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## Restless legs syndrome and Parkinson's disease in men

**Xiang Gao, MD, PhD, Michael A. Schwarzschild, MD, PhD, Eilis J O'Reilly, ScD, Hao Wang, MD, PhD, and Alberto Ascherio, MD, DrPH**

Channing Laboratory (XG, AA), Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Department of Nutrition (XG, EJO, HW, and AA), and Department of Epidemiology (AA, EJO), Harvard University School of Public Health, Boston, MA; and Department of Neurology (MAS), Massachusetts General Hospital, Boston, MA

### Abstract

We examined whether men with restless legs syndrome (RLS) have a higher prevalence of Parkinson's disease (PD) among 23,119 US participants of the Health Professional Follow-up Study who were free of diabetes and arthritis. RLS was assessed using a set of standardized questions recommended by the International RLS Study Group. PD cases were identified by self-reported questionnaires and confirmed by review of medical records. Compared to men without RLS, multivariate-adjusted odds ratios for PD were 1.1 (95% confidence interval: 0.4, 3.0) for men with RLS symptoms 5-14 times per month and 3.09 (95% confidence interval: 1.5, 6.2;  $P$  trend=0.003) for those with symptoms 15 times or more per month, after adjusting for age, smoking, use of antidepressant, and other covariates. In conclusion, men with RLS are more likely to have concurrent PD. Prospective studies are warranted to clarify the temporal relationship between RLS and PD.

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Restless legs syndrome (RLS) is the most common movement disorder, affecting 5-15% adults.<sup>1,2</sup> Because dopaminergic hypofunction in the central nervous system is involved in the disease pathophysiology of both RLS and Parkinson's disease (PD),<sup>3</sup> it has been suggested that RLS is a possible pre-clinical marker of PD.<sup>4</sup> However, previous epidemiologic studies of RLS and PD generated inconsistent results.<sup>5-7</sup> We, therefore, conducted a cross-sectional analysis to examine whether men with RLS have a higher likelihood of having PD in the Health Professional Follow-up Study (HPFS), a large ongoing cohort of men.

### Materials and methods

#### Study populations

The HPFS was established in 1986, when 51,529 male US health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40-75 years completed a mailed questionnaire about their medical history and lifestyle. Follow-up questionnaires have been mailed to participants every 2 years to update information on potential risk factors and to ascertain newly diagnosed diseases in both cohorts. The institutional review board at Brigham and Women's Hospital reviewed and approved this study, and receipt of each questionnaire implies participant's consent.

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Correspondence and reprint requests to: Dr. Xiang Gao, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, 181 Longwood Ave, Boston, MA; Phone: 1-617-432-5080; Fax: 1-617-432-2435; xiang.gao@channing.harvard.edu.

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## Assessment of RLS

We asked questions in 2002 about RLS symptoms and severity based on the International RLS Study Group criteria (n=37,431, mean age  $68.7 \pm 9$  y) among participants who were still actively participating in the study.<sup>8,9</sup> The following question was asked: “Do you have unpleasant leg sensations (like crawling, paraesthesia, or pain) combined with motor restlessness and an urge to move?” with the possible responses of: no; less than once/month; 2-4 times/month; 5-14 times/month; and 15 or more times per month. Those who answered that they had these feelings were asked the following two questions: 1) “Do these symptoms occur only at rest and does moving improve them?”; and 2) “Are these symptoms worse in the evening/night compared with the morning?” A participant who had symptoms 5-14 times per month and answered yes to the subsequent questions was considered to have RLS for these analyses.

The questions on RLS were completed by 31,729 (85%) men. Men who did not complete the RLS questions had a similar mean age to those who did (69.0 vs. 68.6 years), and a non-significant slightly higher prevalence of PD (0.95 vs. 0.62%). To reduce possible misclassification of RLS, we excluded participants with diabetes and arthritis, leaving 23,119 men in primary analyses. In a secondary analysis, we further examined the association between RLS and PD with including all participants with RLS information.

## Assessment of PD and covariates

Assessment of PD has been described elsewhere.<sup>10-13</sup> Briefly, we identified new PD cases by biennial self-reported questionnaires. We then asked the treating neurologists to complete a questionnaire to confirm the diagnosis of PD or to send a copy of the medical records. A case was confirmed if a diagnosis of PD was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of PD made by a neurologist, or evidence of at least two of the three cardinal signs (rest tremor, rigidity, bradykinesia) in the absence of features suggesting other diagnoses. Overall, the diagnosis was confirmed by the neurologist in >80% of the cases. PD cases included only confirmed definite and probable cases up to 2004.

Information on potential confounders, including age, ethnicity, smoking status, weight, height, physical activity, use of medicines, phobic anxiety scale, and history of major chronic diseases, was collected via biennial questionnaires throughout the follow-up period. Body mass index (BMI) was calculated as weight (kg) / height (m)<sup>2</sup>. The phobic anxiety scale was assessed by the Crown-Crisp phobia index.<sup>14-16</sup>

## Statistical analyses

Statistical analyses were completed with SAS version 9.1 (SAS Institute, Inc, Cary, NC). We categorized participants into three groups: no RLS, RLS with symptoms 5-14 times per month, and RLS with symptoms 15 or more times per month. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) and to test differences in prevalence of PD across categories of RLS status. Analyses were adjusted for age (y), ethnicity (Caucasian, African-American, and Asian and others), BMI (<23, 23-24.9, 25-26.9, 27-29.9, or  $\geq 30$  kg/m<sup>2</sup>), smoking (never smoked, former smoker, or current smoker: cigarettes/d, 1-14 or  $\geq 15$ ), physical activity (quintiles), use of antidepressants (yes/no), the Crown-Crisp phobic anxiety index (0-1, 2, 3, or  $\geq 4$ ), and presence of stroke, hypertension, or myocardial infarction (each of them, yes/no). We examined potential effect modification of the association between RLS and PD by age (< or  $\geq 70$  years, approximate median value), obesity (yes/no, based on BMI  $\geq 30$  kg/m<sup>2</sup>), and smoking status (never versus ever), by including multiplicative terms in the logistic regression models, with adjustment for other potential confounders.

## Results

Men with RLS were older and more likely to be whites and current smokers, to use antidepressants, score higher on the anxiety test, have been diagnosed with hypertension and stroke, and have high BMI and low exercise levels than participants without RLS (Table 1). Men with RLS had a higher prevalence of PD relative to those without RLS in each age group (Figure). Compared to men without RLS, the OR for PD was 1.99 (95% CI: 1.1 to 3.6;  $P=0.02$ ) for those with RLS symptoms, after adjusting for age, smoking, and other covariates. Higher frequency of RLS symptoms, a marker for the disease severity, was associated with increased prevalence of PD (Table 2). The multivariable-adjusted ORs for PD were 1.10 and 3.09 (95% CI: 1.5, 6.2;  $P$  for trend=0.003) for men with RLS symptoms 5-14 times per month, and 15 or more times per month, respectively. Among participants with PD, there was a non-significant difference in disease duration comparing those with RLS to those without RLS ( $9.0 \pm 4.8$  vs.  $7.5 \pm 4.2$  y;  $P=0.7$ ).

Similar significant results were observed in several sensitivity analyses. Multivariable-adjusted ORs did not materially change after excluding participants with the highest level of phobic anxiety, with MI, stroke, PD or hypertension, or those who used antidepressant (data not shown). Further inclusion of participants with diabetes or arthritis did not change the association between RLS and PD (OR=2.16; 95% CI: 1.2, 3.9). We did not find significant interaction between presence of RLS and age, obesity, and smoking status ( $P$  interaction  $>0.2$  for all), in relation to prevalence of PD.

## Discussion

In this large cohort of men, we observed that men with RLS had a higher prevalence of PD than those without RLS, across all age groups. Compared to men without RLS, those who reported having RLS symptoms 15 or more times per month had approximately three-fold higher prevalence of PD. Strengths of the current study include a large sample size, which enabled us to obtain a relatively stable estimate for the associations, and use of standardized questionnaire to assess RLS. As we did not collect information on several RLS-like syndrome (e.g., peripheral neuropathy, leg cramps, positional discomfort, radiculopathy), some misclassification in RLS assessment is possible. However, results were similar when we included or excluded men with diabetes, the most common cause of peripheral neuropathy, in our analyses. Another limitation is that we included only men and therefore our results cannot be generalized to women. Further, because of the cross-sectional design of our study, we are not able to know whether RLS occurred before onset of PD or vice versa.

Associations between RLS and PD have been noticed for long time;<sup>17, 18</sup> both conditions are associated with dopamine hypofunction in CNS. Our findings are consistent with the results of some previous epidemiological studies,<sup>5, 6, 19</sup> but not others.<sup>7</sup> In a sample of 125 PD patients in Singapore, Tan et al reported that none of them met IRLSSG diagnostic criteria of RLS.<sup>7</sup> However, recently, Loo and Tan found a marginally significant higher prevalence of RLS among PD cases ( $n=400$ ) than controls (3% vs. 0.5%;  $P=0.07$ ) in Singapore.<sup>19</sup> In a cross-sectional study by Ondo et al, 20.8% of 303 PD patients had RLS symptoms.<sup>20</sup> In a study examining prevalence of PD among RLS patients,<sup>21</sup> Walters et al. found that 4 out of 85 RLS cases (4.7%) had PD, compared to ~1% PD prevalence expected among the general population over age 60. A recent report showed that in a family with a high prevalence of RLS, two (6.7%) out of 30 family member with RLS also had PD.<sup>22</sup> However, none of these three studies included control groups. Interestingly, a recent genome-wide association study found that MEIS1, a gene involved in embryonic development of substantia nigra, was associated with RLS risk.<sup>23</sup> The relation between

MEIS1 and PD risk has only been reported in one case-control study, and was not significant.<sup>24</sup>

In conclusion, we found a concurrence between RLS and PD in men. Further prospective studies are warranted to clarify whether the presence of RLS precedes onset of classic motor symptom of PD; if so, screening for RLS could help to identify individuals at high risk for PD.

## Appendix

### Full Financial Disclosures of all Authors for the Past Year

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<b>Gao:</b>	
<b>Stock Ownership in medically-related fields</b>	None
<b>Intellectual Property Rights</b>	None
<b>Consultancies</b>	None
<b>Expert Testimony</b>	None
<b>Advisory Boards</b>	Dr. Gao serves on the Monitoring Committee of the Parkinson Study Group
<b>Partnerships</b>	None
<b>Contracts</b>	None
<b>Employment</b>	Instructor in Medicine at Harvard Medical School; Research Scientist at Harvard School of Public Health; Associate Epidemiologist, Brigham and Women's Hospital
<b>Honoraria</b>	None
<b>Royalties</b>	None
<b>Grants</b>	PI for NHI/NINDS grant "Prospective study of restless legs syndrome" (R01 NS062879-01A2)
<b>Schwarzschild:</b>	
<b>Stock Ownership in medically-related fields</b>	None
<b>Intellectual Property Rights</b>	None
<b>Consultancies</b>	None
<b>Expert Testimony</b>	None
<b>Advisory Boards</b>	None
<b>Partnerships</b>	None
<b>Contracts</b>	None
<b>Employment</b>	Associate Professor in Medicine at Harvard Medical School and Mass General Hospital
<b>Honoraria</b>	Non-industry-sponsored speaker honoraria
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<b>O'Reilly:</b>	
<b>Stock Ownership in medically-related fields</b>	None
<b>Intellectual Property Rights</b>	None

<b>Consultancies</b>	None
<b>Expert Testimony</b>	None
<b>Advisory Boards</b>	None
<b>Partnerships</b>	None
<b>Contracts</b>	None
<b>Employment</b>	Research fellow at Harvard School of Public Health
<b>Honoraria</b>	None
<b>Royalties</b>	None
<b>Grants</b>	None
<b>Wang:</b>	
<b>Stock Ownership in medically-related fields</b>	None
<b>Intellectual Property Rights</b>	None
<b>Consultancies</b>	None
<b>Expert Testimony</b>	None
<b>Advisory Boards</b>	None
<b>Partnerships</b>	None
<b>Contracts</b>	None
<b>Employment</b>	Research fellow at Harvard School of Public Health
<b>Honoraria</b>	None
<b>Royalties</b>	None
<b>Grants</b>	None
<b>Ascherio:</b>	
<b>Stock Ownership in medically-related fields</b>	None
<b>Intellectual Property Rights</b>	None
<b>Consultancies</b>	None
<b>Expert Testimony</b>	None
<b>Advisory Boards</b>	Dr. Ascherio serves on the scientific advisory board of the Michael J Fox Foundation
<b>Partnerships</b>	None
<b>Contracts</b>	None
<b>Employment</b>	Professor in Nutrition and Epidemiology at Harvard School of Public Health and Professor in Medicine at Harvard Medical School
<b>Honoraria</b>	None
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Gao: 1A, 1B, 1C, 2A, 2B, 3A

Schwarzschild, 1A, 2C, 3B

O'Reilly: 1C, 2C, 3B

Wang: 1C, 2C, 3B

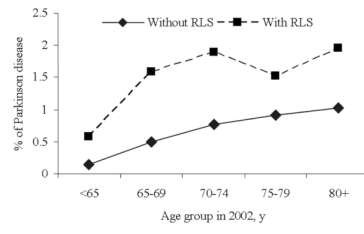
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**Figure.**  
Prevalence of Parkinson's disease (PD) according to restless legs syndrome status.



**Table 1**

Basic characteristics according to restless legs syndrome status in 2002 in the Health Professionals Follow-up Study\*

	Restless legs syndrome status in 2002		
	No RLS	RLS 5-14 times/mo	RLS 15+ times/mo
n	22175	549	395
Age, y	67.6	69.2	70.0
Current smokers, %	3.6	3.7	6.1
Past smokers, %	52.5	57.4	55.1
African Americans, %	0.6	0.5	0.9
Asian & other ethnicity, %	3.0	1.1	1.5
BMI, kg/m <sup>2</sup>	25.9	26.4	26.2
Physical activity, Mets/wk	36.7	35.2	31.7
Phobic anxiety index	1.9	2.3	2.5
Use of antidepressant, %	4.4	8.0	11.3
Presence of stroke in or prior to 2002, %	1.3	2.4	2.9
Presence of hypertension in or prior to 2002, %	41.8	44.6	43.4
Presence of myocardial infarction in or prior to 2002, %	3.7	3.7	3.7

\* Values were standardized to the age distribution of the overall cohort.

**Table 2**

Odds ratios (ORs) and 95% confidence interval (CI) of Parkinson's disease according to restless legs syndrome status in the Health Professional Follow-up Study

	No RLS (n=22175)	RLS 5-14 times/mo (n=549)	RLS 15+ times/mo (n=395)	P <sub>trend</sub>
# cases	132	4	9	
Age adjusted OR	1(ref.)	1.10 (0.40, 2.98)	3.24 (1.63,6.44)	0.002
Multivariate adjusted OR <sup>1</sup>	1(ref.)	1.10 (0.41, 3.03)	3.09 (1.54,6.19)	0.003

Logistic regression models were used to calculate ORs, adjusted for age (in years), smoking status (never smoker, former smoker, or current smoker: cigarettes/d, 1-14 or  $\geq 15$ ), BMI (<23, 23-24.9, 25-26.9, 27-29.9, or  $\geq 30$  kg/m<sup>2</sup>), use of antidepressant drugs (yes/no), physical activity (quintiles), the Crown-Crisp phobic anxiety index (0-1, 2, 3, or  $\geq 4$ ) and presence of stroke, hypertension, or myocardial infarction (each of them, yes/no)