ORIGINAL ARTICLE

Association of Restless Legs Syndrome With Incident Parkinson's Disease

Szabolcs Szatmari, Jr, MD[1,2,3]; Daniel Bereczki, MD, PhD, DSc[3,4]; Katalin Fornadi, MD, PhD[4]; Kamyar Kalantar-Zadeh, MD, MPH, PhD[5]; Csaba P. Kovesdy, MD[6,7]; Miklos Z. Molnar, MD, PhD[6,8]

[1]Department of Neurology, Sibiu County Emergency Hospital, Sibiu, Romania; [2]2nd Department of Neurology, Targu Mures Emergency Clinical County Hospital, Targu Mures, Romania; [3]Szentágothai Doctoral School, Semmelweis University, Budapest, Hungary; [4]Department of Neurology, Semmelweis University, Budapest, Hungary; [5]Division of Nephrology, University of California, Irvine, CA; [6]Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN; [7]Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN; [8]Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary

Study Objectives: The association between restless legs syndrome (RLS) and Parkinson's disease (PD) has been extensively studied with inconclusive results; therefore, we prospectively examined the associations of the presence of RLS with development of incident PD.

Methods: From a nationally representative prospective cohort of almost 3.5 million US veterans (age: 60 ± 14 years, 93% male, median follow-up time of 7.8 years [interquartile range: 6.4–8.4 years]), we created a propensity-matched cohort of 100 882 PD-free patients and examined the association between prevalent RLS and incident PD. This association was also assessed in the entire cohort. Associations were examined using Cox models.

Results: There were 68 incident PD events (0.13%, incidence rate 1.87 [1.48–2.37]/10 000 patient-years) in the RLS-negative group, and 185 incident PD events (0.37%, incidence rate 4.72 [4.09–5.45]/10 000 patient-years) in the RLS-positive group in the propensity-matched cohort. Prevalent RLS was associated with more than twofold higher risk of incident PD (hazard ratio [HR]: 2.57, 95% confidence interval [CI]: 1.95–3.39) compared to RLS-negative patients. Qualitatively similar results were found when we examined the entire 3.5 million cohort: Prevalent RLS was associated with more than twofold higher risk of incident PD (multivariable adjusted HR: 2.81, 95%CI: 2.41–3.27).

Conclusion: RLS and PD share common risk factors. In this large cohort of US veterans, we found that prevalent RLS is associated with higher risk of incident PD during 8 years of follow-up, suggesting that RLS could be an early clinical feature of incident PD.

Keywords: restless legs syndrome, Parkinson's disease.

Statement of Significance

The association of restless legs syndrome (RLS) and Parkinson's disease (PD) is a less studied topic with conflicting and debatable results. The findings of our study show that RLS is associated with a higher risk of PD, suggesting that RLS could be an early clinical feature of PD. These results could be highly significant and beneficial to neurologists or other physicians who play an important role in the management of RLS patients. Also, for researchers it justifies the need for more effective investigation approach on pathological basis of RLS and RLS development into PD. In addition, future researchers can set this study as a point reference.

INTRODUCTION

Restless legs syndrome (RLS) is a common disorder characterized by a convincing urge to move the lower limbs, accompanied by unpleasant sensations, symptoms that are aggravated during rest and alleviated by activity.[1,2] RLS may be idiopathic or secondary, with several cross-sectional studies indicating an association between RLS and various chronic diseases including hypertension, cardiovascular diseases, obesity, diabetes, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, depression, cancer, and hyperthyroidism.[3] RLS is also known to develop secondary to other medical conditions such as iron deficiency and chronic kidney disease or can be of a familial origin.[1,4] There are factors that may exacerbate RLS symptoms such as excessive alcohol, caffeine, and nicotine use, drugs (tricyclic antidepressants, dopamine antagonists, and serotonin reuptake inhibitors) as well as older age.[5]

The association between RLS and Parkinson's disease (PD) has been extensively studied[6] on the basis that dopaminergic hypofunction in the central nervous system is present in both diseases,[7] and it has been suggested that RLS is a possible preclinical marker of PD.[8] However, there is still insufficient evidence to support an identical pathophysiologic mechanism for both the diseases.[9] Previous cross-sectional, prospective, and retrospective studies showed that RLS symptoms appeared before the onset of PD,[10–12] but the majority of them were limited by low event numbers and gave inconclusive results. Two recent, cross-sectional studies concluded that men with RLS are more likely to have concurrent PD, suggesting that RLS could be an early clinical feature of PD.[13,14] However, a recent study showed that prevalence of RLS in PD patients was not significantly different from the general population, which suggests that these two diseases may not share the same mechanism.[15] Until now, epidemiologic studies assessing the association between RLS and PD generated conflicting results.[11–13]

Given that previous studies reported contradictory results, and the fact that majority of them had cross-sectional designs with low event numbers, we examined in a historic prospective cohort study the association of RLS with the development of incident PD in a large, nationally representative contemporary group of US veterans. Based on previous findings, we hypothesized that RLS is associated with higher risk of development of incident PD.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the institutional review committees of the Memphis and Long Beach Veterans Affairs (VA) Medical Centers. Given the large sample size, anonymity of the patients studied, and nonintrusive nature of the research, the requirement for written consent was waived.

Study Setting and Cohort Definition

We used data from the Racial and Cardiovascular Risk Anomalies in chronic kidney disease (CKD) (RCAV) study. This study examines risk factors and outcomes of incident CKD, as detailed previously.[16,17] RCAV cohort selected patients with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m^2 from among all US veterans who had serum creatinine measurements performed between October 1, 2004, and September 30, 2006 (n = 4 447 691), which comprised approximately 94% of the entire VA patient population receiving medical care in a VA health-care facility during this time period.[18] We identified RLS from the VA Inpatient and Outpatient Medical SAS Datasets using The International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*) diagnostic codes (Table e-1). Figure e-1 shows the algorithm used for cohort definition. We included patients with baseline eGFR ≥60 ml/min/1.73m^2 and without a diagnosis of PD prior to the diagnosis of RLS. The final cohort included 3 481 506 patients, of which 3 423 031 patients were without RLS and 58 475 patients had prevalent RLS. Using this cohort, we created a propensity score-matched cohort of 50 441 patients in each group using 1:1 matching, as shown in Figure e-1.

Exposure Outcomes and Covariates

We defined incident PD as our outcome of interest. RLS was defined by the presence of a relevant *ICD-9-CM* code at baseline, and incident PD was defined as a new *ICD-9-CM* code for PD (Table e-1) during the follow-up period. Patients with an existing diagnosis of PD before or within 60 days of the diagnosis of RLS were excluded. Sensitivity analyses were also performed in which patients with an existing diagnosis of PD before or within 365 days of the diagnosis of RLS were excluded.

Sociodemographic characteristics and comorbid conditions were obtained, as described previously.[17] We obtained data on patients' age, gender, and race from the VA Corporate Data Warehouse and from Medicare and on comorbidities from the VA Inpatient and Outpatient Medical SAS Datasets using *ICD-9-CM* diagnostic and procedure codes and Current Procedural Terminology codes, as shown in Table e-2. All comorbidities were detected at baseline. Anemia was defined as follow: baseline hemoglobin <13 g/dL for men and <12 g/dL for women.

Statistical Analysis

We generated summary statistics using proportions, means ± *SD*, or medians (interquartile ranges [IQR]). We compared continuous variables with the Student's t test or the Mann–Whitney U test, as appropriate. The associations between prevalent RLS and incident PD were assessed using the Kaplan–Meier method, and Cox proportional hazard models (for time to event analyses).

The start of the follow-up period was the date when patients were diagnosed with RLS. Patients were followed until the diagnosis of PD or were censored at the date of last health care or administrative visit or on July 26, 2013.

We applied a propensity score matching method to account for baseline differences in clinical and demographic characteristics between those with and without RLS. We used logistic regression (see Table 1) to determine characteristics associated with RLS, which we then used to calculate propensity scores with STATA's "psmatch2" command suite. We used a one-to-one nearest neighbor matching without replacement. The propensity score was calculated from the following variables: gender, age, race/ethnicity, marital status, income, baseline eGFR, comorbidities at baseline (hypertension, diabetes, congestive heart failure, cardiovascular disease, peripheral vascular disease, rheumatic heart disease, cerebrovascular disease, dementia, lung disease, liver disease, rheumatic disease, HIV/AIDS, malignancy, depression, thyroid disease, iron deficiency, insomnia, anemia, and gout), baseline neuroleptic usage, and body mass index (BMI). After propensity score matching the standardized differences were minimal (Table 2), and the distribution of the propensity score was very similar in RLS-positive and RLS-negative patients (Figure e-2).

All associations were examined in unadjusted models using our propensity-matched cohort of 100 882 patients. We performed subgroup analyses, and effect modification was detected based on interaction terms. We also analyzed the entire cohort in a sensitivity analysis. For each of these analyses, four models were examined based on the level of multivariable adjustment: 1, crude model; 2, Model 1: adjusted for age and sex; 3, Model 2: variables from Model 1 and race, income, marital status, and baseline eGFR; 4, Model 3: variables from Model 2 and comorbidities (diabetes, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, lung disease, dementia, rheumatic disease, liver disease, malignancy, AIDS/HIV, depression, thyroid disease, rheumatic heart disease, iron deficiency, insomnia, anemia, and gout), BMI, and baseline neuroleptic use. Statistical analyses were performed using Stata MP version 12 (Stata Corporation, College Station, Texas).

RESULTS

Baseline Characteristics

The mean ± *SD* age of the cohort at baseline was 60 ± 14 years, 93% were male, 78% and 17% of patients were white and black, respectively, 44% were unmarried, 24% of the patients were diabetic, and the mean baseline eGFR was 84 ± 16 ml/min/1.73m^2. Baseline characteristics of patients categorized by RLS status are shown in Table 2. In the original cohort (n = 3 481 506), patients with RLS were more likely to be white, female, and married; had higher prevalence of hypertension, CVD, depression, diabetes mellitus, thyroid disease, chronic lung disease, insomnia, gout, and iron deficiency; and were slightly younger. These differences disappeared after propensity score matching and the baseline characteristics became balanced (Table 2).

Predictors of RLS

In our multivariable logistic regression model, younger age, female gender, white race, being married, lower eGFR, higher BMI, and most of the comorbidities (such as diabetes, hypertension, peripheral artery disease, chronic lung disease, rheumatologic disease, depression, thyroid disease, rheumatic heart

Table 1—Predictors of Presence of Restless Legs Syndrome Using Logistic Regression Analysis in the Entire Cohort.

	Odds Ratio (OR)	95% confidence interval of OR
Age (+10 years)	0.95	0.94–0.95
Gender: female vs. male (ref.)	1.40	1.36–1.45
Race:		
White (ref.)	1.00	1.00–1.00
African American	0.36	0.34–0.37
Hispanic	0.40	0.37–0.44
Other race	0.71	0.66–0.76
Income (+1 log)	1.01	0.99–1.02
Marital status: Unmarried vs married (ref.)	0.68	0.66–0.69
Baseline eGFR (+10 ml/min./1.73m^2)	0.97	0.96–0.98
Presence of diabetes vs absence of diabetes (ref.)	1.05	1.02–1.07
Presence of hypertension vs absence of hypertension (ref.)	1.07	1.05–1.09
Presence of cardiovascular disease[a] vs. absence of cardiovascular disease[a] (ref.)	1.07	1.05–1.10
Presence of congestive heart failure vs. absence of congestive heart failure (ref.)	0.87	0.83–0.91
Presence of cerebrovascular disease vs. absence of cerebrovascular disease (ref.)	1.02	0.99–1.06
Presence of peripheral arterial disease vs. absence of peripheral arterial disease (ref.)	1.13	1.09–1.17
Presence of chronic lung disease vs. absence of chronic lung disease (ref.)	1.31	1.28–1.34
Presence of dementia vs. absence of dementia (ref.)	0.63	0.55–0.72
Presence of rheumatologic disease vs. absence of rheumatologic disease (ref.)	1.13	1.06–1.22
Presence of liver disease vs. absence of liver disease (ref.)	0.86	0.79–0.93
Presence of malignancy vs. absence of malignancy (ref.)	0.85	0.83–0.88
Presence of AIDS/HIV vs. absence of AIDS/HIV (ref.)	1.01	0.88–1.16
Presence of depression vs. absence of depression (ref.)	1.51	1.47–1.55
Presence of thyroid disease vs. absence of thyroid disease (ref.)	1.27	1.24–1.30
Presence of rheumatic heart disease vs. absence of rheumatic heart disease (ref.)	1.42	1.35–1.49
Presence of iron deficiency vs. absence of iron deficiency (ref.)	1.74	1.69–1.79
Presence of insomnia vs. absence of insomnia (ref.)	2.89	2.84–2.95
Presence of anemia vs. absence of anemia (ref.)	0.87	0.84–0.90
Presence of gout vs. absence of gout (ref.)	1.10	1.06–1.13
Presence of neuroleptic use vs. absence of neuroleptic use (ref.)	1.01	0.97–1.05
Body mass index (+5 kg/m^2)	1.10	1.09–1.11

Abbreviations: AIDS, Acquired immundeficiency syndrome; eGFR, estimated glomerular filtration rate; HIV, human immundeficiency virus; OR, odds ratio.
[a] Cardiovascular disease was defined as acute myocardial infraction, angina, coronary artery disease, previous coronary artery bypass grafting, or percutaneous coronary intervention.

disease, iron deficiency, insomnia and gout) were associated with a higher risk of prevalent RLS (Table 1).

Incident PD in the Propensity-Matched Cohort

The median follow-up time was 8.1 years (IQR: 7.2–8.5 years) in the propensity-matched cohort. There were 253 incident PD events (0.25%, incidence rate 3.35 [2.96–3.79]/10 000 patient-years) in the propensity-matched cohort. There were 68 incident PD events (0.13%, incidence rate 1.87 [1.48–2.37]/10 000 patient-years) in the RLS-negative group, and 185 incident PD events (0.37%, incidence rate 4.72 [4.09–5.45]/10 000 patient-years) in the RLS-positive group. Figure 1 shows the associations between prevalent RLS and probability of the incident PD event in the propensity-matched cohort. Prevalent RLS was associated with a more than twofold higher risk of incident PD (hazard ratio [HR]: 2.57, 95% confidence interval [CI]: 1.95–3.39) compared to RLS-negative patients (Table 3). Similar results were found

Table 2—Baseline Characteristics of the Study Population.

	Before matching			After matching		
	RLS negative (*n* = 3 423 031)	**RLS positive (*n* = 58 475)**	**Std. Diff.**	**RLS negative (*n* = 50 441)**	**RLS positive (*n* = 50 441)**	**Std. Diff.**
Age, years	60 ± 14	59 ± 12	−0.039	59 ± 14	59 ± 12	−0.001
Gender (male)	3 190 956 (93)	53 390 (91)	0.099	46 313 (92)	46 276 (92)	0.003
Outcome						
Incident Parkinson disease	3175 (0.09)	192 (0.3)	N/A	68 (0.1)	185 (0.3)	N/A
Race			−0.260			−0.006
White	2 417 842 (78)	49 861 (90)		44 280 (87)	45 463 (90)	
African American	537 759 (18)	3798 (7)		5306 (11)	3551 (7)	
Hispanic	70 608 (2)	565 (1)		440 (1)	532 (1)	
Other race	66 472 (2)	989 (2)		415 (1)	895 (2)	
Marital status						
Married	1 821 040 (56)	36 108 (64)	−0.187	31 611 (63)	31 442 (62)	0.007
Single	367 114 (11)	3523 (6)		4428 (9)	3359 (7)	
Divorced	845 666 (26)	13 225 (24)		11 584 (23)	12 611 (25)	
Widow	240 770 (7)	3427 (6)		2818 (6)	3029 (6)	
Other sociodemographic						
Mean per capita income, USD	22 824 (11 647–35 989)	24 241 (13 041–33 982)	0.058	24 046 (12 454–35 485)	23 846 (12 937–33 522)	−0.001
Other						
Baseline eGFR, ml/min./1.73m^2	84 ± 16	83 ± 15	−0.076	83 ± 15	83 ± 15	0.006
BMI, kg/m^2	29.2 ± 5.7	30.1 ± 5.9	0.169	30.2 ± 6.2	30.2 ± 5.9	0.001
Comorbidities						
Hypertension	2 023 591 (59)	36 778 (63)	0.050	31 812 (63)	31 816 (63)	<0.001
Diabetes mellitus	808 359 (24)	15 448 (26)	0.053	13 510 (27)	13 627 (27)	0.005
Cardiovascular disease[a]	387 355 (11)	7906 (14)	0.063	7066 (14)	7070 (14)	<0.001
Congestive heart failure	149 982 (4)	2779 (5)	0.014	2441 (5)	2501 (5)	0.006
Cerebrovascular disease	204 286 (6)	3819 (7)	0.016	3481 (7)	3377 (7)	−0.008
Peripheral arterial disease	185 129 (5)	3871 (7)	0.046	3455 (7)	3464 (7)	0.001
Chronic lung disease	621 355 (18)	14 239 (24)	0.142	12 715 (25)	12 632 (25)	−0.004
Dementia	26 619 (0.8)	262 (0.4)	−0.041	213 (0.4)	236 (0.4)	0.007
Rheumatologic disease	47 515 (1)	1055 (2)	0.031	909 (2)	915 (2)	0.001
Liver disease	41 265 (1)	649 (1)	−0.011	571 (1)	601 (1)	0.006
All malignancies	352 076 (10)	5222 (9)	−0.053	4606 (9)	4522 (9)	−0.006
AIDS/HIV	21 348 (1)	235 (0.4)	−0.035	218 (0.4)	217 (0.4)	<−0.001
Depression	309 509 (9)	9290 (16)	0.195	8382 (17)	8422 (17)	0.002
Thyroid disease	403 609 (12)	10 010 (17)	0.140	8738 (17)	8635 (17)	−0.005
Rheumatic heart disease	68 647 (2)	2031 (3)	0.085	1801 (4)	1829 (4)	0.003
Iron deficiency	205 857 (6)	6417 (11)	0.166	5620 (11)	5731 (11)	0.007
Insomnia	371 468 (11)	16 903 (29)	0.445	14 853 (29)	14 814 (29)	−0.002
Anemia	276 095 (8)	4176 (7)	−0.040	3667 (7)	3629 (7)	−0.003
Gout	241 801 (7)	4970 (9)	0.040	4351 (9)	4340 (9)	−0.001

Table2—*Continued*

	Before matching			After matching		
	RLS negative (*n* = 3 423 031)	RLS positive (*n* = 58 475)	Std. Diff.	RLS negative (*n* = 50 441)	RLS positive (*n* = 50 441)	Std. Diff.
Medication						
Neuroleptic use at baseline	155 346 (5)	3297 (6)	0.042	3001 (6)	3006 (6)	<0.001

Dichotomous/dummy variables are presented as number of patients and (percentage); continous variables are presented as mean ± *SD* or median (interquartile range, IQR).
Abbreviations: AIDS, Acquired immuno deficiency syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; HIV, human immundeficiency virus; N/A, not applicable; IQR, interquartile range; RLS, restless legs syndrome; Std.Diff, standardized difference; USD, US dollars.
[a] Cardiovascular disease was defined as acute myocardial infraction, angina, coronary artery disease, previous coronary artery bypass grafting or percutaneous coronary intervention.

in almost all subgroups (Figure 2). Results were qualitatively similar when we included antidepressant medication use in our propensity score (HR: 2.77, 95%CI: 1.94–3.97) and also when we excluded PD cases diagnosed during the first year after the RLS diagnosis (HR: 3.41, 95%CI: 2.39–4.86) in the sensitivity analyses.

Incident PD in the Entire Cohort

The median follow-up time was 7.8 years (IQR: 6.4–8.4 years) in the entire cohort. There were 3175 incident PD events (0.09%, incidence rate 1.35 [1.31–1.40]/10 000 patient-years) in the RLS-negative group and 192 incident PD events (0.33%, incidence rate 4.24 [3.68–4.88]/10 000 patient-years) in the RLS-positive group. Figure e-3 shows the associations between prevalent RLS and the probability of incident PD in the overall cohort. Prevalent RLS was associated with a more than threefold higher risk of incident PD (HR: 3.20, 95%CI: 2.77–3.71) compared to RLS-negative patients in our crude model (Table 3). This association remained qualitatively similar (HR: 2.81, 95%CI: 2.41–3.27) after adjustment for important confounders in our final Cox regression model (Table 3). Similar results were found in almost all subgroups (Figure e-4).

DISCUSSION

In this large cohort of US veterans, we examined the association between RLS and the development of incident PD. Our findings confirm that prevalent RLS is associated with higher risk of incident PD during 8 years of follow-up. In our study, the explanation for the observed association between RLS and PD is unclear. Since the cause of RLS remains unknown and the absolute incidence of PD in patients with RLS is very low, it is difficult to postulate a common pathophysiological background for the two diseases, although the response to dopaminergic agents in both the conditions may suggest this.

Several pathophysiologic mechanisms have been described which indicate a potential pathophysiological connection between RLS and PD. The nigrostriatal dopaminergic system is primarily affected in PD, and RLS is also believed to have an underlying dopaminergic pathophysiology.[19] In addition, there is pathological evidence of dopamine dysfunction in both the diseases,[20] and previous data support the hypothesis that primary iron deficiency produces a dopaminergic abnormality characterized by an overly activated dopaminergic system, rather than dopamine cell depletion, as part of the RLS pathology. The findings of functional imaging studies in RLS have been inconclusive, showing mild reduction in postsynaptic dopaminergic status.[21] Another study suggested presynaptic dopaminergic dysfunction in the striatum,[22] in contrast to PD. However, a fourth study showed normal values for presynaptic dopaminergic function.[23] It is possible that the extrastriatal dopaminergic system may be variably involved in RLS,[9] but the association of RLS severity with the severity of nondopaminergic symptoms in PD, such as cognitive, autonomic, mood, or psychotic disorders, raises the possibility of a nondopaminergic mechanism in RLS as well.[24] Nondopaminergic systems, such as the noradrenergic system, might play a role in the possible link between RLS and PD.[24] As far as we know, there are no studies that used animal models specifically examining the link between RLS and PD. Two sonographic studies suggest different pathological processes underlying idiopathic and PD-associated RLS,[25,26] revealing a significant decrease in substantia nigra region echogenicity in idiopathic RLS compared to other groups (RLS–PD, idiopathic PD, and healthy control group). In contrast, the RLS–PD group had increased echogenicity of the substantia nigra area compared to the control group. As for genetic studies, the literature appears to support a link between the parkin mutation and idiopathic RLS.[27] A recent genetic study identified the MEIS1 locus for RLS in the basal ganglia,[28] suggesting that RLS has components of a neurodevelopmental disorder. In addition, pathways within the basal ganglia circuit are affected in PD as well; hence, the pathophysiological relation of RLS and PD is even more likely. A recent study of patient with idiopathic PD found the prevalence of RLS to be 45%,[29] providing stronger evidence of this association. Other genetic studies have yielded mostly negative or inconclusive results.[30] However, earlier studies using olfactory tests suggested that the pathophysiology of RLS differs from PD.[31] PD and RLS may share similar pathophyisiological mechanisms as mentioned earlier, but smoking plays an uncertain role in these diseases. Several studies have shown that smoking relieves Parkinson symptoms, and it is associated with a lower risk of developing PD.[32,33] However,

the relationship between smoking and RLS is controversial. Some studies show that smoking alleviates RLS symptoms,[34,35] others concluded that there is no influence,[36–38] yet others found a higher incidence of smokers among RLS patients.[39] Sleep disorders are a common feature in PD.[40] Insomnia is thought to be a nonspecific, prodromal symptom in PD, whereas sleep disturbances in RLS are a common consequence due to the nocturnal occurrence of symptoms.[41] Accordingly, the approach to insomnia should be cautious because it may be difficult to differentiate RLS sleep-onset insomnia from prodromal insomnia in PD. The association between RLS and PD remained present even after matching and adjusting for insomnia in our models.

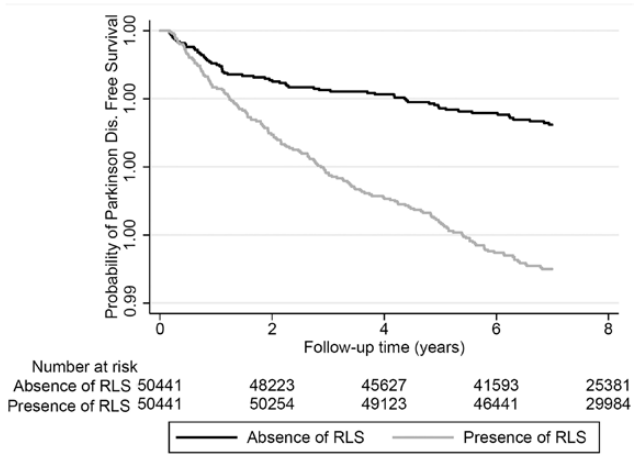

Figure 1—Kaplan–Meier curves of incident Parkinson Disease in patients with and without restless legs syndrome in the propensity-matched cohort.Abbreviations: RLS, restless legs syndrome.

Table 3—Association Between Presence of Restless Legs Syndrome and Incident Parkinson Disease Using Cox Proportional Regression Models in the Propensity-Matched Cohort (*n* = 100 882) and the Entire Cohort (*n* = 3 481 506) With Different Levels of Adjustment.

Presence of RLS vs absence of RLS (ref.)	Hazard ratios (HR)	95% Confidence interval of HR
PS matched cohort	2.57	1.95–3.39
Entire cohort crude model	3.20	2.77–3.71
Entire cohort Model 1[a]	3.36	2.90–3.88
Entire cohort Model 2[b]	3.55	3.05–4.12
Entire cohort Model 3[c]	2.81	2.41–3.27

Abbreviations: AIDS, acquired immundeficiency syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; HIV, human immundeficiency virus; HR, hazard ratios; PS, propensity score; RLS, restless legs syndrome.
Model 1[a]: Adjusted for age, sex.
Model 2[b]: Adjusted for age, sex, race, income, marital status, and baseline eGFR.
Model 3[c]: Adjusted for age, sex, race, income, marital status, baseline eGFR, comorbidities (diabetes, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, lung disease, dementia, rheumatic disease, liver disease, malignancy, AIDS/HIV, depression, thyroid disease, rheumatic heart disease, iron deficiency, insomnia, anemia, and gout), BMI, and neuroleptic use at baseline.

Most of the predictors of RLS, such as female gender, white race, lower eGFR, higher BMI, diabetes, hypertension, chronic lung disease, rheumatologic disease, depression, thyroid disease, rheumatic heart disease, iron deficiency, gout, and insomnia were similar in our study as in previous studies.[1–3,37,42,43] In contrast to previous epidemiological studies,[44] we found younger age (≤65 years) to be a predictor of RLS.[1,45] The explanation for this discrepancy could be due to differences in how RLS patients were identified (*ICD*-9 codes vs. standardized or self-reported questionnaires) or to differences in the source populations (male, elderly, and chronic kidney disease US veterans vs. other populations). We identified some predictors that were never examined in previous studies such as peripheral artery disease. This association can be explained by the fact that the symptoms in these cases did not meet RLS diagnostic criteria, and the results were actually due to misclassification in RLS assessment.

It must be acknowledged that the pathophysiologic basis of RLS remains poorly understood, and RLS may be an especially complex disease,[46] however the symptoms of RLS respond to drugs increasing dopamine, dopaminergic hypofunction in the central nervous system.[7] Therefore, neuroleptics, drugs that block dopamine receptors may cause or exacerbate symptoms of RLS. Based on a few case reports of neuroleptic-induced RLS,[47–54] the interaction between neuroleptic use and RLS should be recognized and taken into account, although the quality of some of this data has been questioned[55] and has provided conflicting results.[56–58] In our study, neuroleptic use at baseline was not associated with higher risk of prevalent RLS.

There are few studies that examined the development of PD after the onset of RLS,[59,60] and these yielded inconclusive results. Major limitations of these studies were their cross-sectional and/or retrospective design or having had very low numbers of events. In a study examining the prevalence of PD among RLS patients, 4 out of 85 patients referred for RLS developed PD, which was higher than the ~1% prevalence of PD in the general population older than 60 years.[61] In a recent study examining a family with high prevalence of RLS, 2 of the 30 members with RLS also suffered from PD.[62] However, none of these studies included control groups. To the best of our knowledge, there were only two recent studies (a cross-sectional and a prospective longitudinal study) including mostly men, which concluded that RLS was associated with a higher prevalence of PD across all age-groups and that RLS was an early clinical feature of PD, not a risk factor.[10,14] In these studies, RLS was assessed based on self-report by standardized questionnaires corresponding to the International RLS Study Group (IRLSSG) criteria, without verification by physical examination, and PD was identified by biannual self-reported questionnaires and by reviewing the medical records and death certificates of deceased study participants. The findings of these cross-sectional studies support our results, namely, that there is an association between RLS and PD. To the best of our knowledge, our study has the largest sample size, and it is one of the few studies that followed patients who were PD-free at baseline in a

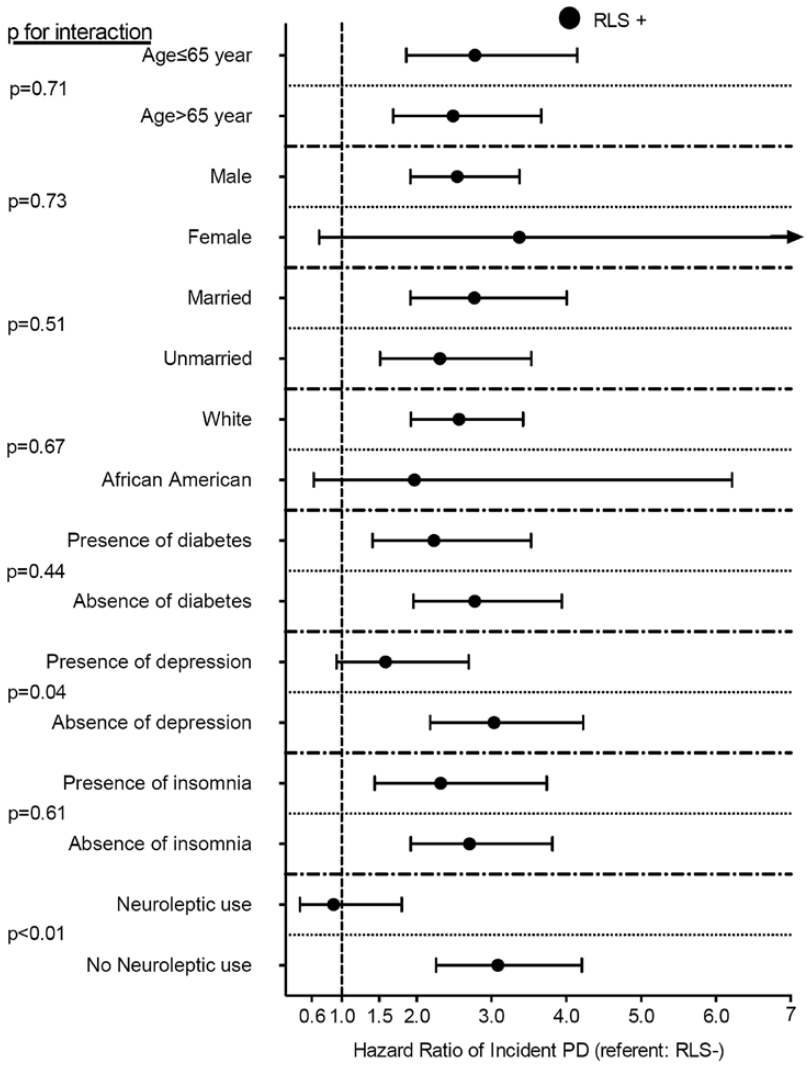

Figure 2—Association between restless legs syndrome and incident Parkinson Disease in different subgroups of patients in the propensity-matched cohort.Abbreviations: PD, Parkinson Disease; RLS, restless legs syndrome.

historical prospective manner. It remains unclear if the observed associations are explained by a pathological link leading from RLS to PD, versus both diseases having a common root.

It is important to note that in our study, the estimated risk of incident PD events in the RLS group is relatively small, suggesting that the connection between the two diseases may not be very strong and/or specific. In contrast, other diseases such as idiopathic rapid eye movement (REM) sleep behavior disorder have stronger effects.[63] Iranzo et al. indicated that the majority of patients with idiopathic REM sleep behavior disorder develop incident PD or dementia with Lewy bodies within a median of 7.5 years.[63]

Strengths of our study are the large sample size and event numbers and the fact that it is representative of veterans in the entire United States. Second, to our knowledge, this is one of the first large studies using a propensity score-matched approach to balance measured confounders. This epidemiological approach serves to balance the measured confounders between the subcohort with exposures and the subcohort without it. Third, the historical prospective design allowed us to conclude that RLS might be an early indicator of PD, whereas previous cross-sectional studies could only conclude associations. Finally, the long follow-up time and relatively high event numbers provided enough power to conduct adjusted analyses.

Our study also has several limitations that need to be acknowledged. The method of propensity score matching only accounts for confounding by variables that are available for analysis. Therefore, we cannot rule out residual confounding. We used diagnostic codes to define all conditions in lieu of standardized or self-reported questionnaires or clinical diagnosis to diagnose RLS and PD. The diagnostic performance of these codes is not well documented, and they may not correlate well with clinical diagnoses. A report from 2010 indicated that the *ICD*-9 code for Parkinsonism has good sensitivity (75%) and excellent specificity (99.1%).[64] Additionally, we were not able to differentiate the source of the RLS *ICD*-9 codes, which could have been assigned by neurologists or other physicians. A potential restriction to a diagnosis assigned by a neurologist might be more valid for RLS than one assigned by nonneurologists. The limitation of using an *ICD*-9 code for RLS is important, as there is a possibility of inexperienced physicians coding leg

motor restlessness as RLS, which was previously shown to be a predictor of PD.[65] In addition, the significant predictors of RLS in our study were similar to those found in previous studies.[1–3,37,42,43] We were unable to assess the associations between the severity of RLS and PD. We also have no data about the treatment of RLS. The clinical severity of RLS can vary, and its natural course can involve transient episodes of remissions and relapses, especially in milder forms seen in young to middle-aged adults. It is therefore possible that patients suffering from milder forms of RLS or those in remission during the evaluation period may have been misclassified in our study. Although excessive alcohol, caffeine intake, and nicotine use may aggravate RLS symptoms, we do not have reliable information about these in our database; therefore, we could not match and adjust for these confounders in our models. In addition, we did not have data regarding usage of dopamine agonists or levodopa. Patients with more comorbidities could have more frequent follow-up visits with their physicians, which may result in higher recognition rate of PD in these patients. However, we adjusted for these comorbidities in our multivariable models. In addition, the study population consisted mostly of male and elderly US veterans. Hence, the results may not be accurately representative of other populations such as women, younger patients, non-US patients, or patients with chronic kidney disease. Finally, we did not have information about several RLS-like syndromes (e.g., akathisia, nocturnal leg cramps, peripheral neuropathy, painful legs and moving toes, positional discomfort, lumbosacral radiculopathy, and attention-deficit/hyperactivity disorder), which could have resulted in a possible overestimation or misclassification in RLS assessment. However, results were similar when we adjusted for all the comorbidities that may cause the enumerated disorders.

In this large cohort of US veterans, we found that prevalent RLS is associated with higher risk of incident PD during 8 years of follow-up. Our results suggest that RLS could be an early clinical feature of incident PD. However, there are several remaining open questions. First, the pathological basis of RLS development into PD remains unanswered. Second, based on the iron–dopamine theory, it would be interesting to examine the relationship between RLS and schizophrenia (hyperdopaminergic activity). Finally, it would be interesting to know whether treatment of RLS could help prevent or delay the development of PD. Further studies are needed to confirm our results and answer these proposed questions.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at *SLEEP* online.

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Address correspondence to: Miklos Z Molnar, MD, PhD, FEBTM, FERA, FASN, Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center ,956 Court Ave, Suite B216B, Memphis, TN, 38163, USA. Telephone: 1-901-448-5372; Fax: 1-901-448-5513; Email: mzmolnar@uthsc.edu

AUTHORS' NOTE

This paper is dedicated for the memory of Dr Ferenc Fornadi.

This is not a clinical trial. The institution at which the work was performed: VA Medical Center, Memphis, TN, USA.

Opinions expressed in this paper are those of the authors' and do not necessarily represent the opinion of the Department of Veterans Affairs. The results of this paper have not been published previously in whole or part. Molnar and Kovesdy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

AUTHORS' ROLE

Study concept and design. MZM, CPK, SS and DB.
Acquisition of data. CPK, MZM.
Analysis and interpretation of data. MZM, CPK, SS, DB, and KKZ.
Drafting of the manuscript and approval of the final version. SS and MZM.
Critical revision of the manuscript for important intellectual content and approval of the final version. MZM, CPK, SS, DB, KF and KKZ.

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SS reports no disclosures. DB reports no disclosures. KF reports no disclosures. KKZ is an employee of the Department of Veterans affairs. He reports no other disclosures. CPK is an employee of the Department of Veterans affairs. He reports no other relevant disclosures. MZM reports no disclosures.