## Title

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## Authors

Van Den Eeden, Stephen K
Albers, Kathleen B
Davidson, Julie E
et al.

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# Risk of Cardiovascular Disease Associated with a Restless Legs Syndrome Diagnosis in a Retrospective Cohort Study from Kaiser Permanente Northern California

Stephen K. Van Den Eeden, PhD[1]; Kathleen B. Albers, MPH[1]; Julie E. Davidson, PhD[2]; Clete A. Kushida, MD[3]; Amethyst D. Leimpeter, MS[1]; Lorene M. Nelson, PhD[4]; Rita Popat, PhD[4]; Caroline M. Tanner, MD, PhD[5]; Kristen Bibeau, PhD[2]; Charles P. Quesenberry, PhD[1]

*[1]Division of Research, Kaiser Permanente Northern California, Oakland, CA; [2]Worldwide Epidemiology, GlaxoSmithKline, Research Triangle Park, NC and Stockley Park, UK; [3]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA; [4]Division of Epidemiology, Department of Health Research and Policy, Stanford University, Stanford, CA; [5]The Parkinson's Institute, Sunnyvale, CA*

**Introduction:** Recent cross-sectional studies suggest that restless legs syndrome (RLS) may be associated with an increased prevalence of cardiovascular disease (CVD) comorbidity or risk factors. We evaluated whether primary or secondary RLS was associated with an increased risk of incident cardiovascular disease in a retrospective cohort study within Kaiser Permanente Northern California (KPNC).

**Methods:** We identified members of KPNC with primary RLS and secondary RLS between 1999 and 2008 by an algorithm that incorporated longitudinal clinical records related to the diagnosis and treatment of RLS and comorbidities. We then matched each RLS case with up to 50 individuals with no clinical records of RLS by age, sex, race/ethnicity, zip code, and membership duration. For the analyses we excluded any individual with coronary artery disease (CAD: angina, acute myocardial infarction, coronary revascularization procedure, CAD death), CVD (CAD plus stroke), and hypertension at baseline. New cardiovascular events were determined from clinical records. Follow-up ended at an outcome event, disenrollment from KPNC, or death, whichever occurred earliest. There were over 473,358 person-y of follow-up in this cohort analysis with a mean follow-up time of 3.91 y and range from 6 mo to 12 y. Survival analysis techniques, including survival curves and proportional hazard regression models, were used to assess the association between RLS status and CVD.

**Results:** There were 7,621 primary RLS and 4,507 secondary RLS cases identified and included in the study. In general, primary RLS cases were younger and had less comorbidity than secondary RLS cases. During the follow-up period, CVD was diagnosed in 478 primary RLS cohort members, CAD was diagnosed in 310, and hypertension events were identified in 1,466. Diagnosis in secondary RLS cohort members was made during the follow-up period with 451, 338, and 598 CVD, CAD, and hypertension events, respectively. Subjects with primary RLS had a similar risk of incident CVD (hazard ratio (HR) = 0.95; 95% confidence interval (CI) = 0.86–1.04) and CAD (HR = 0.99; 95% CI = 0.89–1.13) to the comparison cohort, with a slight elevation in the risk of hypertension events (HR = 1.19; 95% CI = 1.12–1.25), after multivariable adjustment. Individuals classified as secondary RLS had a significant increased risk of CVD (HR = 1.33; 95% CI = 1.21–1.46), CAD (HR = 1.40; 95% CI = 1.25–1.56), and hypertension (HR = 1.28; 95% CI = 1.18–1.40).

**Conclusion:** Primary restless legs syndrome (RLS) was not associated with new-onset cardiovascular disease (CVD) or coronary artery disease (CAD) but was associated with a slight increased risk of hypertension. In contrast, secondary RLS was associated with an increased risk of CVD, CAD, and hypertension.

**Keywords:** cardiovascular disease, restless legs syndrome, cohort study, epidemiology

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## INTRODUCTION

Restless legs syndrome (RLS) is a common sensorimotor disease that typically causes sleep disruption, which itself has been associated with an increased risk of cardiovascular disease (CVD).[1,2] The Sleep Heart Health Study[3] reported that individuals who answered positively to a series of questions related to RLS were more likely to report a prior or current diagnosis of coronary artery disease (CAD) (odds ratio [OR] 2.05, 95% confidence interval [CI] 1.38, 3.04) and CVD (OR 2.07, 95% CI 1.43, 3.00) than individuals without RLS after adjustment for putative confounders. Since then many, but not all, other cross-sectional studies have reported similar associations.[4,5] Two recent prospective studies that used self-reported RLS and CVD outcomes reported contradictory results.[6,7] To date, no large prospective study has sought to assess this association using clinically defined RLS and to independently consider primary and secondary RLS.

The aim of this study was to determine whether individuals with primary RLS and secondary RLS had an increased risk of incident CAD, CVD, and hypertension in a longitudinal multiethnic cohort within an integrated healthcare system with access to detailed clinical information.

A commentary on this article appears in this issue on page 995.

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Address correspondence to: Corresponding Author: Stephen K. Van Den Eeden, PhD, Senior Epidemiologist, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612. Tel: (510) 891-3718; Fax: (510) 891-3761; Email: Stephen.vandeneeden@kp.org

## METHODS

### Setting

This study was conducted within Kaiser Permanente Northern California (KPNC), which provides comprehensive care to more than 3.3 million individuals in an integrated

health delivery system. KPNC provides medical care to approximately 25–30% of all people living in the geographic area served and the membership has been found to be broadly representative of the population in the geographic area based on race/ethnicity and income.[8] The setting is particularly suited to studying the research question given the longitudinal and integrated clinical records of KPNC, and the large stable and well-defined population under study enables the cross-validation of a subset of RLS diagnoses identified through electronic clinical records and a determination of primary versus secondary RLS. A long follow-up for KPNC members allows a greater time window for the identification of outcomes.

### Identification and Classification of RLS Cases

To identify cases of RLS for study, we developed a computerized algorithm to identify and classify cases of RLS using the extensive longitudinal electronic clinical records in the integrated KPNC health delivery system. Development of the algorithm included medical record diagnoses of RLS, survey data from the California Men's Health Study,[9] and clinical expert evaluation of a sample of electronic medical records.

The algorithm was initially developed by combining data from the participants in the California Men's Health Study, a large cohort[9] that responded to an expanded set of questions on RLS based on the International Restless Legs Syndrome Study Group (IRLSSG) criteria[10] on a follow-up survey in 2007–2008 and clinical records. We cross-referenced these survey data with electronic clinical records to develop an initial algorithm.

Individuals with probable RLS were further classified as having secondary RLS if the initial RLS diagnosis was in proximity to a diagnosis commonly known to cause secondary RLS, such as anemia, pregnancy, or chronic renal failure (or renal dialysis) within 2 y of their initial diagnosis of RLS. Individuals were classified as having primary RLS if these conditions were absent.

Our final algorithm was developed using a Classification and Regression Tree (CART) analysis (Salford Systems, San Diego, CA, USA) based on available electronic data used as the reference standard for probable RLS subjects participants in the California Men's Health Study who were determined to have RLS based on the response to the expanded IRLSSG questions and who had a positive diagnosis in the KPNC electronic data. To refine the algorithm, an expert (CAK) reviewed 130 individual medical records from the California Men's Health Study that endorsed RLS in the questionnaire as well as had a history of an RLS diagnosis to determine RLS status blinded to CAD, CVD, and hypertension outcomes. From this review, the final algorithm was further modified to classify KPNC members as having primary RLS or secondary RLS. A classification of primary RLS was based on the RLS diagnoses and their longitudinal pattern of assigned diagnoses and treatment, type of physician making the diagnosis (i.e., neurologist/sleep specialist versus other) and the absence and timing of conditions that are either considered for secondary RLS, or are mimics of the disease. An individual was classified as having secondary RLS if the following conditions preceded the first RLS diagnosis or followed within 1 y of the initial RLS diagnosis: spinal stenosis, myelopathy, radiculopathy, leg cramps, varicose veins, claudication, akathisia, neuropathy, folate deficiency, vitamin $B_{12}$ deficiency, leukemia, nocturnal myoclonus, myoclonus, Sjögren syndrome, anemia, iron deficiency, chronic renal disease/failure, end-stage renal disease, uremia, chorea, or neurologic lesions such as brain or nerve cancer. Additionally, a pregnancy within 6 mo of the initial RLS diagnosis precluded the case from being classified as primary RLS. The remainder of the individuals with a clinical record of RLS were considered unclear or not having RLS, and were excluded from our analyses.

### Formation of Cohort

Individuals eligible for inclusion in the study were KPNC members between January 1, 1999 and December 31, 2008. Only individuals age 20 y or older at first RLS diagnosis, who had at least 3 y of membership prior to and 6 mo after their first RLS diagnosis were included. All individuals with any indication of RLS in any electronic data system, whose first clinical mention of RLS was after January 1, 1999, were captured for evaluation and classification (n = 14,172). The aforementioned algorithm was applied to classify the individuals as probable primary RLS (n = 7,621) or probable secondary RLS (n = 4,507). Individuals the algorithm classified as unclear RLS (i.e., not classified as probable primary RLS or probable secondary RLS) were excluded from the study (n = 2,404). Cohort entry date for these individuals was defined as the date of first diagnosis of RLS.

For the comparison arm of the cohort, each probable RLS case was matched with up to 50 individuals without any record of RLS by age, sex, race/ethnicity, duration of membership, and zip code at the time the index RLS individual was included into the cohort. The cohort entry date for a comparison group member was defined as the date of the first RLS diagnosis of the corresponding patient to which they were matched. There were 296,574 comparison subjects matched to primary RLS cases, and, separately, 272,417 comparison subjects matched to secondary RLS cases.

### Outcomes and Covariate Data

All data on outcomes and covariates were derived from the electronic clinical databases at KPNC. These systems include complete capture of diagnoses and procedures in outpatient and inpatient encounters/visits, pharmacy, and mortality data. We defined the following outcomes at their initial diagnosis: CAD (International Classification of Diseases, Ninth Revision [ICD-9] 410, and 413, or a coronary revascularization procedure); CVD (CAD plus ischemic stroke [ICD-9 434], or transient ischemic attack [ICD-9 435]); and hypertension (ICD-9 401). In addition, KPNC-specific codes for these conditions were also used to identify individuals with these conditions seen in the outpatient setting. Covariate data that were available and used include sociodemographic factors, health-related behaviors, comorbidities, and treatment of comorbidities.

### Statistical Methods

The analyses directed at estimating the risk of each of the outcomes used survival or failure time approaches. Censoring events included disenrollment from KPNC or death (from a nonoutcome cause) or the end of follow-up (December 31, 2011).

Multivariable analyses were undertaken using proportional hazards regression to estimate the hazard ratio (HR) and 95%

confidence intervals (CI) for CVD, CAD, and hypertension. In these models, the underlying hazard function was estimated to describe how the hazard (rate) varies in response to explanatory covariates (exposures or confounders) where age was used as the time scale.

Follow-up time in the cohort began for the individual at entry into the cohort; age was determined at this same point and used as a covariate in the analyses. The risk of each outcome was estimated using the comparison group selected for each RLS group (e.g., primary RLS and secondary RLS). Patients with the outcome of interest in the analysis (e.g., CVD, CAD, or hypertension) at baseline were not included in that analysis.

The main analyses were (1) primary RLS patients versus a set of non-RLS comparison individuals; and (2) secondary RLS patients versus a second set of non-RLS comparison individuals. As sensitivity analyses we also analyzed (3) primary RLS patients versus all comparison individuals; (4) secondary RLS patients versus all comparisons individuals; and (5) restricting the analysis to individuals with 3 y or more of follow-up.

Covariates included in the models as dichotomous or indicator variables were age (in 5-y age groups), sex, race/ethnicity (African-American, Hispanic, Asian/Pacific Islander, White (reference) and unknown), smoking (never (reference), former, current, unknown), diabetes status (no/yes), hyperlipidemia diagnosis (no/yes), use of lipid- lowering drugs (no/yes), body mass index (BMI; underweight < 18.5 BMI, normal 18.5–24.9 BMI (reference), overweight 25.0–29.9 BMI, obese ≥ 30 BMI, and unknown). For additional covariates to use for our restricted model of secondary RLS and secondary RLS comparison subjects with a history of anemia, renal failure and/or pregnancy within 6 mo, we created binary variables of anemia history prior to or up to 2 y after reference date (yes/no), renal failure history prior to or up to 2 y after reference date (yes/no), and pregnancy within 6 mo of reference date (yes/no). For models assessing CAD and CVD, we also included a hypertension history (no/yes) and use of hypertensive therapy (no/yes). Model fit and model assumptions (e.g., proportional hazard assumption) were assessed.

## RESULTS

A total of 14,172 individuals had any clinical record of RLS in the study period. After application of the classification algorithm, 7,621 individuals were classified as having received a new diagnosis of primary RLS and 4,507 individuals having received a new diagnosis of secondary RLS in the study period. These were matched to 713,916 individuals without any clinical record of RLS. Of the primary and secondary RLS individuals, 6,657 primary RLS patients (87.4%) and 2,946 secondary RLS patients (65.4%) did not receive a diagnosis of CVD at the time of cohort entry and these individuals were included in the analyses. For CAD, 7,158 and 3,488 individuals with primary and secondary RLS (93.9% and 77.3%), respectively, were included. For the outcome of hypertension, these numbers were 4,976 (65.3%) and 1,539 (34.1%), respectively. The study population has a mean follow-up time of 3.91 years with a range from 6 mo to 12 y.

Table 1 shows sociodemographic, health-related behaviors, and clinical factors at baseline for each study participant by study group (e.g., primary and secondary RLS cases and various configurations of the comparison groups). On average, the secondary RLS case group was older and had more comorbidities than the primary RLS cases. With regard to race/ethnicity, the secondary group was somewhat more likely to be in a minority group. The two RLS case groups were similar in distribution by sex. Smoking and BMI differed by RLS status after exclusion of missing data.

Table 2 shows the risk of CVD, CAD, and hypertension by primary and secondary RLS from proportional hazard models. Subjects with primary RLS had similar risk as the comparison cohort for incident CVD (HR = 0.95; 95% CI 0.86–1.04) and CAD (HR = 0.99; 95% CI 0.89–1.13), after multivariable adjustment for age, race/ethnicity, sex, smoking, diabetes, BMI, and the presence or treatment of hypertension or hyperlipidemia. The primary RLS group had a 20% increase in risk relative their comparison group for hypertension (HR = 1.19; 95% CI 1.12–1.25).

Individuals classified as having secondary RLS had a significant increased risk of CVD (HR = 1.33, 95% CI 1.21–1.46), CAD (HR = 1.40, 95%CI 0.25–1.56), and hypertension (HR = 1.28, 95% CI 1.18–1.40) relative to the secondary comparison group.

In sensitivity analyses, we found little difference in the magnitude of the effect when the analysis was restricted to the primary RLS group who were treated (with, for example, dopamine agonists). Our risk estimates were essentially the same when we excluded those with follow-up time of less than 3 y. We also conducted an analysis where the secondary RLS comparison group was restricted to those with a history of anemia and/or renal failure prior to or within 2 y of reference date, and/or pregnancy code within 6 mo of reference date, in an attempt to match secondary cases as closely as possible on the conditions that drove the RLS classification, and we observed a shift in the effect estimates. There was no risk of CVD (HR = 0.94; 95% CI 0.85–1.04), CAD (HR = 0.98; 95% CI 0.87–1.10), and hypertension (HR = 0.96; 95% CI 0.87–1.07) when using the restricted secondary RLS comparison group. In this cohort, RLS cases were more likely to have a history of anemia compared with the restricted comparison group (72.8% and 61.3%, respectively) and less likely to have renal failure (55.6% and 64.6%, respectively). Therefore, we reran the previous model adding dummy variables for anemia, renal failure, and pregnancy within 6 mo to account for differences between cases and their comparators. When doing so, we found that the risk of CAD, CVD, and hypertension remained insignificant (HR = 0.90; 95% CI 0.82–1.00; HR = 0.93, 95% CI 0.83–1.05; HR = 0.95, 95% CI 0.85–1.05, respectively).

Similarly, when excluded from the comparison component diagnoses that may mimic RLS or be part of the etiology, we observed little or no change in the effect estimates (data not shown). In other sensitivity analyses we compared results restricted to men or to women and observed essentially the same results (data not shown).

## DISCUSSION

In this study primary RLS was not associated with incident CVD overall or CAD, but was associated with a small increased risk of hypertension. In contrast, secondary RLS was significantly associated with incident CVD, CAD, and hypertension.

**Table 1**—Demographic and comorbidity by restless legs syndrome status, Kaiser Permanente Northern California Study.[a]

| | Primary RLS | | Comparison Group Primary RLS Specific[b] | | Secondary RLS | | Comparison Group Secondary RLS Specific[c] | |
|---|---|---|---|---|---|---|---|---|
| N | 7,621 | | 296,574 | | 4,507 | | 272,417 | |
| Age in y, mean (SD) | 58.1 (14.1) | | 55.3 (13.5) | | 66.5 (14.6) | | 64.6 (14.8) | |
| < 40 | 734 | 9.6% | 33,923 | 11.4% | 218 | 4.8% | 14,799 | 5.4% |
| 40–49 | 1,316 | 17.3% | 64,527 | 21.8% | 432 | 9.6% | 31,492 | 11.6% |
| 50–59 | 2,061 | 27.0% | 88,767 | 29.9% | 704 | 15.6% | 51,482 | 18.9% |
| 60–69 | 1,823 | 23.9% | 64,109 | 21.6% | 980 | 21.7% | 58,816 | 21.6% |
| 70–79 | 1,156 | 15.2% | 32,413 | 10.9% | 1,282 | 28.4% | 70,322 | 25.8% |
| ≥ 80 | 531 | 7.0% | 12,835 | 4.3% | 891 | 19.8% | 45,506 | 16.7% |
| Gender | | | | | | | | |
| Male | 2,350 | 30.8% | 99,908 | 33.7% | 1,454 | 32.3% | 99,176 | 36.4% |
| Female | 5,274 | 69.2% | 196,666 | 66.3% | 3,053 | 67.7% | 173,241 | 63.6% |
| Race | | | | | | | | |
| non-Hispanic white | 6,197 | 81.3% | 243,717 | 82.2% | 3,489 | 77.4% | 205,139 | 75.3% |
| Black | 215 | 2.8% | 7,492 | 2.5% | 214 | 4.7% | 14,948 | 5.5% |
| Hispanic | 658 | 8.6% | 23,519 | 7.9% | 497 | 11.0% | 30,367 | 11.1% |
| Asian | 441 | 5.8% | 17,539 | 5.9% | 258 | 5.7% | 19,674 | 7.2% |
| Other or unknown | 111 | 1.5% | 4,307 | 1.5% | 49 | 1.1% | 2,289 | 0.8% |
| Smoking | | | | | | | | |
| Current smoker | 294 | 3.9% | 7,862 | 2.7% | 227 | 5.0% | 7,590 | 2.8% |
| Former smoker | 855 | 11.2% | 19,107 | 6.4% | 1,121 | 24.9% | 31,088 | 11.4% |
| Never smoker | 4,714 | 61.9% | 251,496 | 84.8% | 2,716 | 60.3% | 224,456 | 82.4% |
| Unknown smoking status | 1,758 | 23.1% | 18,109 | 6.1% | 443 | 9.8% | 9,283 | 3.4% |
| Body mass index | | | | | | | | |
| < 25 | 1,674 | 22.0% | 86,410 | 29.1% | 1,247 | 27.7% | 87,902 | 32.3% |
| 25–29 | 1,787 | 23.4% | 82,229 | 27.7% | 1,116 | 24.8% | 78,820 | 28.9% |
| ≥ 30 | 2,323 | 30.5% | 93,459 | 31.5% | 1,581 | 35.1% | 82,008 | 30.1% |
| Unknown BMI | 1,837 | 24.1% | 34,476 | 11.6% | 536 | 11.9% | 23,687 | 8.7% |
| Anemia within 1 y of reference date | 0 | 0.0% | 0 | 0.0% | 3,281 | 72.8% | 37,687 | 13.8% |
| Arthritis within 1 y of reference date | 1,304 | 17.1% | 27,307 | 9.2% | 1,682 | 37.3% | 50,401 | 18.5% |
| Renal disease within 1 y of reference date | 0 | 0.0% | 0 | 0.0% | 2,506 | 55.6% | 39,700 | 14.6% |
| Diabetes | 1,189 | 15.6% | 33,508 | 11.3% | 1,664 | 36.9% | 54,726 | 20.1% |
| Hypercholesterolemia | 4,635 | 60.8% | 138,282 | 46.6% | 3,443 | 76.4% | 163,938 | 60.2% |
| Hx CVD at reference date | 964 | 12.6% | 20,269 | 6.8% | 1,561 | 34.6% | 44,217 | 16.2% |
| Hx of CAD at reference date | 463 | 6.1% | 11,560 | 3.9% | 1,019 | 22.6% | 26,797 | 9.8% |
| Hx of hypertension at reference date | 2,645 | 34.7% | 104,742 | 35.3% | 2,968 | 65.9% | 148,615 | 54.6% |
| Pregnancy | 0 | 0.0% | 848 | 0.3% | 5 | 0.1% | 711 | 0.3% |
| Average time follow-up | 4.9 (2.5) | | NR | | 4.0 (2.2) | | NR | |

[a]Independent comparison groups were matched on age, sex, race, membership history and zip code to each RLS group with restrictions described below. [b]Excludes spinal stenosis/myelopathy/radiculopathy, varicose veins/claudication, akathisia, neuropathy, folate or vitamin $B_{12}$ deficiencies, leukemia, nocturnal myoclonus, myoclonus, neurologic lesions/brain cancer, arthritis, magnesium deficiencies, Sjörgren syndromes, chorea, tremor, anemia, chronic kidney disease/failure, renal insufficiency, end-stage renal disease, or uremia. [c]Restricted to patients with the following conditions: anemia, chronic kidney disease, chronic kidney failure, renal Insufficiency, end-stage renal disease, or uremia. BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; Hx, medical history; NR, not reported; RLS, restless legs syndrome; SD, standard deviation.

However, when matched to a comparison group with similar baseline comorbidities, the associations of secondary RLS with CVD, CAD, and hypertension all moved toward a null value. These associations were robust to refined definitions of case status by treatment or comorbidity status.

These results are in contrast with cross-sectional studies summarized in two recent reviews[4,5] that have reported a generally consistent association between RLS and various CVD outcomes. Interest in the relationship between RLS and CVD largely arose with the publication of results of a cross-sectional analysis from the Sleep Heart Health Study, which showed that RLS was associated with an increased prevalence of CAD (OR 2.05, 95% CI 1.38, 3.04) and CVD (OR 2.07, 95% CI 1.43, 3.00) relative to individuals without RLS.[3] Additional analyses suggested an increase in the association of RLS with CAD and CVD with increased RLS symptom frequency and in those with "extremely"

or "a lot" bothersome symptoms versus "moderately" bothersome symptoms, although not with an increased duration of symptoms. Positive associations between RLS and hypertension and between RLS and diabetes were also observed after adjustment for age, sex, and BMI, but were found to demonstrate only weak and statistically nonsignificant effects.

The direction of the association is important and not possible to determine in cross-sectional analyses. Analyses of five prospective cohorts, including ours, have not found any association with CVD related to the heart.[6,11,12] One of these cohorts reported a significantly elevated risk of stroke.[12] Although we did not include stroke as a separate outcome, it was not associated in our data. In a cohort of men followed prospectively, an increased risk of all-cause mortality and a nonstatistically significant increase in cardiovascular mortality were reported.[13]

In contrast, a single prospective cohort study reported an association with CVD among individuals with RLS that was of 3 y or longer in duration.[7] A study of periodic leg movement did find that a greater number of these movements was associated with peripheral artery disease and all-cause CVD, but not incident CAD or CVD.[14]

Although numerous studies of RLS and hypertension have been reported,[15] essentially all are cross-sectional and cannot help determine the directionality of the RLS-hypertension association. Moreover, some studies have found an association,[16] whereas others have not. No association was observed in two prospective cohorts in Germany.[11] Although this study provides evidence that both primary and secondary RLS are related to clinically documented hypertension, other similar studies are needed to confirm this finding. However, RLS may be related to hypertension through disturbances by RLS in autonomic function.[5,17]

None of these studies formally examined the difference in risk between primary and secondary RLS, although some attempted to do proxy assessments by exclusion. Other differences among the studies include the self-reported RLS and outcomes in most of the studies.[6,7,11,12] RLS was determined by various self-reported methods, including the use of a single question, typically inquiring if a physician had told the individual they had RLS, or by use of the four IRLSSG criteria questions, related to the cardinal features of desire to move, relief with movement, being more common at rest, and occurring more often later in the day or at night. However, RLS can also occur secondary to a host of conditions, including anemia, pregnancy, and other conditions and if these are not included in the assessment, may result in the affected cases including both primary and secondary cases. The differential diagnosis includes consideration of peripheral neuropathy (particularly secondary to diabetes), periodic leg movements, myopathies, leg cramps, and other conditions.[18] Few of these studies determined the role of these other conditions to defining RLS as primary or secondary. Defining RLS solely with the IRLSSG criteria has been found to include a number of individuals with "mimics" that do not have RLS.[19–21] To the extent that secondary cases carry a higher risk of CVD, studies not able to properly assign RLS status (i.e., primary versus secondary) may overestimate the true risk of primary RLS.

Our study had several important distinctions and limitations from other studies. First, we developed an algorithm that uses comprehensive and longitudinal information from electronic clinical databases including diagnoses, type of physician making the diagnosis (neurologist versus not), use of pharmaceutical treatment, presence or absence and timing (vis-à-vis the RLS diagnosis) of conditions that are part of the differential diagnosis, and the presence and timing of conditions that are known to cause secondary RLS. The algorithm was developed using multiple data sources on RLS, including self-report, combined with expert review and classification. Our analyses included only individuals with clear clinical records of RLS (e.g., records without inconsistent diagnoses that suggest clinical uncertainty, had essentially equal access to care and neurologists, and we were able to establish clear temporal relationships between RLS diagnosis and diagnoses that may be a mimic of RLS or help define it as a secondary case (e.g., anemia, iron deficiency, pregnancy, chronic renal disease, etc.)). Because of the large number of individuals, we were not able to individually review each suspected case. This approach may, however, include in our comparison groups individuals with RLS who did not seek and/or have recognized the condition. If an association between primary RLS and CVD truly exists, the presence of unrecognized RLS in our comparison group would bias our results toward the null. Although some false-positive cases are likely included, we suspect this has been minimized by the review and classification process. For example, in a sample of 30 individuals that the algorithm classified as primary RLS, expert review classified 29 the same way. The other individual was classified by expert review as unclear. These data suggest that our algorithm has excellent performance with regard to classification. We do not know the extent to which individuals with true RLS might have been classified as having secondary or unclear RLS. If there is a differential association between primary RLS and CVD by

**Table 2**—Risk of cardiovascular disease, coronary artery disease, and hypertension by restless legs syndrome status, Kaiser Permanente Northern California Study.

| | Primary RLS Cases | Secondary RLS Cases |
|---|---|---|
| Cardiovascular disease[a] | | |
| No. in group | 6,657 | 2,946 |
| No. with group with outcome | 478 (7.2%) | 451 (15.3%) |
| Hazard ratio (95% CI) | 0.95 (0.86–1.00) | 1.33 (1.21–1.46) |
| Coronary artery disease[a] | | |
| No. in group | 7,158 | 3,488 |
| No. with group with outcome | 310 (4.3%) | 338 (9.7%) |
| Hazard ratio (95% CI) | 0.99 (0.89–1.10) | 1.40 (1.25–1.56) |
| Hypertension[b] | | |
| No. in group | 4,976 | 1,539 |
| No. with group with outcome | 1,466 (29.5%) | 598 (38.9%) |
| Hazard ratio (95% CI) | 1.20 (1.10–1.30) | 1.28 (1.18–1.40) |

[a]Controlling for age, race, sex, smoking status, body mass index, diabetes, hypertension, hypertension treatment, hyperlipidemia, and hyperlipidemia treatment. [b]Controlling for age, race, sex, smoking status, body mass index, diabetes, hyperlipidemia, and hyperlipidemia treatment. CI, confidence interval; RLS, restless legs syndrome.

correctly or incorrectly classified cases, our results could be biased. Nonetheless, we believe this approach significantly improves on studies that rely on using self-report and/or responses limited to the IRLSSG criteria questions. Our RLS clinical data did not include information on RLS characteristics such as frequency, discomfort, and associated level of sleep disturbance, as some other studies have been able to do. Given the insidious onset and real or potentially long natural history of both RLS and CVD, our relatively modest mean follow-up may not represent the full picture of the RLS-CVD association. Our study also relied on covariate data from electronic records that may be more detailed (comorbidity) in some cases, and less well captured (e.g., smoking) for other factors, relative to studies that included questionnaire data. Another important difference was that our data were prospective in that we were able to determine the temporal sequence of RLS and CAD, hypertension, and overall CVD (accepting the fact these conditions have an insidious onset).

We also used detailed and comprehensive electronic records to capture our outcome measures of CAD, hypertension, and overall CVD. These electronic records at KPNC are clinical records rather than a claims database and we have used definitions that have been used in numerous prior studies of CAD/CVD in this setting.[22,23] Other factors, such as differential surveillance (for CVD) by RLS status is not likely to explain our results because we observed no association of CVD with primary RLS but a positive association for secondary RLS and CVD. It is unlikely that these two groups received differential scrutiny with regard to cardiovascular health.

Although mechanisms have been suggested as to why RLS may be related to CVD,[3,24] it may be driven by the fact that RLS causes poor sleep quality or quantity because the latter factors are independent risk factors for cardiovascular outcomes.[25] Our observation that primary RLS was not a risk factor for CVD suggests that RLS-related sleep disturbances may not increase risk of CVD among patients free of these conditions at RLS diagnosis. The increased association found for our secondary RLS subjects could be explained by the presence of conditions in this group (e.g., renal disease) that are known to increase the risk of CVD.

In summary, our study suggests that although RLS and CVD are common comorbid conditions, a primary RLS diagnosis was not associated with CVD, but may be associated with a modest increased risk of hypertension. In contrast, we found secondary RLS was associated with CVD and hypertension.

## DISCLOSURE STATEMENT

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