.97-1.21)	1.06 (0.94-1.19)	
25-29.9	9120	1249	1.17 (1.06-1.28)	1.11 (1.00-1.22)	
30-34.9	4221	634	1.28 (1.14-1.43)	1.18 (1.04-1.33)	
≥35	2240	394	1.50 (1.32-1.72)	1.35 (1.17-1.56)	
Smoking Status					
Never	13,800	1694	1.00	1.00	
Past	10,673	1589	1.21 (1.13-1.31)	1.22 (1.13-1.31)	
Current < 15 cigarettes/d	1084	154	1.16 (0.97-1.38)	1.19 (1.00-1.42)	
Current ≥ 15 cigarettes/d	1081	187	1.41 (1.20-1.66)	1.41 (1.19-1.66)	
Alcohol consumption					
Rarely/never	11,412	1645	1.00	1.00	
1-3 drinks/mo	3096	411	0.92 (0.82-1.03)	0.93 (0.83-1.04)	.04
1-6 drinks/wk	9065	1170	0.89 (0.83-0.97)	0.92 (0.84-1.00)	
≥1 drink/d	3065	398	0.90 (0.80-1.01)	0.92 (0.81-1.04)	
Exercise					
Rarely/never	10,066	1439	1.00	1.00	
<1/wk	5287	753	1.00 (0.91-1.09)	1.02 (0.93-1.12)	.03
1-3 times/wk	8313	1101	0.93 (0.85-1.01)	0.98 (0.90-1.06)	
≥4 times/wk	2972	331	0.78 (0.69-0.88)	0.84 (0.74-0.95)	
Parental history of myocardial infarction	4571	692	1.14 (1.04-1.25)	1.10 (1.00-1.20)	

BMI = body mass index; CI = confidence interval; OR = odds ratio; RLS = restless legs syndrome.

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

dial 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 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 without coronary 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 similar; however, the observed association for diabetes was no longer significant (data presented in Appendix Table 1, online). 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, online). Excluding diabetes as a confounder did not substantially change the associations (data not presented).

DISCUSSION

In this large cross-sectional study of female health professionals aged 45 years or more at study entry, the cardiovascular disease risk factors history of diabetes, history of cholesterol ≥ 240 mg/dL, smoking status, exercise, and BMI 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

Table 3 Age- and Multivariable-adjusted* Odds Ratios (95% Confidence Interval) for Restless Legs Syndrome According to Prevalent Cardiovascular Disease Events (n = 30,262)

	No RLS n = 26,638	RLS n = 3624
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)

CVD = cardiovascular disease; RLS = restless legs syndrome.
*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.

restless legs syndrome, this association 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] BMI,[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 ($\geq$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, not 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; thus, 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, whereas smoking was only related to restless legs syndrome in younger participants after stratifying for age.[15] In addition, the association between BMI, 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 pathophysiologic 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 pathophysiologic pathways of restless legs syndrome should be drawn carefully because the underlying mechanisms of restless legs syndrome are not fully understood. The potential relationship between restless legs syndrome and obesity also might be mediated by sleep deprivation, a feature affecting most people with restless legs syndrome.[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 (eg, 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] the 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 attenuated supporting the notion that the association between cardiovascular disease and restless legs syndrome is mediated by comorbidities and might be limited to those with restless legs syndrome 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] Results of another study suggest that women with a history of at least 3 years of restless legs syndrome may be at increased risk of coronary heart disease.[37]

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 have included coronary revascularization procedures or angina in their cardiovascular disease definition[6,9,13,14] or chosen self-reported heart disease,[10-12] whereas we have distinguished among 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 study and previous studies does not allow a final answer to the question of whether restless legs syndrome 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 4 minimal diagnostic criteria of the International Restless Legs Study Group, and the detailed information on prevalent cardiovascular disease events that 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, the restless legs syndrome prevalence of 12.0% in the current study 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.[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.[38,39] Last, our cohort consists of female health professionals aged 45 years or more at study entry, which limits the generalizability of our results to other populations.

CONCLUSIONS

Several cardiovascular disease risk factors, including diabetes, hypercholesterolemia, BMI, 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.

ACKNOWLEDGMENTS

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Appendix Table 1 Sensitivity Analysis:* Age- and Multivariable-adjusted† Odds Ratios (95% Confidence Interval) for Restless Legs Syndrome According to Vascular Risk Factors (n = 28,015)

	No RLS 24,732	RLS 3283	Age Adjusted OR (95% CI)	Multivariable Adjusted OR (95% CI)
History of hypertension	11,569	1652	1.16 (1.08-1.25)	1.04 (0.96-1.13)
History of diabetes	1610	268	1.28 (1.12-1.46)	1.13 (0.98-1.30)
History of cholesterol ≥ 240 mg/dL	13,106	1908	1.24 (1.15-1.33)	1.17 (1.08-1.26)
BMI Categories				
<23	5864	679	1.00	1.00
23-24.9	4524	559	1.07 (0.95-1.20)	1.04 (0.93-1.18)
25-29.9	8480	1148	1.17 (1.06-1.29)	1.12 (1.01-1.24)
30-34.9	3856	558	1.25 (1.11-1.41)	1.16 (1.02-1.32)
≥35	2008	339	1.46 (1.27-1.69)	1.34 (1.15-1.56)
Smoking Status				
Never	12,901	1550	1.00	1.00
Past	9868	1441	1.22 (1.13-1.31)	1.22 (1.13-1.32)
Current < 15 cigarettes/d	985	139	1.17 (0.98-1.41)	1.21 (1.00-1.46)
Current ≥ 15 cigarettes/d	978	153	1.30 (1.09-1.56)	1.31 (1.09-1.57)
Alcohol Consumption				
Rarely/never	10,397	1449	1.00	1.00
1-3 drinks/mo	2883	384	0.96 (0.85-1.08)	0.96 (0.85-1.08)
1-6 drinks/wk	8553	1087	0.91 (0.84-0.99)	0.92 (0.84-1.00)
≥1 drink/d	2899	363	0.90 (0.80-1.02)	0.90 (0.80-1.03)
Exercise				
Rarely/never	9258	1285	1.00	1.00
<1/wk	4894	673	0.99 (0.90-1.09)	1.01 (0.91-1.12)
1-3 times/wk	7797	1017	0.94 (0.86-1.03)	0.98 (0.90-1.07)
≥4 times/wk	2783	308	0.80 (0.70-0.91)	0.85 (0.74-0.97)
Parental history of myocardial infarction	4207	625	1.15 (1.05-1.26)	1.11 (1.01-1.22)

BMI = body mass index; CI = confidence interval; OR = odds ratio; RLS = restless legs syndrome.

*A total of 2247 women with a history of polyneuropathy, kidney disease/kidney failure, liver disease, rheumatoid arthritis, or 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, and oral contraceptive use.

Appendix Table 2   Sensitivity Analysis:* Age- and Multivariable-adjusted† Odds Ratios (95% Confidence Interval) for Restless Legs Syndrome According to Prevalent Cardiovascular Disease Events (n = 28,015)

	No RLS n = 24,732	RLS n = 3283
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)
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)

CVD = cardiovascular disease; RLS = restless legs syndrome.

*A total of 2247 women with a history of polyneuropathy, kidney disease/kidney failure, liver disease, rheumatoid arthritis, or 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, BMI, smoking status, alcohol consumption, history of hypertension, exercise, hypercholesterolemia, history of depression, postmenopausal hormone use, postmenopausal status, and oral contraceptive use.