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Prospective Study of Restless Legs Syndrome and Coronary Heart Disease Among Women

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Abstract

Background—Previous cross-sectional studies suggested a positive association between restless legs syndrome (RLS) and coronary heart disease (CHD). This observation was not confirmed by subsequent prospective studies. However, these prospective studies did not take into account the duration of RLS symptoms. We thus prospectively examined whether RLS was associated with an increased risk of CHD in women who participated in the Nurses' Health Study taking into account the duration of RLS symptoms.

Methods and Results—A total of 70,694 women (mean age 67 years) who were free of CHD and stroke at baseline (2002) were followed until 2008. Physician-diagnosed RLS was collected via questionnaire. CHD was defined as nonfatal myocardial infarction or fatal CHD. Women with RLS at baseline had a marginally higher risk of developing CHD (multivariable-adjusted hazard ratio (HR), 1.46; 95% confidence interval (CI), 0.97–2.18) as compared with women without RLS. The risk was dependent on duration of symptoms—0.98 (95% CI, 0.44–2.19) for women with RLS less than three years and 1.72 (95% CI, 1.09–2.73) for women with RLS for three years or longer (*P* trend=0.03). The multivariable-adjusted HRs of women with RLS for three years or longer were 1.80 (95% CI, 1.07–3.01) for nonfatal myocardial infarction and 1.49 (95% CI, 0.55–4.04) for fatal CHD, relative to women without RLS.

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Disclosures

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Conclusions—We observed that women with RLS for at least three years had an elevated risk of CHD. These results suggest that RLS or RLS associated conditions may contribute to the etiology of cardiovascular disease.

Keywords

Restless legs syndrome (Willis Ekblom Disease); coronary heart disease; sleep; prospective cohort study

Several common symptoms reported by primary restless legs syndrome (RLS, also known as Willis Ekblom Disease) sufferers have been associated with risk of coronary heart disease (CHD). For example, 75% of primary RLS sufferers report insufficient and disturbed sleep¹ which may increase the risk of CHD.² The majority of RLS subjects report periodic limb movements of sleep (PLMS), that may occur up to 200–300 times per night.³ Such leg movements are associated with sympathetically induced elevations in heart rate and blood pressure.^{4–9} Further, important CHD risk factors (e.g., hypertension¹⁰, depression¹¹ and obesity¹²) are commonly found among patients with RLS, which may also put them at higher risk of heart disease.

The association between RLS and heart disease was first reported in 4,000 Swedish men where participants with RLS more frequently reported heart problems with an odds ratio of 2.5.¹³ This study was followed by a large multi-national sample of European adults that reported an odds ratio of 1.4 between RLS and self-reported heart disease.¹⁴ In the following 10 years, similar significant associations were also observed in other studies.^{15,16} However, the cross-sectional design of those studies precludes conclusions regarding direction or causality of the observed associations. Excluding the CHD cases at baseline and prospectively examining the association between RLS and incident CHD cases would provide stronger evidence on the causal relationship between RLS and CHD. To date, only two studies have prospectively examined RLS and subsequent risk of CHD and failed to find a significant association.^{17,18} However, these studies did not take into account the duration of RLS symptoms as a potential causal factor for CHD.

The purpose of the current study was to prospectively examine whether women in the Nurses' Health Study (NHS) with physician-diagnosed RLS have an increased risk of CHD taking in to account the duration of RLS symptoms.

Methods

Study population

The NHS cohort was established in 1976, when 121 700 female registered nurses aged 30 to 55 years residing in 11 states responded to a mailed questionnaire regarding their medical history and health practices. Exposure information and newly diagnosed medical illnesses have been updated every 2 years via mailed questionnaires.¹⁹

In 2002, we asked 82,160 participants who were still alive and actively feedback the long version of the questionnaires in the NHS whether they had ever been diagnosed with RLS by a physician. We, therefore, used 2002 as the baseline in the present analysis and excluded women who had ever reported physician-diagnosed myocardial infarction (MI), coronary bypass, coronary angioplasty, angina pectoris or stroke in or prior to 2002, leaving 70,977 women for this analysis. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard School of Public Health.

Case ascertainment

We included nonfatal MI and fatal CHD in our endpoint of CHD. We requested permission to review medical records when a woman reported a nonfatal CHD event. We also sought medical records for deceased participants, whose deaths were identified by families and postal officials and through the National Death Index. Physicians blinded to the participants' questionnaire reports reviewed all medical records. Nonfatal MI and fatal CHD were identified primarily through review of medical records, as previously described.^{19,20} MI was confirmed if the criteria of the World Health Organization were met, specifically, on the basis of symptoms and either electrocardiographic changes or elevated cardiac enzyme concentrations.²⁰

Assessment of physician-diagnosed RLS and covariables

In the 2002 survey, the nurses were asked whether they had physician-diagnosed RLS and date of first diagnosis. The possible diagnosis date were 1996 or before, 1997–1999, 2000, 2001 or 2002. Information on potential confounders, including age, body weight, menopause status and estrogen hormone therapy, smoking status, physical activity, use of aspirin, multiple vitamin supplements, antidepressants, antihypertensive, anti-arrhythmic, and a history of major chronic conditions, including hypertension, elevated cholesterol, diabetes, arthritis and cancer, were collected via biennial questionnaires throughout the follow-up. Every other year, we also asked the participants whether they had a physical exam in the past two years, if yes, whether it was for screening or for symptoms. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared from self-reported weight and height. Dietary intake was collected using validated food frequency questionnaires²¹ every four years. In 2002, we also collected information on sleep duration and snoring frequency.

Statistical methods

We categorized participants into 3 groups: no RLS, RLS duration less than three years (the mid-point of the RLS duration), and RLS duration for 3 years or longer. Person-years for each participant were calculated from the date the 2002 questionnaire was returned to the diagnosed date of CHD or death, or June 1, 2008 or the date of return of their last questionnaire, whichever came first. Time-dependent Cox proportional hazards models were used to estimate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of CHD for women with different RLS duration relative to women without RLS.

We adjusted for age, ethnicity, smoking status, major chronic disease, alcohol drinking, BMI, physical activity, diet quality as assessed by the alternative healthy eating index²², menopause status, sleep characteristics, medication and hormones use at baseline, that may associate with both CHD²² and RLS²³, and then may confound their association. Time-varying covariates were also used in the final model, except for ethnicity, sleep duration and snoring frequency.

We examined potential interactions of presence of RLS (yes versus no) with age (< or ≥ 65 years, approximate mean age of the studied population), overweight (yes/no, based on BMI ≥ 25 kg/m²), smoking status (never versus ever), and physical activity level (top two quintiles versus the other three quintiles) by including multiplicative terms in the Cox models, with adjustment for other potential confounders.

To test the robustness of our observations, we conducted several sensitivity analyses by (1) excluding the women who had ever been diagnosed with diabetes or arthritis, which are considered common mimics of RLS.²⁴ (2) excluding women who had reported frequent

snoring, another common sleep complaints; (3) excluding women who had ever been diagnosed with Parkinson's disease, cancer or renal failure by the end of the follow-up; and (4) excluding the CHD cases diagnosed during the first two years of follow-up (i.e., 2002–2004), to minimize the possibility that these were sub-clinical or undiagnosed CHD cases at the baseline; (5) there was a possibility that women who were diagnosed as RLS would visit physicians more frequently and thus more likely to be found to have CHD. To tackle this potential bias, we conducted a sensitivity analysis by further adjustment for whether participants underwent physical exam for symptoms. We also examined the association between RLS and CHD after excluding those who had physical exam for symptoms; (6) in order to reduce the residual confounding from the severity of hypertension and diabetes, we further adjusted the blood pressure, duration of diabetes and use of medications for diabetes.

We used the SAS statistical package (version 9: SAS Institute, Cary, NC) for the analyses. All P values were 2-tailed ($P < 0.05$).

Results

At baseline, 1484 out of 70,977 women reported having ever been diagnosed with RLS. Compared to women without RLS, women with RLS were more likely to be older, Caucasian, to use iron supplements, and have a higher prevalence of major chronic conditions, such as hypertension, arthritis and diabetes (Table 1).

During a mean of 5.6 years of follow-up, we identified 698 incident cases of CHD. A significant association between RLS and CHD was only found among women with longer RLS duration. The multivariable-adjusted HRs were 1.72 (95% CI, 1.09–2.73) for women with RLS for three years or longer as compared with women without RLS (P trend=0.03) (Table 2). The results did not materially change when we used the continuous variables for covariates (data not shown). The interactions between RLS and other risk factors (older age, overweight, smoking, and low physical activity) were not significant (P for interaction > 0.1 for all).

We further examined the association between RLS and risk of fatal CHD and non fatal MI, specifically. The multivariable-adjusted HRs were 1.80 (95% CI, 1.07–3.01) for nonfatal MI (Table 2) and 1.49 (95% CI, 0.55–4.04) for fatal CHD, comparing women with RLS for three years or longer to those without RLS.

We obtained similar results in the sensitivity analyses. Multivariable adjusted HRs for women with RLS for three or more years vs. those without RLS were 1.94 (95% CI, 1.11–3.37) for CHD after excluding participants with a history of diabetes or arthritis, 1.80 (95% CI, 1.09–2.97) after excluding participants with snoring frequency of every night or most nights, and 2.06 (95% CI, 1.27–3.35) after excluding participants with Parkinson's disease, cancer or renal failure. When we excluded the incident CHD cases diagnosed during the period of 2002–2004, the multivariable-adjusted HR was 1.97 (95% CI, 1.13–3.43) for CHD. Comparing women with RLS for three or more years to those without RLS, the multivariable-adjusted HRs for CHD were 1.72 (95% CI: 1.09–2.73) after further adjustment for the self-report of a recent regular physical exam due to unspecified symptoms, and 1.78 (95% CI: 1.04–3.03) after further just excluding participants who reported a physical exam due to unspecified symptoms, and 1.70 (95% CI, 1.07–2.68) after further adjustment of blood pressure, diabetes duration and diabetes medications.

Discussion

In this well established prospective cohort, we observed that women with physician-diagnosed RLS at baseline had a higher risk of developing CHD during six years of follow

up. The observed association between RLS and CHD risk appeared independent of major known risk factors for CHD, such as age, smoking status, physical activity, dietary pattern, body mass index, use of antidepressant medications, history of hypertension, diabetes, high total cholesterol, short or long sleep duration and frequent snoring.

The association between RLS and heart disease has been reported in previous cross-sectional studies,^{13,14} but not been confirmed in prospective studies.^{17,18} The South Wales study found a positive but non-significant association (adjusted HR=1.24; 95% CI, 0.89–1.74) between baseline RLS and increased risk of ischemic heart disease.¹⁷ The Women's Health Study found RLS was not associated with increased risk of MI among women with an adjusted relative risk of 1.01 (95% CI, 0.65–1.57).¹⁸ However, neither studies provided detailed information on the duration of RLS symptoms thus preventing a direct comparison with our results.

RLS may lead to heart disease through several potential mechanisms: its negative effect on sleep quality and duration, the coexisting sympathetic activation accompanying periodic limb movements of sleep (PLMS), or the presence of common risk factors for heart disease. Reduced sleep quality could be an intermediate factor between the observed association of RLS and CHD. Insufficient and disturbed sleep has been noted among 75% of primary RLS sufferers.¹ Both short and long sleep duration had been reported to increase the risk of heart disease in our cohort of nurses.²⁵ In the current study, when we adjusted for sleep duration and snoring frequency or excluded participants with frequent snoring, the association between RLS of at least 3 years duration and CHD remained significant, suggesting that RLS was not merely leading to CHD through an effect on reduced sleep duration.

The presence of other common chronic conditions and lifestyles in patients with RLS may also increase the risk of CHD, such as hypertension,¹⁰ depression,¹¹ and obesity,¹² as well as physical inactivity and an unhealthy life style. Although serious diseases, such as Parkinson's disease, cancer and renal failure may also confound the association, and controlling for those factors attenuated the association notably, the association still remained significant. Furthermore, after we excluded women with Parkinson's disease, cancer and renal failure from the analysis, the association persisted.

Individuals with RLS may be at an increased risk of developing CHD because of the presence of periodic limb movements of sleep (PLMS),²⁶ seen in 80% of patients with RLS. Coexisting PLMS are associated with sympathetically mediated elevations in both heart rate and blood pressure.^{4–9} Arousals from sleep have also been shown to increase daytime pulse rate and blood pressure through elevated peripheral sympathetic tone in individuals without PLMS.^{27,28} The repeated long-standing increased heart rate and blood pressure may in turn increase the risk of CHD. Recent study suggest that RLS is characterized by autonomic dysregulation.²⁹

The strength of the current study is that we collected detailed information on lifestyle and chronic conditions using validated questionnaires, which enabled us to control for the potential confounders that may be associated with both RLS and heart disease. Strengths of the current study also include its prospective design. By this prospective approach, the potential for recall and selection biases is reduced. In order to reduce the bias of possible reverse causation due to pre-clinical or undiagnosed CHD, we reexamined the association between RLS and CHD after excluding the incident cases occurring between 2002 and 2004, and found similar results.

Our study has important limitations that warrant discussion. Firstly, this cohort included mostly Caucasian elderly women,³⁰ thus these findings might not be generalizable to younger individuals, male or nonwhite female populations. The rate of incident CHD in this

population (1.75 events/1000 person-years) was lower than the age-standardized rate reported in the Atherosclerosis Risk in Communities (ARIC) study (4.4 events/1000 person-years in white women),³¹ a representative sample of US adults.³² The risk of CHD is even greater among men or black women.³¹ Compared to the general population, the participants in our cohort were relatively healthy, which has been reported in previous study.³⁰ For example, the prevalence of obesity was 35% in Non-Hispanic white women aged 40 years or above in the 2001–2002 National Health and Nutrition Examination Survey³³ compared with 23% in present cohort at 2002. However, the relative homogeneity of the study population in educational attainment and socioeconomic status enhances the internal validity of this study, which is the basis of generalizability.

Secondly, we only collected information on physician-diagnosed RLS cases. However, because RLS is generally under-diagnosed,³⁴ the prevalence of 2.4% observed in the entire NHS (including those with cardiovascular disease at the baseline) might thus under-estimate the true prevalence. In previous studies, approximate 6–11% of women^{1,12,35,36} and 4–8% of men^{12,16,20,37} were found to have RLS, as assessed by detailed questionnaire or in-person interview. Thus, misclassification of RLS as non RLS in present study is inevitable. If participants with RLS were misclassified as not having RLS, the observed hazard ratios reflect a bias towards a null and an underestimation of the true effect. However, it may also lead to a selective identification of women with more severe RLS, and thus our results may not be applicable to all women with RLS. Further studies using more precise diagnostic strategies for identifying RLS in the community are warranted. Thirdly, we cannot exclude the possibility that the association of RLS and CHD may be due to RLS treatment, especially among the individuals with long duration of RLS. Several RLS treatments, including low-dose pergolide, have been reported to be associated with a higher risk of valvular heart disease.^{38–39} However, based on the results from the REST (RLS Epidemiology, symptoms, and treatment) primary care study,⁴⁰ patients with RLS were generally not treated with dopamine agents (like pergolide) during this time period.

Fourthly, although we already had adjusted for a wide range of potential confounders, we still could not rule out the possibility of residual confounding, such as the severity of hypertension and diabetes. To address this issue, we did a sensitivity analysis by further adjustment for blood pressure, duration of diabetes and use of diabetes medications, the results did not change materially. Finally, we only followed up these patients for a mean of 5.6 years. However, given that, in this short period of time, RLS patients with longer disease duration were more likely to have heart disease, we would anticipate that longer periods of follow up would show an even stronger association between RLS and heart disease. Such longer term follow up studies need to be performed.

Despite these limitations, and even in the absence of a clear understanding of mechanism—or if RLS turns out to be a marker for some other as yet unknown risk factor for CHD—the fact that RLS independently predicted CHD may have practical implications for selecting of high risk population for future primary prevention.

Conclusion

In this large-scale prospective study, we found that women with physician-diagnosed RLS of at least 3 years duration had a higher risk of developing coronary heart disease during six years of follow-up. The fact that the association between cardiovascular diseases only was found for women with longer duration RLS suggests that it is the long-term impact of RLS or RLS associated conditions that may contribute to cardiovascular disease. Among other possibilities, this may occur through the well-known increased sympathetic activation seen in RLS.²⁹ Future study is needed to verify these associations and their respective

hypotheses. Investigating the potential effects of RLS on disease progression and mortality in CHD patients is also warranted.

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CLINICAL PERSPECTIVE

Restless legs syndrome (RLS), also known as Willis Ekbohm Disease, is a common bothersome sensorimotor disorder that is characterized by an almost irresistible urge to move the legs accompanied by unpleasant sensation in the legs and a worsening of the symptoms in the evening or during the night. The cross-sectional epidemiologic studies have suggested a positive association between RLS and coronary heart disease (CHD) but not confirmed by the two subsequent prospective studies. In this article, the association was prospectively examined taking into account the duration of RLS symptoms based on the Nurse Health Study, a well-characterized prospective cohort comprising 70,694 women. It is found that women with physician diagnosed RLS, especially those with longer disease duration, tend to have a higher risk of developing CHD. In this analysis, RLS preceded the development of coronary heart disease, which suggests but can not prove a causal role for RLS in coronary heart disease. The results suggest that it is the long-term impact of RLS or RLS associated conditions that may contribute to cardiovascular disease. If the association between RLS and coronary heart disease is confirmed in future studies, we would suggest that clinicians should screen for RLS because it may be helpful for judging a patient's cardiovascular risk combined with other known risk factors for CHD.

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Table 1

Baseline characteristics according to restless legs syndrome status in the Nurses' Health Study (2002)

	Status of Physician-diagnosed Restless Legs Syndrome in 2002	
	No (n=69493)	Yes (n=1484)
Age (years)	67.4 (7.0)	67.5 (7.0) *
Body mass index (kg/m ²)	26.6 (5.3)	27.4 (5.9) *
Past smokers (%)	46.4	50.7 *
Current smoker (%)	8.3	7.0
Caucasian (%)	97.5	98.8 *
Hormone replacement therapy user (%)	35.2	39.6 *
Alcohol (g/day)	6.1 (10.7)	5.1 (9.8) *
Physical activity (met-h/week) [†]	17.8 (22.0)	16.5 (21.5) *
Regular use of aspirin (%)	46.1	44.7
Sleep duration (hours/day)	7.1 (1.0)	7.1 (1.1)
Frequent snoring (%) [‡]	18.6	25.5 *
Alternative Healthy Eating Index	47.3 (11.6)	46.9 (11.7)
Use of iron specific supplement (%)	1.8	3.2 *
Use of antidepressant (%)	10.7	27.9 *
Use of antihypertensive (%)	42.9	52.9 *
Use of anti-arrhythmic (%)	3.8	11.6 *
Physical exam in previous 2 years (%)		
for screening	84.7	80.3 *
for symptoms	14.5	24.9 *
for any purpose	94.4	96.6 *
History of diseases (%)		
Arthritis	10.3	16.9 *
Diabetes	8.5	13.0 *
Hypertension	55.7	66.5 *
Hypercholesterolemia	62.4	70.9 *
Cancer	17.5	20.2 *
Parkinson's disease	0.3	0.9 *
Renal failure	0.4	0.9 *

Values were mean (standard deviation) or percentage.

* Linear regression and chi-squared test were used to compare the differences between women with RLS and women without RLS (* $P < 0.05$).

[†] Metabolic equivalents from recreational and leisure-time activities.

[‡] Frequent snoring: snoring every night or most nights.

Table 2

Adjusted hazard ratio (HRs) and 95% confidence intervals (CIs) of coronary heart disease* according to baseline restless legs syndrome (RLS) status

	Restless legs syndrome status in 2002					P trend
	RLS vs. no RLS	No RLS	RLS Duration < 3 years	RLS Duration 3 years		
Total coronary heart disease						
Person years (PY)	8172/391041	391041	2794		5378	
No of cases	25/673	673	6		19	
Incident rate (per 10 ⁵ PY)	306/172	172	215		353	
Age adjusted RR (95%CI)	1.68 (1.13–2.51)	1 (referent)	1.19 (0.53–2.65)		1.94 (1.23–3.06)	0.005
Multivariable adjusted model 1 [†]	1.59 (1.07–2.38)	1 (referent)	1.09 (0.49–2.43)		1.88 (1.19–2.96)	0.009
Multivariable adjusted model 2 [‡]	1.46 (0.98–2.19)	1 (referent)	0.98 (0.44–2.20)		1.73 (1.09–2.74)	0.03
Multivariable adjusted model 3 [§]	1.45 (0.97–2.17)	1 (referent)	0.97 (0.43–2.17)		1.72 (1.09–2.72)	0.03
Multivariable adjusted model 4	1.46 (0.97–2.18)	1 (referent)	0.98 (0.44–2.19)		1.72 (1.09–2.73)	0.03
Nonfatal myocardial infarction						
Person years (PY)	19521	521	4		15	
No of cases	233/133	133	143		279	
Incident rate (per 105 PY)	1.67 (1.05–2.64)	1 (referent)	1.02 (0.38–2.74)		2.00 (1.20–3.35)	0.01
Age adjusted RR (95%CI)	1.58(1.00–2.50)	1 (referent)	0.94 (0.35–2.51)		1.93(1.15–3.23)	0.02
Multivariable adjusted model 1 [†]	1.47 (0.93–2.34)	1 (referent)	0.87 (0.33–2.34)		1.80 (1.08–3.02)	0.04
Multivariable adjusted model 2 [‡]	1.46 (0.92–2.32)	1 (referent)	0.86 (0.32–2.31)		1.79 (1.07–3.00)	0.047
Multivariable adjusted model 3 [§]	1.47 (0.93–2.33)	1 (referent)	0.87 (0.32–2.33)		1.80 (1.07–3.01)	0.045

* Coronary heart disease (CHD) included nonfatal myocardial infarction and fatal coronary heart diseases.

[†] Model 1 estimated from Cox proportional hazards models and adjusted for baseline age (years), BMI (<23, 23–, 25–, 30–, 35+ kg/m²), ethnicity (Caucasian or not), smoking status (never, past, or current smoker: 1–14, 15–24, 25+ cigarettes/day), menopausal status (pre- or post-menopausal), menopausal hormone use (never, past, or current user), alcohol intake (g/d: 0.0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and >15), physical activity (quintiles), alternative healthy eating index (quintile) and use of aspirin (yes or no).

[‡] Model 2 further adjusted for use of antidepressant, antihypertensive and anti-arrhythmic, and presence of diabetes, arthritis, hypertension, high cholesterol, Parkinson's disease, cancer or renal failure (each, yes/no) at baseline.

[§] Model 3 further adjusted for use of iron specific supplements, sleep duration (hrs: 5, 6, 7, 8, or 9 per 24 hr) and frequent snoring (yes/no or missing).

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Model 4: all covariables included in the model were treated as time-varying variables except for ethnicity, sleep duration and frequent snoring.