ORIGINAL RESEARCH

Treating Restless Legs Syndrome Was Associated With Low Risk of Cardiovascular Disease: A Cohort Study With 3.4 Years of Follow-Up

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BACKGROUND: Restless legs syndrome (RLS) is associated with higher cardiovascular disease (CVD) risk. However, it remains unknown whether treatment of RLS lowers the cardiovascular risk associated with RLS.

METHODS AND RESULTS: All data were collected retrospectively, but subjects were prospectively followed forward in time to determine outcomes of interest. We used the Truven Health MarketScan Commercial Claims and Encounters database from January 1, 2006, through December 31, 2014. Participants were 169 393 individuals, which included 24 199 nonpregnant participants with an RLS diagnosis (16 694 receiving treatments for RLS and 7505 without treatment) during 2006 to 2008 and 145 194 age- and sex-matched participants without RLS. All participants were free of CVD before January 1, 2009 (analysis baseline). Incident CVD cases (myocardial infarction, angina, stroke, atrial fibrillation, and heart failure) were identified. We adjusted for potential confounders, such as presence of chronic conditions and medication use. We identified 16 574 incident CVD cases during 2009 to 2014. Relative to the non-RLS group, the adjusted hazard ratio (HR) for future CVD was 1.26 (95% CI, 1.20–1.32) ($P<0.001$) for the RLS with treatment group, and 1.53 (95% CI, 1.42–1.65) ($P<0.001$) for the RLS without treatment group. Significant lower CVD risk was observed for all different RLS treatments, including dopaminergics, anticonvulsants, benzodiazepines, and opiates (adjusted HRs range, 0.71-0.84; $P<0.001$ for all), except for ergot-dopamine use.

CONCLUSIONS: RLS was associated with higher future CVD risk. However, RLS was associated with statistically significantly less future cardiovascular risk in RLS patients with treatment than in those without treatment.

Key Words: cardiovascular disease ■ cohort study ■ restless legs syndrome ■ stroke ■ treatment

The restless legs syndrome (RLS) is characterized by 4 obligate criteria: (1) an urge to move the legs, usually in response to discomforting sensations in the legs; (2) worsening of symptoms later in the evening or at night; (3) worsening of the symptoms while at rest (ie, lying or sitting); and (4) at least partial and temporary relief by activity.[1] A survey indicates that the quality of life in patients with RLS is as low as that seen in diabetes mellitus, depression, or osteoarthritis with hypertension.[2] Even after treatment, it is estimated that up to one third of those who seek medical attention are getting incomplete relief.[3]

Treatments include the following: dopaminergic agents with 3 of these, pramipexole, ropinirole, and rotigotine, Food and Drug Administration approved for use in RLS; α-2-Δ calcium channel anticonvulsant drugs, such as pregabalin and gabapentin enacarbil, with the latter Food and Drug Administration approved

CLINICAL PERSPECTIVE

What Is New?
- Restless legs syndrome (RLS) previously has been shown to be associated with high cardiovascular risk.
- There is no previous study to determine whether treatment of RLS with RLS medications lowers cardiovascular risk.
- In this epidemiological cohort study in which retrospective data were followed forward in time, treatment with well-proven medications for RLS is significantly associated with lower future cardiovascular risk among those with RLS, and this was observed for all treatments studied, except ergotamine-based dopamine agonists; the wide variety of agents showing improvement of cardiovascular disease in RLS suggests that this effect is specific to the improvement of RLS.

What Are the Clinical Implications?
- The results of this study add further evidence to the premise that RLS may lead to cardiovascular disease.
- Treatment of RLS symptoms may decrease the cardiovascular risk associated with RLS, but further studies are needed to more fully explore this possibility.

Nonstandard Abbreviations and Acronyms

NHS   Nurses' Health Study
PLMS   periodic limb movements in sleep
RLS   restless legs syndrome

for use[1,3]; and opioids, such as the agonist/antagonist combination drug oxycodone/naloxone, approved for use in refractory RLS in 20 countries throughout Europe, including France, Germany, and the United Kingdom.[4] Iron therapy, particularly intravenous iron therapy in the form of ferric carboxymaltose, is effective in double-blind studies; and benzodiazepines can be helpful in selective cases, particularly when insomnia is involved.[1,3]

Over the past 15 years, there have been several publications suggesting a link between RLS and heart disease, stroke, and hypertension. Patients with RLS also have a nondipping pattern for nocturnal blood pressure, a known risk factor for cardiovascular disease (CVD),[5] and studies of vascular endothelial function in RLS have also shown abnormalities.[6] Magnetic resonance imaging studies of the brain have shown

increased microvascular disease in RLS, which is a prestroke condition.[7] The relationship of RLS to heart disease, hypertension, and stroke could be a reciprocal one, with some epidemiological studies indicating that RLS can be a risk factor for the development of CVD and other epidemiological studies indicating that CVD could be a risk factor for the development of RLS.[8–11] Yet other epidemiological studies indicate no relationship whatsoever when comorbidities are taken into account.[12] In an analysis based on 57 417 female participants of the NHS (Nurses' Health Study), we found that physician-diagnosed RLS was significantly associated with 43% increased future CVD mortality.[10] On the other hand, we did not observe this same relationship in men.[13] Direct observational studies do indicate that RLS can occur acutely after stroke in a large series of patients, presumably because of anatomic considerations.[14]

If RLS is a risk factor for the development of CVD, a major question in the field has been whether treatment of the RLS/periodic limb movements in sleep (PLMS) can defray this increased cardiovascular risk. The current study is an exploration of this nexus with 24 199 nonpregnant participants with RLS diagnosis (16 694 receiving RLS-related treatment and 7505 without treatment) during 2006 to 2008 and 145 194 age- and sex-matched participants without RLS.

METHODS

Data, Materials, and Code Disclosure Statement

The data that support the findings of this study are available from Xiang Gao, MD, PhD, Nutritional Epidemiology Lab, Department of Nutritional Sciences, The Pennsylvania State University, 109 Chandlee Lab, University Park, PA 16802; telephone 814-867-5959; fax 814-863-6103.

Source of Data

This is a prospective cohort study. All data were collected retrospectively, but subjects were followed forward in time to determine outcomes of interest. The study was based on the IBM Truven Health MarketScan Commercial Claims and Encounters data (IBM Truven Health Analytics) from January 1, 2006, through December 31, 2014, which contains individual-level, longitudinal, and comprehensive healthcare use data for a sample of privately insured people, aged 0 to 64 years, in the United States from all 50 states and the District of Columbia, as detailed elsewhere.[15] The IBM Truven Health Analytics (MarketScan) database was obtained through agreement with Penn State.

This study protocol was submitted to the Pennsylvania State College of Medicine institutional review board and was not considered to be human subject research. Because data of the study participants were deidentified, informed consent was waived.

Cohort Derivation and Assessment of Exposure

We identified patients with RLS, aged ≥20 years, with the RLS *International Classification of Diseases, Ninth Revision* (*ICD-9*), code (333.94) during January 1, 2006, through December 31, 2008. To increase statistical power, a 1:6 matching ratio was used for participants with RLS versus controls. For each patient with RLS, we randomly matched 6 individuals without RLS, who had the same birth year and sex. All participants met the following criteria: (1) free of CVD (including coronary heart disease, stroke, atrial fibrillation, and heart failure; see Table S1 for codes used), malignancy (*ICD-9* codes: 140–172, 174–199.1, and 200–208), and end-stage renal disease (*ICD-9* code 585.6) before January 1, 2009 (the analysis baseline), (2) not pregnant at least a year before the RLS diagnosis data (the date of the first RLS *ICD-9* code), (3) having a 3-year (2006–2008) continuous enrollment in a medical and pharmacy benefits program, and (4) having complete data on the exposure, outcome, and covariates. Finally, 24 199 participants with RLS and 145 194 age- and sex-matched participants without RLS (average age, 49 years; 31% men) were included in the current analysis. We identified 16 694 patients with RLS with any prescription of RLS-related medications during 2006 to 2008, including non–ergot-dopaminergic agents, ergot-dopaminergic agents, benzodiazepines, anticonvulsants, and opiates (Table S2), and 7505 patients with RLS without treatment. We used the first date of receiving RLS treatment as the index date for the patients with RLS with treatment and the first date of RLS diagnosis for patients with RLS without treatment in the current analysis.

Participants were divided into 3 categories in our primary analysis, according to the RLS and treatment status: non-RLS, RLS with treatment, and RLS without treatment. Because different RLS treatments may have different impact on cardiovascular health,[16,17] we also examined whether these different treatments were specifically associated with altered CVD risk in the secondary analysis.

Assessment of Outcomes

The primary outcome was the composite end of any CVDs (coronary heart disease, stroke, atrial fibrillation, and heart failure) that occurred during 2009 to 2014.

Incident CVD cases were identified by searching the *ICD-9* codes and Current Procedural Terminology (Table S1). We also created an alternate composite CVD outcome, in which we did not include atrial fibrillation, coronary atherosclerosis, and other unspecified forms of chronic ischemic heart disease. As the secondary outcome, association of RLS and related treatment with these individual CVDs was explored.

Assessment of Covariates

On the basis of a comprehensive literature review, we derived 4 groups of potential confounders: demographics (age, sex, and region), lifestyle (smoking, alcohol consumption, and obesity), presence of chronic conditions, and medications from the baseline period. Because the MarketScan data did not contain detailed information on smoking status, presence of chronic obstructive pulmonary disease was used as a surrogate, as done previously.[18] We assessed the chronic conditions, including depression, obstructive sleep apnea, insomnia, diabetes mellitus, hypertension, peripheral neuropathy, arthritis, iron-deficiency anemia, Parkinson disease, and chronic kidney disease. We evaluated the medications, including antiplatelets, anticoagulants, statins, other lipid-lowering drugs, and antihypertensive and hypoglycemic agents. We selected these factors because they could be associated with both exposure (RLS status) and outcome (CVD risk). However, for some factors, such as smoking and social economic status factors, although the current literature does not support that they are well-established risk factors for RLS (thus, do not meet the criteria for confounder),[19,20] we still included their surrogate factors as covariates because they are associated with CVD risk.

Statistical Analysis

The person-time for each participant was accumulated from the index data to the first occurrence of an outcome of interest, inpatient death, end of enrollment, or end of study period (December 31, 2014), whichever took place first. Statistical comparisons were made across 3 RLS categories (non-RLS, RLS with treatment, and RLS without treatment), and an ANOVA test was used to for continuous variables and χ^2 analysis was used for categorical variables.

We used the Kaplan-Meier method to estimate the cumulative CVD rate, with between-group comparisons of cumulative event rates calculated by means of the log-rank test. Cox proportional hazards regression analysis was used to calculate hazards ratios (HRs) and corresponding 95% CIs for the risk of developing CVD across the 3 RLS categories, with the "non-RLS" as reference group, adjusted for age, sex, region, alcohol

consumption, obesity, presence of chronic obstructive pulmonary disease, depression, obstructive sleep apnea, insomnia, diabetes mellitus, hypertension, peripheral neuropathy, arthritis, iron-deficiency anemia, Parkinson disease, chronic kidney disease, and use of antiplatelets, anticoagulants, statins, and antihypertensive and hypoglycemic medications. The proportional hazards assumption was violated ($P<0.001$), which could be because of the large sample size of the current study. We thus further reported HRs, stratified by follow-up duration (<1, 1–1.99, and ≥2 years).

We also conducted an analysis to examine whether RLS treatment was associated with altered CVD risk, in which the RLS without treatment group was used as reference group (P for proportional hazards assumption=0.11). Interactions of RLS, with age (years) and sex (the 2 most important determinants for risk of RLS and CVD), in relation to CVD risk were assessed by likelihood ratio testing, adjusting for aforementioned covariates. Subgroup analyses were further conducted when the significant interaction was observed.

We conducted a sensitivity analysis with inverse probability of treatment weighting using the propensity score as a different approach, which could significantly reduce the effects of confounders and achieve a better balance between the 3 RLS groups.[21] To reduce the possible misclassification for RLS ascertainment caused by errors in *ICD-9* coding, record entry, or diagnosis, we repeated analyses by restricting the RLS cases with ≥2 RLS *ICD-9* codes. Because some RLS-related medicines are not specific, which could be used for other conditions, we further excluded 50 981 participants without RLS who used any RLS-related medications. Because individuals with RLS were more likely to have other sleep disorders, we conducted another sensitivity analysis by excluding individuals with insomnia and obstructive sleep apnea. Finally, we restricted our analyses among an apparently healthy population, who were free of sleep apnea, insomnia, depression, obesity, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, hyperlipidemia, peripheral neuropathy, rheumatic arthritics, osteoarthritis, chronic kidney disease, iron-deficiency anemia, and Parkinson disease, and did not use common medications (ie, antiplatelets, anticoagulants, statins, and antihypertensives and hypoglycemics). This could minimize the residual confounding attributable to uneven distribution of these factors across 3 RLS groups.

RESULTS

During 661 215 person-years of follow-up, we identified 16 574 incident CVD cases. Individuals with RLS, particularly those without treatment, had higher likelihood of having chronic conditions, such as metabolic abnormities, sleep disorders, iron-deficiency anemia, depression, and Parkinson disease, relative to those without RLS (Table 1). Of note, individuals in the RLS without treatment group also had lower prevalence of use of other medications, such as lipid-lowering, antihypertensive, and hypoglycemic medications, although they experienced higher prevalence of chronic conditions (Table 1).

Presence of RLS was associated with higher risk of developing CVD (Figure 1 and Table 2). Relative to the non-RLS group, the adjusted HR was 1.26 (95% CI, 1.20–1.32; $P<0.001$) for the RLS with treatment group, and 1.53 (95% CI, 1.42–1.65; $P<0.001$) for the RLS without any treatment group, after adjusting for the potential confounders (Table 2). Stratified analysis based on follow-up duration showed a similar pattern (Table 2). Propensity score adjustment or restricting to patients with RLS with at least 2 RLS *ICD-9* codes did not materially change the observed results (Table 2). Significant results were consistently obtained when we excluded individuals without RLS but using any RLS treatment (Table 2). We obtained similar results when we excluded atrial fibrillation and other nonischemic diseases from the primary composite CVD outcome: the adjusted HR was 1.29 (95% CI, 1.22–1.35) for those with RLS treatment and 1.51 (95% CI, 1.39–1.63) for RLS without treatment. Excluding participants with other common chronic conditions (eg, sleep disorders and depression) and use of common medications (eg, statins and antihypertensives) also generated similar results (Table 2). A similar pattern was observed when individual CVDs were examined as outcome (Table S3). Slightly stronger association was observed in women, relative to men (P-interaction=0.04) (Table S4). The interaction between RLS and age was not significant (P-interaction=0.07).

Among patients with RLS, treatment was associated with 13% lower CVD risk (95% CI, 4%–20%; $P<0.001$), relative to those without RLS treatment (Figure 2). Excluding those with major chronic conditions and use of common medications generated similar results (adjusted HR, 0.81; 95% CI, 0.69–0.95). Using alternate CVD outcome, excluding atrial fibrillation, atherosclerosis, and forms of chronic ischemic heart disease other than myocardial infarction and angina, generated similar significant results (adjusted HR, 0.90; 95% CI, 0.82–0.99; $P=0.03$). Similarly, RLS treatment was associated with significantly lower risk of atrial fibrillation (adjusted HR, 0.69; 95% CI, 0.56–0.87; $P<0.001$) but not for other unspecified chronic ischemic heart disease (adjusted HR, 0.92; 95% CI, 0.79–1.07; $P=0.25$). Significant lower CVD risk was observed for all different RLS treatments (dopaminergics, anticonvulsants, benzodiazepines, or opiates; adjusted HR range, 0.71–0.84; $P<0.001$ for all), except for ergot-dopamine use (adjusted HR, 1.01; 95% CI, 0.48–2.15; $P=0.98$) (Figure 2). Specifically, the

Table 1.   Baseline Basic Characteristics, According to RLS Status

| Characteristic | No RLS (n=145 194) | RLS | | P Value for Difference* |
		With Treatment (n=16 694)	Without Treatment (n=7505)	
Age, mean±SD, y	49.4±9.1	49.4±8.9	49.4±9.6	0.99
Male sex, %	31.5	30.9	32.9	0.008
Rural residence, %	19.4	24.5	25.5	<0.001
Region of United States, %				<0.001
South	40.0	47.0	59.9	
West	22.6	14.9	8.2	
Midwest	27.6	31.8	25.9	
Northeast	0.2	0.3	0.1	
Unknown	9.6	6.0	5.9	
Diabetes mellitus, %	7.3	9.6	10.2	<0.001
Hypertension, %	19.2	26.4	29.5	<0.001
Obesity, %	1.5	4.5	5.4	<0.001
Hyperlipidemia, %	2.7	4.2	5.5	<0.001
Obstructive sleep apnea, %	1.7	13.5	12.6	<0.001
Depression, %	3.0	9.0	6.5	<0.001
Insomnia, %	1.1	6.8	7.0	<0.001
Peripheral neuropathy, %	0.4	2.6	2.6	<0.001
Rheumatologic disease, %	1.1	2.0	2.0	<0.001
Osteoarthritis, %	4.9	12.6	12.0	<0.001
Iron-deficiency anemia, %	1.0	2.7	2.7	<0.001
CKD, %	0.3	0.5	0.6	<0.001
Parkinson disease, %	0.1	0.2	0.2	<0.001
COPD, %	6.0	13.2	14.6	<0.001
Alcohol drinking, %	0.29	0.65	0.55	<0.001
Antiplatelets, % (n)	0.2 (284)	0.43 (71)	0.07 (5)	<0.001
Anticoagulants, % (n)	0.02 (30)	0.01 (3)	0 (1)	0.38
Statins, % (n)	13.9 (20 228)	14.9 (2459)	3.8 (313)	<0.001
Other lipid-lowering drugs, % (n)	4.7 (6755)	6.1 (1014)	1.4 (117)	<0.001
Antihypertensive drugs, % (n)	27.8 (40 559)	31.9 (5286)	8.3 (648)	<0.001
Hypoglycemic drugs, % (n)	10.9 (15 903)	11.9 (1970)	3.1 (243)	<0.001

CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; and RLS, restless legs syndrome.

*On the basis of comparison between any 2 of the 3 RLS groups.

association between RLS treatment and low CVD risk was statistically significant only for patients with RLS who received combinations of different medications for the treatment of RLS (n=10 559; adjusted HR, 0.73; 95% CI, 0.67–0.80) but not for those receiving a single medication for the treatment of RLS (n=6135; adjusted HR, 1.09; 95% CI, 0.99–1.21), relative to those without any treatment.

DISCUSSION

In this large-scale national claim's data set, physician-diagnosed RLS was associated with higher future CVD risk, as has been documented in much of the previous literature.[8–12,14] Treating RLS appeared to alleviate this potential harmful impact. This was true of all the agents commonly used for the treatment of RLS, except for ergot-based dopaminergic alkaloids, a result compatible with the known deleterious effect of ergot alkaloids on cardiovascular health (eg, cardiac valvular fibrosis).[16,17] The wide variety of agents showing improvement of CVD risk in RLS suggests that this effect is specific to the improvement of RLS. To our knowledge, our study represents the first attempt to determine if treatment of RLS lowers the increased cardiovascular risk associated with RLS. Using RLS treatment statistically significantly lowers the cardiovascular risk associated with RLS but not to the level of subjects without RLS. One of the major strengths of this study is its prospective nature. All of
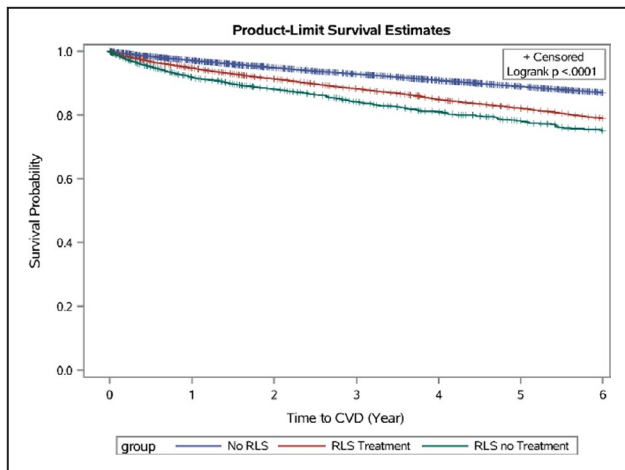
Figure 1. The Kaplan-Meier survival curves for cardiovascular disease (CVD) during 2009 to 2014, according to baseline restless legs syndrome (RLS) status.

the data were collected prospectively, and subjects were followed forward in time to determine outcomes of interest. Another one of the major strengths of this study is that it is not an industry-sponsored study and thus multiple treatments well known to be effective in the treatment of RLS were able to be evaluated.

Because this study is based on claims data, we do not have before and after ratings of the severity of RLS and thus we do not know for sure that the improvement in RLS-related CVD with RLS treatment is really paralleled by an improvement in RLS. However, the numerous large clinical trials showing a positive benefit on RLS from the medications chosen for this study would suggest that this is so.[1,3] Another limitation is that we did not have information on why some patients with RLS use medications and why some patients with RLS did not receive any treatment. One potential explanation is that this difference could be because of RLS severity. However, we found that patients with RLS with treatment had lower future CVD risk, relative to those without treatment. Using *ICD-9* codes to identify patients with RLS could lead to misclassification of the non-RLS group, as RLS is an underdiagnosed disease. Therefore, the observed association between presence of RLS and CVD could be underestimated. For the same reason, measurement errors could be introduced or other sleep disorders (eg, insomnia and obstructive sleep apnea) could be assessed via searching *ICD-9* codes, which could introduce residual confounding. Our study is also limited by lack of direct assessment on several covariates, such as smoking (we used the presence of chronic obstructive pulmonary disease as a surrogate measure of smoking) and social economic status (we used region and residence as surrogates).

However, although these factors are associated with CVD risk, whether they are risk factors for RLS remains unclear.[19,20] Furthermore, sensitivity analyses excluding participants with major chronic diseases, which are closely related to smoking and social economic status, generated similar results. This suggests that the impact of residual confounding attributable to these factors on the RLS-CVD relationship could be small.

The reason why a putative improvement in RLS would cause an improvement in RLS-related cardiovascular risk is unknown. An intermediary mechanism may be an improvement in sleep, as it is well known that RLS causes severe insomnia[1] and it is also well known that insomnia alone can increase cardiovascular risk. However, again, because our current study was based on claims data, we did not have access to detailed sleep schedule histories. On the other hand, it is likely, if there is an impact of the medications on sleep, that this is as a result of the improvement in RLS symptoms rather than a direct impact on sleep because none of the medications studied are used as hypnosedatives, minus the benzodiazepines.[1,3] One could also consider the possibility that the dopaminergic agents could lower cardiovascular risk by their hypotensive effect. However, this antihypertensive effect is not characteristic of the other therapeutic agents in this study. Again, this suggests that the improvement in CVD could be as a result of the direct impact of the various therapeutic modalities in this study on the RLS symptoms themselves.

The agents in this study have been shown to ameliorate the symptoms of RLS in both short-term and long-term studies.[1,3,4] In some cases, however, long-term treatment with dopaminergic therapy may lead to a paradoxical worsening for the symptoms called augmentation.[1,3,4] As this study was based on claims data, we did not have any long-term measure of augmentation. However, despite the fact that we did not have this measure, our study shows that long-term the dopaminergic agents were associated with lower cardiovascular risk.

One of the weaknesses of the current study was that we did not include the effect of iron therapy on future cardiovascular risk. However, at the time of the initiation of the study, we believed that iron therapy is so frequently used as an adjunct to other medications in RLS that it would be difficult to exclude it as a confounding factor in the determination of the cardiovascular lowering risk of other individual drugs. In addition, despite the fact that iron deficiency has a strong pathophysiologic link to RLS, the therapeutic response of RLS to oral iron is rather low and dependent on months of treatment for therapeutic benefit to be obtained, as opposed to the pharmacological agents where improvement is immediate once the proper

Table 2. Hazard ratios for the Development of Future CVD Among 169 393 Participants When the RLS With Treatment Group and the RLS Without Treatment Group Were Each Individually Compared With the Group With No RLS

Variable	No RLS	RLS With Treatment	RLS Without Treatment
Person-years	580 070	60 287	20 858
CVD case, n	13 659	2128	787
Incident rate, per 1000 person-years	24	35	38
Model 1	1 (Reference)	1.51 (1.44–1.58)	1.61 (1.49–1.73)
Model 2	1 (Reference)	1.42 (1.35–1.48)	1.44 (1.34–1.55)
Model 3	1 (Reference)	1.26 (1.20–1.32)	1.53 (1.42–1.65)
Stratified by follow-up duration, y			
<1	1 (Reference)	1.04 (0.92–1.17)	1.06 (0.89–1.27)
1–1.9	1 (Reference)	1.22 (1.10–1.35)	1.53 (1.33–1.75)
≥2	1 (Reference)	1.37 (1.29–1.46)	1.80 (1.33–1.75)
Sensitivity analyses*			
Propensity score adjustment	1 (Reference)	1.46 (1.41–1.52)	1.72 (1.65–1.80)
Alternate composite CVD outcome‡	1 (Reference)	1.29 (1.22–1.35)	1.51 (1.39–1.63)
Restricting to 6946 patients with RLS with at least 2 RLS *ICD-9* codes during 2006–2008	1 (Reference)	1.30 (1.19–1.41)	1.75 (1.52–2.01)
Excluding 50 981 participants without RLS but using any RLS-related treatments	1 (Reference)	1.38 (1.31–1.46)	1.68 (1.55–1.82)
Excluding 16 362 participants with insomnia or obstructive sleep apnea	1 (Reference)	1.32 (1.25–1.39)	1.59 (1.46–1.73)
Excluding 78 528 participants with common chronic conditions and use of antiplatelets, anticoagulants, statins, antihypertensives, and hypoglycemics§	1 (Reference)	1.31 (1.19–1.45)	1.58 (1.38–1.80)

Data are given as HR (95% CI), unless otherwise indicated. Model 1, age and sex adjusted. Model 2, further adjustment for residence (rural vs urban), region (east, south, Midwest, and unknown), alcohol consumption, obesity, and chronic obstructive pulmonary disease (surrogate for smoking). Model 3, further adjustment for presence of diabetes mellitus, hypertension, hyperlipidemia, sleep apnea, depression, insomnia, peripheral neuropathy, rheumatic arthritis, osteoarthritis, chronic kidney disease, iron-deficiency anemia, or Parkinson disease (each yes/no), and use of antiplatelets, anticoagulants, statins, antihypertensives, and hypoglycemics (each yes/no). *P*<0.001 for all comparisons in the table. CVD indicates cardiovascular disease; HR, hazard ratio; *ICD-9*, *International Classification of Diseases, Ninth Revision*; and RLS, restless legs syndrome.

*On the basis of model 3.

†*P* values for proportional hazard assumption were 0.01 for follow-up duration <1 years, 0.07 for follow-up duration 1 to 1.9 years, and 0.33 for follow-up duration ≥2 years.

‡Excluding atrial fibrillation and other forms of chronic ischemic heart disease. Alternate CVD outcome included myocardial infarction, angina, coronary artery bypass grafting, percutaneous coronary intervention, heart failure, ischemic stroke, hemorrhagic stroke, and other strokes.
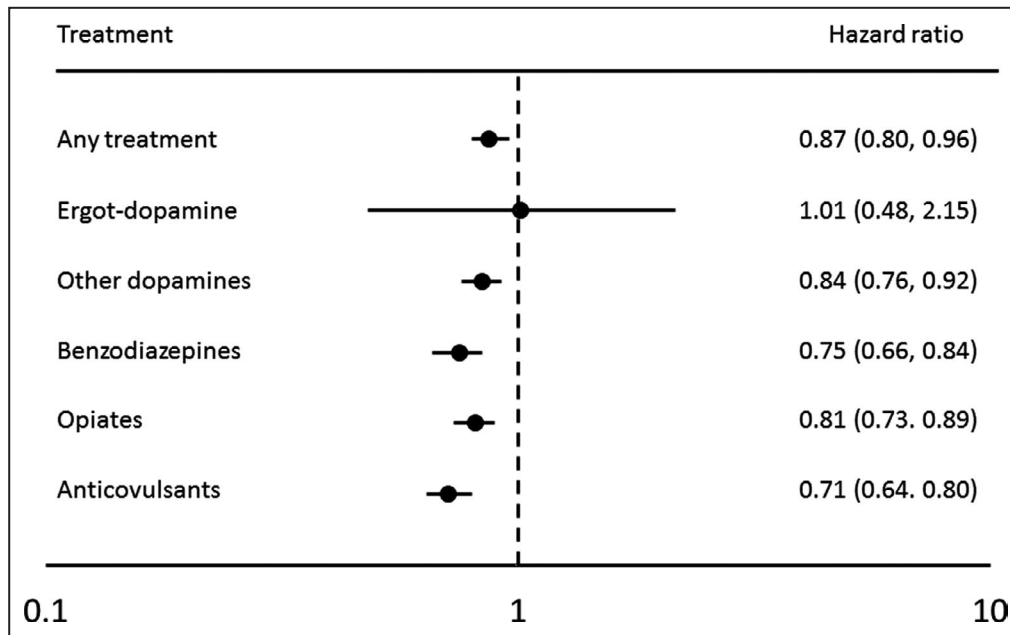
§Common chronic conditions include obesity, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, hyperlipidemia, sleep apnea, depression, insomnia, peripheral neuropathy, rheumatoid arthritis, osteoarthritis, chronic kidney disease, iron-deficiency anemia, and Parkinson disease. These variables were thus not included in the model.

doses are obtained. We believed that this also would interfere with the proper determination of the impact of iron on CVD.

Because this study was a secondary data analysis based on existing data, we did not have the opportunity to bring patients into the laboratory and do an overnight polysomnography to determine whether our subjects had PLMS. Although not necessary for the diagnosis of RLS, PLMS or repetitive involuntary leg movements occur during sleep in ≈80% of patients with RLS, although PLMS may also occur in isolation.[1] There is also a strong literature connecting PLMS to CVD. More specifically, early studies showed a link of PLMS to congestive heart failure, and in a separate study, the number of PLMS were shown to parallel the level of daytime hypertension.[22–24] Echocardiographic abnormalities have been shown to be related to PLMS.[25,26] Patients with PLMS

also have a higher prevalence of cardiac arrhythmias than would be expected by chance alone.[27] Magnetic resonance imaging studies of the brain have shown that the level of PLMS is also related to transient ischemic attack or minor stroke.[28] Studies also show that marked increases in pulse and blood pressure accompany PLMS in patients with RLS.[29–32] Among the mechanisms proposed for the connection between RLS/PLMS and heart disease/hypertension and stroke are the nocturnal hypertension generated by the PLMS. In general, all the medications that improve RLS also improve PLMS.[1] In this light, it is interesting that the dopamine agonist rotigotine, which is one of the main treatments for RLS, lowers the pulse and blood pressure elevations seen with PLMS in patients with RLS.[33]

In patients with RLS, there is a nondipping pattern observed in nocturnal blood pressure, which is

Treatment	Hazard ratio
Any treatment	0.87 (0.80, 0.96)
Ergot-dopamine	1.01 (0.48, 2.15)
Other dopamines	0.84 (0.76, 0.92)
Benzodiazepines	0.75 (0.66, 0.84)
Opiates	0.81 (0.73, 0.89)
Anticovulsants	0.71 (0.64, 0.80)

0.1   1   10

Figure 2. Adjusted hazard ratios of cardiovascular disease, according to restless legs syndrome (RLS) treatment status (RLS with treatment vs RLS without treatment), among 24 199 participants with RLS.
Adjusted for age, sex, residence (rural vs urban), region (east, south, Midwest, and unknown), alcohol consumption, presence of obesity, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, hyperlipidemia, sleep apnea, depression, insomnia, peripheral neuropathy, rheumatic arthritics, osteoarthritis, chronic kidney disease, iron-deficiency anemia, or Parkinson disease (each yes/no), and use of antiplatelets, anticoagulants, statins, antihypertensives, and hypoglycemics (each yes/no). *P* values were <0.001 for all, except for ergot-dopamine (*P*=0.98).

a well-known risk factor the development of CVD.[5] Other mechanisms for the development of CVD in RLS have been reviewed in detail and include daytime hypertension, sympathetic overactivity, increased atherosclerotic plaque formation and rupture, insomnia, hypoxia, and upregulation of inflammatory markers.[34,35]

A randomized controlled trial of a single agent for the treatment of RLS, where controls as well as patients receive drug and placebo, is necessary to definitively prove that RLS treatment lowers cardiovascular risk. However, the large number of participants and the length of follow-up that would generally be needed for such a study are challenges that would need to be overcome with unique experimental paradigms.

CONCLUSIONS

In conclusion, this study shows that RLS is associated with increased cardiovascular risk, consistent with the previous literature, and we show for the first time that RLS treatment with various known effective treatments for RLS lowers this increased cardiovascular risk. The large number and type of medications used suggest that the effect is specific to the amelioration of RLS,

but large randomized clinical trials will be needed to further delineate this effect.

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Supplementary Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 codes or procedure code used to define cardiovascular diseases.

cardiovascular disease	2015 ICD-9-CM Diagnosis Codes
Myocardial infarction	410
Angina	411, 413
Other forms of chronic ischemic heart disease	414.0, 414.8, 414.9
Coronary artery bypass grafting	36.1 (2015 ICD-9-CM Procedure Codes)
Percutaneous coronary intervention	36.0 (2015 ICD-9-CM Procedure Codes)
Atrial fibrillation	427.3
Heart failure	428
Ischemic stroke	433, 434, 436
Hemorrhagic stroke	431,432
Subarachnoid hemorrhage	430
Other or unspecified stroke	435

Table S2. Restless legs syndrome treatment.

DRUG NAME	GROUP
Acetaminophen/codeine Phosphate	Opiates
Acetaminophen/hydrocodone Bitartrate	Opiates
Acetaminophen/oxycodone Hydrochloride	Opiates
Aspirin/oxycodone Hydrochloride	Opiates
Codeine Phos/dexbrompheniramine Maleate/pse Hcl	Opiates
Codeine Phos/dexchlorpheniramine Mal/phenyleph Hcl	Opiates
Codeine Phos/gg/pse Hcl	Opiates
Codeine Phos/phenyleph Hcl/promethazine Hcl	Opiates
Codeine Phos/phenyleph Hcl/pyril Mal	Opiates
Codeine Phosphate/guaifenesin	Opiates
Codeine Phosphate/phenylephrine Hydrochloride	Opiates
Codeine Phosphate/promethazine Hydrochloride	Opiates
Codeine Phosphate/pseudoephedrine Hydrochloride	Opiates
Codeine Sulfate	Opiates
Hydrocodone Bitartrate	Opiates
Hydrocodone Bitartrate/ibuprofen	Opiates
Hydrocodone Bitartrate/phenylephrine Hydrochloride	Opiates
Hydrocodone Bitartrate/potassium Guaiacolsulfonate	Opiates
Hydrocodone Tannate/pseudoephedrine Tannate	Opiates
Methadone Hydrochloride	Opiates
Oxycodone Hydrochloride	Opiates
Clonazepam	Benzodiazepines
Diazepam; lubricant	Benzodiazepines
Gabapentin	Anticonvulsants

Gabapentin Enacarbil	Anticonvulsants
Gabapentin; gabapentin	Anticonvulsants
Pregabalin	Anticonvulsants
Pramipexole Dihydrochloride	Dopaminergic
Ropinirole Hcl; ropinirole Hcl; ropinirole HclPregabalin	Dopaminergic
Ropinirole Hydrochloride Ropinirole Hcl; ropinirole Hcl; ropinirole Hcl	Dopaminergic
RotigotineRopinirole Hydrochloride	Dopaminergic
Rotigotine	Dopaminergic
Pergolide (Permax)	Ergot-dopamine
bromocriptine (Parlodel)	Ergot-dopamine
cabergoline (Dostinex)	Ergot-dopamine

Table S3. Hazard ratios (HRs) for the future development of different cardiovascular diseases (CVDs when the RLS with treatment group and the RLS without treatment group were each individually compared to the group with no RLS.

Individual cardiovascular disease	No RLS	RLS with treatment	RLS without treatment
Myocardial infarction	1 (Ref.)	1.25(1.05, 1.50)*	1.32(0.97, 1.79)
Angina	1 (Ref.)	1.43(1.30, 1.58)***	1.45(1.23, 1.71)***
Other forms of chronic ischemic heart disease	1 (Ref.)	1.35(1.25, 1.46) ***	1.57(1.38, 1.77) ***
Coronary artery bypass grafting	1 (Ref.)	1.25(1.06, 1.48)**	1.45(1.11, 1.89)**
Coronary Artery disease	1 (Ref.)	1.35(1.25, 1.46) ***	1.57(1.38, 1.77) ***
Percutaneous coronary intervention	1 (Ref.)	1.17(0.86, 1.60)	0.56 (0.28, 1.15)
Atrial fibrillation	1 (Ref.)	1.17(1.03, 1.32)*	1.88(1.58, 2.25)***
Heart failure	1 (Ref.)	1.46(1.29, 1.65) ***	1.90(1.57, 2.31) ***
Ischemic stroke	1 (Ref.)	1.26(1.14, 1.38) ***	1.39(1.19, 1.62) ***
Hemorrhagic stroke	1 (Ref.)	0.98(0.69, 1.38)	1.10(0.63, 1.91)
Subarachnoid hemorrhage	1 (Ref.)	1.48(0.92, 2.38)	1.74(0.83, 3.67)
Other or unspecified stroke	1 (Ref.)	1.51(1.32, 1.72) ***	1.77(1.44, 2.18) ***

adjusted for age, sex, residence (rural vs Urban), region (east, south, Midwest, and unknown), alcohol consumption, presence of obesity, COPD, diabetes, hypertension, hyperlipidemia, sleep Apnea, depression, insomnia, peripheral neuropathy, Rheumatic arthritics, Osteoarthritis, CKD, Iron deficiency anemia, or Parkinson disease (each, yes/no), and use of antiplatelets, anticoagulants, statins, antihypertensives and hypoglycemic treatment (each, yes/no).

* P<0.05 ** P<0.01 *** P<0.001, relative to No RLS

Restless legs syndrome, RLS; Chronic kidney disease, CKD; Chronic obstructive pulmonary disease, COPD; cardiovascular disease, CVD

Table S4. HRs for the development of future CVD when the RLS with treatment group and the RLS without treatment group were each individually compared to the group with no RLS stratified by sex.

	No RLS	RLS with treatment	RLS without treatment	P-interaction
Sex				0.04
Men	1(ref)	1.22 (1.12, 1.32)*	1.37 (1.21, 1.55)*	
Women	1(ref)	1.29 (1.21, 1.36)*	1.64 (1.50, 1.80)*	

adjusted for age (y), residence (rural vs Urban), region (east, south, Midwest, and unknown), alcohol consumption, presence of obesity, COPD, diabetes, hypertension, hyperlipidemia, sleep Apnea, depression, insomnia, peripheral neuropathy, Rheumatic arthritics, Osteoarthritis, CKD, Iron deficiency anemia, or Parkinson disease (each, yes/no), and use of antiplatelets, anticoagulants, statins, antihypertensives and hypoglycemic treatment (each, yes/no).

* $P<0.001$, relative to the No RLS group

Restless legs syndrome, RLS; Chronic kidney disease, CKD; Chronic obstructive pulmonary disease, COPD; cardiovascular disease, CVD