American Journal of Epidemiology

Vol. 177, No. 10
DOI: 10.1093/aje/kws364
Advance Access publication:
April 21, 2013

Original Contribution

Prospective Study of Restless Legs Syndrome and Risk of Erectile Dysfunction

Yanping Li, Salma Batool-Anwar, Sehee Kim, Eric B. Rimm, Alberto Ascherio, and Xiang Gao*

* Correspondence to Dr. Xiang Gao, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115 (e-mail: xiang.gao@channing.harvard.edu).

Initially submitted June 19, 2012; accepted for publication August 20, 2012.

In our previous cross-sectional study, we found that restless legs syndrome (RLS) was associated with erectile dysfunction (ED). Thus, we conducted a prospective study to examine whether RLS was associated with a higher risk of developing ED based on 6 years of follow-up among 10,394 men (mean age = 63.4 years) in the Health Professionals Follow-up Study. RLS was assessed in 2002 using a set of standardized questions recommended by the International RLS Study Group. Erectile function was assessed by means of questionnaires in 2000, 2004, and 2008. We identified 1,633 incident ED cases. Men with RLS were more likely to develop ED (relative risk = 1.38, 95% confidence interval: 1.14, 1.68; $P = 0.001$) than were those without the syndrome, after adjustment for potential confounders, such as age, body mass index, smoking, physical activity, other sleep disorders, and snoring status. A higher frequency of RLS symptoms was also associated with an increased risk of ED ($P_{trend} = 0.001$). In conclusion, men with RLS had a higher risk of ED, and the magnitude of the risk increased with a higher frequency of RLS symptoms. Combinations of other sleep disorders with RLS further increased the risk of ED.

erectile dysfunction; prospective studies; restless legs syndrome; sleep disorders

Abbreviations: CI, confidence interval; ED, erectile dysfunction; RLS, restless legs syndrome; RR, relative risk.

Erectile dysfunction (ED) is observed in 26%–47% of older American men (1–4) and is associated with decrements in quality of life. It is recognized that many of the regions of the brain that are assumed to be relevant in the pathogenesis of sexual dysfunction also appear to be involved in the regulation of sleep and wakefulness (5, 6). In our previous cross-sectional study among male US health professionals, we observed that men with restless legs syndrome (RLS) had a higher likelihood of having ED (7). RLS, also known as Willis-Ekbom disease, is one of the most common sleep disorders, affecting approximately 4%–8% of men (7–10). In another study conducted in Sweden, men with RLS were twice as likely to have reduced libido as controls (8).

The observed cross-sectional relationship between RLS and ED could be due to the shared biological mechanisms, such as hypofunction of dopamine in the central nervous system (11, 12) and autonomic dysfunction (13, 14). However, the cross-sectional relationship could also be due to certain lifestyle factors (e.g., smoking and physical inactivity) and chronic conditions (such as cardiovascular diseases) associated with both RLS (15, 16) and ED (1). Other sleep disorders which co-occur with RLS may also affect sexual function through their unfavorable impact on hormonal, neural, and endothelial physiology (5). Understanding the potential roles of RLS in the development of ED could have important public health and clinical implications, since it may provide a useful indicator for earlier detection and possibly lead to the development of novel strategies for prevention and treatment of ED.

Therefore, we conducted a prospective study of over 10,000 men to examine whether men with RLS had an increased risk of developing ED. To increase the understanding of potential mechanisms, here we report results with and without control for the potential cofounders or intermediate factors mentioned above.

MATERIALS AND METHODS

Study participants

The Health Professionals Follow-up Study 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 were mailed to participants every 2 years to obtain updated information on potential risk factors and to ascertain newly diagnosed diseases.

Data collection

In 2002, the RLS questions (7) were investigated among the 37,421 men who were still alive and actively participating in the study, which was completed by 31,729 (85%) men. The RLS questions were developed on the basis of the International RLS Study Group criteria (17). The following question was asked: "Do you have unpleasant leg sensations (like crawling, paresthesia, or pain) combined with motor restlessness and an urge to move?" The possible responses were as follows: no, less than once per month, 2–4 times per month, 5–14 times per month, and 15 or more times per month. Those who answered that they had these feelings were asked 2 subsequent 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 reported having symptoms ≥5 times per month and answered "yes" to the subsequent questions was considered to have RLS; others, including men who had symptoms 1–4 times per month, were classified as not having RLS (the "no RLS" group). We also conducted a sensitivity analysis by excluding men who had symptoms 1–4 times per month and answered "yes" to the above 2 subsequent questions ($n = 698$).

We asked Health Professionals Follow-up Study participants to rate their ability to have and maintain an erection sufficient for sexual intercourse during the past 3 months on the 2000, 2004, and 2008 questionnaires (18, 19). Response options were very poor, poor, fair, good, and very good. Men who answered "poor" or "very poor" were considered to have ED (1, 7).

In 2004, we asked 4 questions regarding other sleep disorders: 1) "How often do you have difficulty falling asleep?"; 2) "How often do you have trouble with waking up during the night?"; 3) "How often are you troubled by waking up too early and not being able to fall asleep again?"; and 4) "How often do you get so sleepy during the day or the evening that you have to take a nap?" The possible responses were 1) most of the time, 2) sometimes, and 3) rarely or never. We coded "most of the time," "sometimes," and "rarely or never" as 2, 1, and 0, respectively, and summed them to create a sleep disorder score. A score equal to or above 4 (i.e., the halfway point of the maximum value) was considered to represent sleep disorders other than RLS (20). Information on frequency of snoring was also collected on the year 2000 questionnaire. Frequent snoring was defined as snoring every night or on most nights.

In the current analysis, we used RLS data from 2002 and other sleep disorder data from 2004 to predict incident ED with onset during 2005–2008. We thus excluded men who had reported ED during or prior to 2004 ($n = 14,557$) and those with incomplete information on erectile function ($n = 2,946$). To reduce possible misclassification of RLS (7), we also excluded participants with diabetes and arthritis ($n = 3,486$) from our primary analyses. Because prostate cancer therapy may result in ED, men who had prostate cancer during or prior to 2008 were also excluded ($n = 346$) (1), leaving 10,394 men in our primary analysis. In a sensitivity analysis, we further examined the association between RLS and erectile function, including all participants with information on RLS and ED (including the participants with diabetes, arthritis, or prostate cancer) ($n = 13,237$).

Information on potential confounders, such as age, ethnicity, smoking status, weight, height, physical activity, medication use (e.g., antidepressants, antihypertensive agents, antihistamines, nonsteroidal antiinflammatory drugs, acetaminophen), use of medication for benign prostatic hyperplasia (e.g., α1-adrenergic receptor blockers and 5α-reductase inhibitors) (21), level of phobic anxiety (22), lower urinary tract symptoms (based on the American Urological Association Symptom Index (23)), surgery for an enlarged prostate, and history of major chronic diseases (including stroke, hypertension, myocardial infarction, diabetes, arthritis, and Parkinson's disease) was collected via biennial questionnaires throughout the follow-up period. Participants who reported having a depressed mood were asked whether they had experienced 2 weeks of feeling sad, blue, or depressed for most of the day in 2004 and 2008. Body mass index was calculated as weight (kg)/height $(m)^2$. We quantified physical activity in metabolic equivalents per week using reported time spent in various activities, weighted by reported intensity level (24). The Crown-Crisp Experiential Index was used as a phobic anxiety scale to assess the level of phobic anxiety (22). Moderate-to-severe lower urinary tract symptoms were defined as an American Urological Association Symptom Index score of ≥15 (21, 23). Information on dietary iron intake and the use of iron-specific supplements was collected every 4 years via a validated food frequency questionnaire.

The institutional review board at Brigham and Women's Hospital and the Office of Human Research Administration of Harvard School of Public Health approved this study.

Statistical analyses

We categorized participants into 3 groups: no RLS, RLS with symptoms 5–14 times per month, and RLS with symptoms ≥15 times per month. To test differences in the incidence of ED across categories of RLS status, we used maximum likelihood estimation with log-binomial models to estimate relative risks and 95% confidence intervals (25). In a few instances where the models did not converge, log-Poisson models with sandwich estimation of variance were used to estimate the relative risk and its 95% confidence interval (26).

Analyses were adjusted for age (<60, 60–64, 65–69, 70–74, 75–79 or ≥80 years), ethnicity (white, African-American, or Asian and other), smoking status (never smoker, former smoker, or current smoker of 1–14 or ≥15 cigarettes/day), alcohol drinking (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, or ≥30 g/day), body mass index (weight (kg)/height $(m)^2$; <23, 23–24.9, 25–26.9, 27–29.9, or ≥30), physical activity (metabolic equivalents per week, in quintiles), use of antidepressants

(yes/no), level of phobic anxiety (0–1, 2, 3, or ≥4), physician-diagnosed stroke (yes/no), hypertension (yes/no), Parkinson's disease (yes/no), or myocardial infarction (yes/no), other sleep disorders (yes/no), and snoring status (every night, most nights, a few nights per week, occasionally, or once a week or less). In a secondary analysis, we further adjusted for updated status regarding major chronic diseases (i.e., stroke, hypertension, Parkinson's disease, myocardial infarction, diabetes, arthritis, and depression) up to 2008 and the use of antihypertensive agents, antihistamines, nonsteroidal antiinflammatory drugs, and acetaminophen. Because iron deficiency has been shown to be associated with RLS (27, 28), we also adjusted for dietary iron intake and the use of iron-specific supplements. To examine whether other sleep disorders modified the association between RLS and ED, we also tested the interaction between RLS and other sleep disorders in relation to risk of ED by adding a multiplicative factor to the model.

To further test the robustness of our findings, we conducted an additional sensitivity analysis by excluding men with a body mass index greater than 30 or a history of hypertension, stroke, Parkinson's disease, or myocardial infarction; those who reported frequent snoring or use of iron-specific supplements; and those who developed diabetes, arthritis, or depression during follow-up (2002–2008). We also conducted a sensitivity analysis by excluding participants who reported having leg cramps or positional discomfort, the 2 conditions that commonly mimic RLS (29). Statistical analyses were completed with SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Compared with men without RLS, those with RLS were more likely to smoke, were more likely to use antidepressant medications and iron-specific supplements, more frequently snored, had higher anxiety scores, and had a higher prevalence of Parkinson's disease, stroke, and myocardial infarction (Table 1).

We identified 1,633 incident ED cases during the years 2005–2008. Among men with RLS at baseline, 23.4%

Table 1. Baseline Characteristics of Participants According to Restless Legs Syndrome Status in the Health Professionals Follow-up Study, United States, 2002[a]

	RLS Status in 2002								
	No RLS (n = 10,063)			RLS 5–14 Times per Month (n = 211)			RLS ≥15 Times per Month (n = 120)		
	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%
Age, years	63.4 (6.6)			63.9 (6.7)			63.6 (7.3)		
Smoking status									
Current smoker		360	3.6		10	4.9		9	8.6
Past smoker		4,774	47.5		104	48.5		61	49.6
Race									
African-American		53	0.5		0	0		2	1.4
Asian and other[b]		280	2.8		3	1.4		1	0.7
Body mass index[c]	26.0 (3.26)			26.6 (3.25)			26.3 (3.27)		
Physical activity, METs/week	40.6 (42.1)			39.3 (42.0)			39.1 (42.0)		
Iron intake									
Dietary iron intake, mg/day	15.9 (6.58)			16.5 (6.55)			16.1 (6.55)		
Use of iron-specific supplements		121	1.2		4	1.9		2	1.5
Frequent snoring		3,002	32.4		64	35.1		46	38.2
Level of phobic anxiety	1.73 (1.81)			2.05 (1.79)			2.39 (1.78)		
Use of antidepressant medication		334	3.3		13	6.2		13	12.3
History of major chronic disease during or prior to 2002									
Parkinson's disease		16	0.2		1	0.4		1	0.7
Stroke		58	0.6		3	1.2		3	3.2
Myocardial infarction		236	2.4		9	4.3		3	3.3
Hypertension		3,544	35.2		77	35.8		38	31.9

Abbreviations: METs, metabolic equivalents; RLS, restless legs syndrome; SD, standard deviation.

[a] All data were standardized to the age distribution of the overall cohort.

[b] Excluding whites.

[c] Weight (kg)/height $(m)^2$.

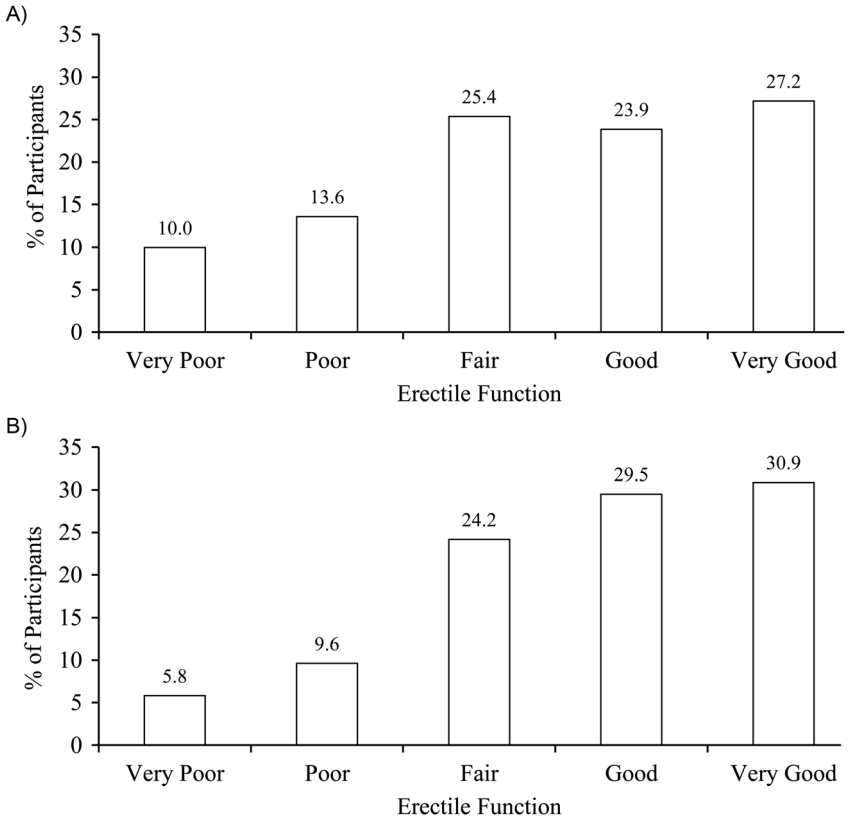

Figure 1. Distribution of participants according to erectile function in 2008 among men with restless legs syndrome (A) and men without restless legs syndrome (B) at baseline in the Health Professionals Follow-up Study, United States, 2002–2008.

developed ED during this period, compared with 15.4% among those without RLS (Figure 1). Consistently, 9.8% of men with RLS at baseline rated their erectile function as "very poor" in 2008, compared with 5.8% among those without RLS (Figure 1). As shown in Table 2, men with RLS were 39% more likely to develop ED (relative risk (RR) = 1.39, 95% confidence interval (CI): 1.15, 1.68; $P = 0.0006$) than were those without the syndrome, after adjustment for age, race, smoking, alcohol drinking, physical activity, body mass index, use of antidepressants, and history of chronic diseases such as hypertension, myocardial infarction, stroke, and Parkinson's disease. The magnitude of the relative risk of ED associated with RLS corresponds to the difference in relative risks observed between participants who were 5 years apart in age in this population. A higher frequency of symptoms was also associated with an increased risk of ED; the adjusted relative risks were 1.34 (95% CI: 1.05, 1.70) and 1.49 (95% CI: 1.11, 2.01; $P_{trend} = 0.0005$) for men with RLS symptoms 5–14 times per month and men with RLS symptoms ≥15 times per month, respectively, relative to those without RLS. When we included other sleep disorders and snoring frequency in the model, the relative risk of ED was attenuated slightly (RR = 1.38, 95% CI: 1.14, 1.68; Table 2); the relative risk was 1.39 (95% CI: 1.14, 1.70) after further adjustment for marital status.

When we further adjusted for dietary iron intake and use of iron-specific supplements; the presence of diabetes, arthritis, and self-reported depressed mood during follow-up (2002–2008); updated status for the major chronic diseases; moderate-to-severe lower urinary tract symptoms; surgery for an enlarged prostate; the use of acetaminophen, antihypertensive agents, antidepressants, antihistamines, and nonsteroidal antiinflammatory drugs; and the use of medications for benign prostatic hyperplasia, the relative risk of ED between men with and without RLS changed to 1.33 (95% CI: 1.09, 1.62), which was comparable to the relative risks of ED associated with diabetes, depression, cardiovascular diseases, current smoking, physical inactivity, and obesity in the Health Professionals Follow-up Study (relative risks ranged from 1.18 to 1.43).

Both RLS and other sleep disorders were independently associated with ED (P for interaction = 0.70). Compared with men who had only other sleep disorders, men who had only RLS, and men with both RLS and other sleep disorders, men with neither RLS nor other sleep disorders were 1.14 (95% CI: 1.02, 1.28), 1.40 (95% CI: 1.05, 1.85), and 1.54 (95% CI: 1.13, 2.10) times more likely to develop ED, respectively (Figure 2).

We did not find significant interaction between RLS and age in relation to risk of ED (P for interaction = 0.85). The

Table 2. Relative Risk of Erectile Dysfunction According to Baseline Restless Legs Syndrome Status in the Health Professionals Follow-up Study, United States, 2002–2008

RLS Status in 2002	No. of ED Cases	Cumulative Incidence of ED, %	Age-Adjusted RR	95% CI	P_{trend}	Multivariate RR[a]	95% CI	P_{trend}	Multivariate RR[b]	95% CI	P_{trend}
No RLS ($n = 10,063$)	1,555	15.5	1	Reference	<0.0001	1	Reference	0.0005	1	Reference	0.001
RLS 5–14 times per month ($n = 211$)	48	22.8	1.38	1.09, 1.75		1.34	1.05, 1.70		1.34	1.05, 1.72	
RLS ≥15 times per month ($n = 120$)	30	25.0	1.55	1.16, 2.07		1.49	1.11, 2.01		1.45	1.07, 1.98	
RLS vs. no RLS	78	23.5	1.44**	1.19, 1.74		1.39***	1.15, 1.68		1.38*	1.14, 1.68	

Abbreviations: CI, confidence interval; ED, erectile dysfunction; RLS, restless legs syndrome; RR, relative risk.

* $P = 0.001$; ** $P = 0.0001$; *** $P = 0.0006$.

[a] The method of generalized estimating equations with a log-binomial model was used to estimate the RRs and 95% CIs, adjusting for age (<60, 60–64, 65–69, 70–74, 75–79 or ≥80 years), race (white, African-American, or Asian and other), smoking status (never smoker, former smoker, or current smoker of 1–14 or ≥15 cigarettes/day), alcohol drinking (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, or ≥30 g/day), body mass index (weight (kg)/height (m)^2; <23, 23–24.9, 25–26.9, 27–29.9, or ≥30), physical activity (metabolic equivalents/week, in quintiles), level of phobic anxiety (0–1, 2, 3, or ≥4), use of antidepressant medication (yes/no), and history of stroke, hypertension, Parkinson's disease, or myocardial infarction (yes/no for each).

[b] Further adjusted other sleep disorders and snoring frequency (every night, most nights, a few nights per week, occasionally, or once a week or less).

stratified analysis based on the median value of age (62 years) showed similar results. Multivariate-adjusted relative risks comparing men with RLS with men without RLS were 1.40 (95% CI: 0.95, 2.07; $P = 0.09$) among participants younger than 62 years of age and 1.35 (95% CI: 1.07, 1.69; $P = 0.01$) among participants aged 62 years or older. We obtained similar significant results in the sensitivity analyses (Appendix Table 1). Multivariate-adjusted relative risks comparing men with RLS with men without RLS were 1.49 (95% CI: 1.22, 1.83) after excluding participants with a body mass index ≥30, 1.54 (95% CI: 1.20, 1.98) after excluding participants with a history of hypertension, and 1.46 (95% CI: 1.19, 1.79) after excluding participants with a history of myocardial infarction, stroke, or Parkinson's disease. When all of these exclusions were applied simultaneously, the results were slightly stronger (for men with RLS vs. men without RLS, adjusted RR = 1.86, 95% CI: 1.33, 2.59). Excluding participants with frequent snoring or use of iron-specific supplements resulted in multivariate-adjusted relative risks of 1.45 (95% CI: 1.14, 1.84) and 1.42 (95% CI: 1.16, 1.73), respectively, comparing men with and without RLS (Appendix Table 1). When we excluded men who had symptoms 1–4 times per month and answered "yes" to the subsequent 2 questions, the adjusted relative risk of ED was 1.40 (95% CI: 1.15, 1.71) for men with RLS versus men without RLS. After we excluded participants who developed diabetes or arthritis during follow-up (2002–2008), the multivariate-adjusted relative risk of ED was 1.43 (95% CI: 1.11, 1.83). After exclusion of participants who reported having leg cramps or positional discomfort, the 2 conditions that commonly mimic RLS, the multivariate-adjusted relative risk of ED between men with RLS and men without RLS was 1.52 (95% CI: 1.19, 1.93). The adjusted relative risk changed to 1.37 (95% CI: 1.10, 1.69) when we excluded participants with self-reported depressed mood or use of antidepressants, and it changed to 1.40 (95% CI: 1.07, 1.82) when we excluded men who had ever had surgery for an enlarged prostate, had moderate-to-severe lower urinary tract symptoms, or reported use of medication for benign prostatic hyperplasia. After further inclusion of the participants with diabetes, arthritis, or prostate cancer, the association between RLS and ED remained significant (for men with RLS symptoms vs. those without symptoms, multivariate-adjusted RR = 1.37, 95% CI: 1.20, 1.57) (Appendix Table 1).

DISCUSSION

In this prospective study, we observed that men with RLS had a higher risk of developing ED than men without RLS, and there was a clear linear relationship between RLS severity, as assessed by symptom frequency, and the magnitude of the ED risk, which was independent of age, smoking status, physical activity, body mass index, use of antidepressants, history of several chronic diseases, and sleep disorders. The results also indicated that combinations of other sleep disorders with RLS further increased the risk of ED.

RLS is a commonly diagnosed sleep disorder. RLS-related sleep disruption, such as daytime sleepiness and difficulty in concentrating the following day, was observed in

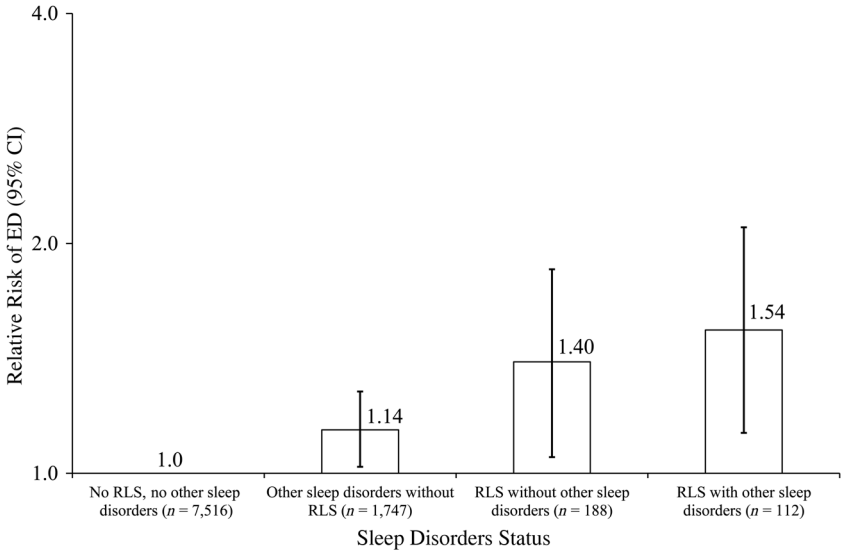

Figure 2. Relative risk of erectile dysfunction (ED) among men with various combinations of restless legs syndrome (RLS) and other sleep disorders in the Health Professionals Follow-up Study, United States, 2002–2008. All *P* values were less than 0.05 in comparison with participants with neither RLS nor a sleep disorder; and the *P* value for interaction was 0.70, after adjustment for age (<60, 60–64, 65–69, 70–74, 75–79, or ≥80 years), race (white, African-American, or Asian and other), smoking status (never smoker, former smoker, or current smoker of 1–14 or ≥15 cigarettes/day), alcohol drinking (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, or ≥30 g/day), body mass index (weight (kg)/height $(m)^2$; <23, 23–24.9, 25–26.9, 27–29.9, or ≥30), physical activity (metabolic equivalents/week, in quintiles), level of phobic anxiety (0–1, 2, 3, or ≥4), use of antidepressant medication (yes/no), and history of stroke, hypertension, Parkinson's disease, or myocardial infarction (yes/no for each). Bars, 95% confidence interval (CI).

many RLS sufferers (8, 30). In the RLS Epidemiology, Symptoms, and Treatment (REST) General Population Study, a significant sleep disturbance was noted among 75% of the primary RLS sufferers (30). Among Swedish men (8), sleepiness and poor performance at work were reported 3 times more often by subjects with RLS than by those without RLS (odds ratio = 3.0, 95% CI: 1.9, 4.5). In clinical practice, men presenting with symptoms of sexual dysfunction often have concomitant sleep disorders requiring treatment (31), and treatment with continuous positive airway pressure among obstructive sleep apnea patients improved overall erectile function (32–34). In the present study, both RLS and other sleep disorders were independently associated with ED, and the combination of other sleep disorders with RLS further increased the risk. These findings support the assumption that assessment of RLS and sleep disorders may provide a useful indicator for earlier detection of ED (35–38). It can be hypothesized that medical treatment of disorders such as insomnia or RLS may improve sleep quality and psychogenic factors and thus erectile function. The performance of more rigorous studies of RLS prevalence and treatment outcome is warranted.

Although the etiology of RLS has not yet been elucidated, dopaminergic dysfunction in the central nervous system is the most supported argument (8, 9, 39). RLS is associated with autonomic dysfunction because of the implication of dopamine sensitivity in the spinal cord; decreased dopamine levels may lead to an increased sympathetic drive in RLS (13, 14, 40). Of note, erectile function is largely controlled by the autonomic nervous system (6, 14). High sympathetic activity may oppose the normal physiological mechanisms that allow for normal erectile function (6). The spinal cord also plays a key role in sexual function; subjects with spinal cord injuries have a higher prevalence of sexual dysfunction (41). Further, periodic limb movement disorder, a key feature of RLS that is generated in the spinal cord, was found to be associated with ED (42). RLS may also increase the risk of ED by inducing sleep disruption (43) and psychological disorders (44, 45), which may increase the risk of psychogenic ED (6).

Several modifiable health behaviors and chronic conditions are associated with both RLS and ED (1, 15, 16), which could also underlie the associations between RLS and ED. We previously reported (46) that persons with RLS were more likely to have overall and abdominal obesity than persons without RLS. Phillips et al. (16) reported that RLS was significantly associated with increased age, increased body mass index, smoking, lack of exercise, low alcohol consumption, and diabetes, which had also been considered risk/protective factors for ED (1). Adjustment for these factors in the present study only marginally attenuated the association between RLS and ED. The robustness of the results to sensitivity analyses excluding men with cardiovascular disease, obesity, or old age implies that those factors may not entirely explain the observed association between RLS and risk of ED.

As far as we know, this was the first prospective study to examine the association between RLS and risk of ED. Although this provides evidence for a possible causal relationship between RLS and ED, we should be cautious about

making such a conclusion. Several limitations should be addressed. First, our study was carried out among US health professionals, and further studies in the general population with different educational and culture backgrounds are needed to replicate our findings. Second, in our study, both RLS and ED were evaluated by means of self-report questions, which inevitably led to some degree of misclassification. In order to reduce the misclassification, we excluded men with diabetes and arthritis, 2 conditions that commonly mimic RLS (29), from our main analysis. We also conducted a sensitivity analysis by further excluding participants who had reported leg cramps or positional discomfort, the other 2 conditions that commonly mimic RLS (29). The results did not materially change. Meanwhile, the validation study (47) that included 137 men aged 55–85 years who participated in the Massachusetts Male Aging Study showed that self-reported ED is able to predict clinician-diagnosed ED (area under the receiver operating characteristic curve = 0.89). Survival bias is another concern, because the participants included in our study were rather old (mean age = 69.4 years at the end of follow-up). We conducted a stratified analysis by age and obtained similar results.

The other limitations include the lack of objective measurements of obstructive sleep apnea and iron deficiency. Thus, in the current analyses, we employed frequent snoring and use of iron-specific supplements as surrogates of obstructive sleep apnea and iron deficiency, respectively. Frequent snoring has been shown to have high sensitivity (88%) for obstructive sleep apnea in men (48) and has been commonly used as a surrogate measure of obstructive sleep apnea in previous epidemiologic studies (49), although misclassification is inevitably introduced. Employing use of iron-specific supplements as a surrogate for iron deficiency is supported by the observation that men using iron-specific supplements had a higher likelihood of having RLS (odds ratio = 1.72, 95% CI: 1.14, 2.46) than nonusers in the Health Professionals Follow-up Study. Adjustment for frequent snoring and use of iron-specific supplements did not change the observed association between RLS and ED materially. Further adjustment for lifetime number of blood donations did not change the observed association between RLS and ED either (the multiply adjusted relative risk of ED comparing men with RLS with those without RLS was 1.38 (95% CI: 1.13, 1.68) after further adjustment for lifetime number of blood donations).

In conclusion, in this large-scale prospective study, we found that men with RLS had a higher risk of developing ED, and the magnitude of the risk was increased with a higher frequency of RLS symptoms. Combinations of other sleep disorders with RLS further increased the risk of ED. Further studies in different populations are warranted.

ACKNOWLEDGMENTS

Author affiliations: Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Yanping Li, Eric Rimm, Alberto Ascherio, Xiang Gao); Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts (Sehee Kim); Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts (Eric Rimm, Alberto Ascherio, Xiang Gao); Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Salma Batool-Anwar); and Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Eric Rimm, Alberto Ascherio).

This study was supported by grant R01 NS062879-01A2 from the National Institute of Neurological Disorders and Stroke and grant P01 CA055075 from the National Cancer Institute.

Drs. Yanping Li and Xiang Gao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The funding sources were not involved in data collection, data analysis, manuscript writing, or publication.

Conflict of interest: none declared.

REFERENCES

1. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: results from the Health Professionals Follow-up Study. *Ann Intern Med*. 2003; 139(3):161–168.
2. Blanker MH, Bosch JL, Groeneveld FP, et al. Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: prevalence, concern, and relation to sexual activity. *Urology*. 2001;57(4):763–768.
3. Panser LA, Rhodes T, Girman CJ, et al. Sexual function of men ages 40 to 79 years: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *J Am Geriatr Soc*. 1995;43(10):1107–1111.
4. Argiolas A, Melis MR. Central control of penile erection: role of the paraventricular nucleus of the hypothalamus. *Prog Neurobiol*. 2005;76(1):1–21.
5. Andersson KE. Pharmacology of penile erection. *Pharmacol Rev*. 2001;53(3):417–450.
6. Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacol Rev*. 2011;63(4):811–859.
7. Gao X, Schwarzschild MA, O'Reilly EJ, et al. Restless legs syndrome and erectile dysfunction. *Sleep*. 2010;33(1): 75–79.
8. Ulfberg J, Nyström B, Carter N, et al. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord*. 2001;16(6):1159–1163.
9. Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO. Memory and Morbidity in Augsburg Elderly study. *Neurology*. 2000;54(5):1064–1068.
10. Berger K, Luedemann J, Trenkwalder C, et al. Sex and risk of restless legs syndrome in the general population. *Arch Intern Med*. 2004;164(2):196–202.
11. Scholz H, Trenkwalder C, Kohnen R, et al. Dopamine agonists for restless legs syndrome. *Cochrane Database Syst Rev*. 2011;3:CD006009.

12. Cikrikcioglu MA, Hursitoglu M, Erkal H, et al. Oxidative stress and autonomic nervous system functions in restless legs syndrome. *Eur J Clin Invest*. 2011;41(7):734–742.
13. Hull EM, Muschamp JW, Sato S. Dopamine and serotonin: influences on male sexual behavior. *Physiol Behav*. 2004; 83(2):291–307.
14. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep*. 2009;32(5): 589–597.
15. de Groat WC, Booth AM. Neural control of penile erection. In: Maggi CA, ed. *Nervous Control of the Urogenital System*. (The Autonomic Nervous System, vol 3). London, United Kingdom: Harwood Academic Publishers; 1993:465–513.
16. Phillips B, Young T, Finn L, et al. Epidemiology of restless legs symptoms in adults. *Arch Intern Med*. 2000;160(14): 2137–2141.
17. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003;4(2):101–119.
18. National Institutes of Health. Impotence. *NIH Consens Statement*. 1992;10(4):1–33.
19. Lewis RW, Fugl-Meyer KS, Bosch R, et al. Definitions, classification, and epidemiology of sexual dysfunction. In: Lue TF, Basson R, Rosen RC, et al, eds. *Sexual Medicine*. Paris, France: Health Publications; 2004:37–72.
20. Jenkins CD, Stanton BA, Niemcryk SJ, et al. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol*. 1988;41(4):313–321.
21. Platz EA, Kawachi I, Rimm EB, et al. Physical activity and benign prostatic hyperplasia. *Arch Intern Med*. 1998;158(21): 2349–2356.
22. Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation*. 1994;89(5):1992–1997.
23. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148(5): 1549–1557.
24. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol*. 1994;23(5):991–999.
25. Greenland S. Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. *Am J Epidemiol*. 2004;160(4): 301–305.
26. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7): 702–706.
27. Sikandar R, Khealani BA, Wasay M. Predictors of restless legs syndrome in pregnancy: a hospital based cross sectional survey from Pakistan. *Sleep Med*. 2009;10(6):676–678.
28. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing*. 1994;23(3): 200–203.
29. Hening WA, Allen RP, Washburn M, et al. The four diagnostic criteria for restless legs syndrome are unable to exclude confounding conditions ("mimics"). *Sleep Med*. 2009;10(9): 976–981.
30. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. 2005;165(11):1286–1292.
31. Zias N, Bezwada V, Gilman S, et al. Obstructive sleep apnea and erectile dysfunction: still a neglected risk factor? *Sleep Breath*. 2009;13(1):3–10.
32. Karacan I, Karatas M. Erectile dysfunction in sleep apnea and response to CPAP. *J Sex Marital Ther*. 1995;21(4): 239–247.
33. Margel D, Tal R, Livne PM, et al. Predictors of erectile function improvement in obstructive sleep apnea patients with long-term CPAP treatment. *Int J Impot Res*. 2005;17(2): 186–190.
34. Taskin U, Yigit O, Acioglu E, et al. Erectile dysfunction in severe sleep apnea patients and response to CPAP. *Int J Impot Res*. 2010;22(2):134–139.
35. Melis MR. Central control of penile erection: role of the paraventricular nucleus of the hypothalamus. *Prog Neurobiol*. 2005;76(1):1–21.
36. Paulus W, Dowling P, Rijsman R, et al. Pathophysiological concepts of restless legs syndrome. *Mov Disord*. 2007; 22(10):1451–1456.
37. Mann K, Pankok J, Connemann B, et al. Sleep investigations in erectile dysfunction. *J Psychiatr Res*. 2005;39(1):93–99.
38. Salin-Pascual R, Gerashchenko D, Greco MA, et al. Hypothalamic regulation of sleep. *Neuropsychopharmacology*. 2001;25(5 suppl):S21–S27.
39. Yeh P, Walters AS, Tsuang JW. Restless legs syndrome: a comprehensive overview on its epidemiology, risk factors, and treatment. *Sleep Breath*. 2012;16(4):987–1007.
40. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. *Neurology*. 2006;67(1):125–130.
41. Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. *Lancet*. 2007;369(9560): 512–525.
42. Hirshkowitz M, Karacan I, Arcasoy MO, et al. The prevalence of periodic limb movements during sleep in men with erectile dysfunction. *Biol Psychiatry*. 1989;26(6):541–544.
43. Picchietti D, Winkelman JW. Restless legs syndrome, periodic limb movements in sleep, and depression. *Sleep*. 2005;28(7): 891–898.
44. Nomura T, Inoue Y, Kusumi M, et al. Prevalence of restless legs syndrome in a rural community in Japan. *Mov Disord*. 2008;23(16):2363–2369.
45. Celle S, Roche F, Kerleroux J, et al. Prevalence and clinical correlates of restless legs syndrome in an elderly French population: the Synapse Study. *J Gerontol A Biol Sci Med Sci*. 2010;65(2):167–173.
46. Gao X, Schwarzschild MA, Wang H, et al. Obesity and restless legs syndrome in men and women. *Neurology*. 2009;72(14):1255–1261.
47. O'Donnell AB, Araujo AB, Goldstein I, et al. The validity of a single-question self-report of erectile dysfunction. Results from the Massachusetts Male Aging Study. *J Gen Intern Med*. 2005;20(6):515–519.
48. Bliwise DL, Nekich JC, Dement WC. Relative validity of self-reported snoring as a symptom of sleep apnea in a sleep clinic population. *Chest*. 1991;99(3):600–608.
49. Ketterer MW, Brymer J, Rhoads K, et al. Snoring and the severity of coronary artery disease in men. *Psychosom Med*. 1994;56(3):232–236.

(Appendix table follows)

Appendix Table 1. Relative Risk of Incident Erectile Dysfunction According to Baseline Restless Legs Syndrome Status Among Different Subgroups of Men in the Health Professionals Follow-up Study, United States, 2002–2008

	No. of Men	RLS 5–14 Times per Month vs. No RLS		RLS ≥15 Times per Month vs. No RLS			RLS vs. No RLS		
		RR[a]	95% CI	RR[a]	95% CI	P_{trend}	RR[a]	95% CI	*P* Value
Exclusion of men with RLS 1–4 times per month[b]	9,696	1.36	1.06, 1.74	1.47	1.08, 2.01	0.0008	1.40	1.15, 1.71	0.0008
BMI[c] ≤30[d]	9,291	1.49	1.15, 1.92	1.51	1.10, 2.07	0.0002	1.49	1.22, 1.83	0.0001
No hypertension[d]	6,735	1.47	1.06, 2.03	1.67	1.14, 2.44	0.0005	1.54	1.20, 1.98	0.0007
No MI, no stroke, and no PD[d]	10,069	1.33	1.01, 1.75	1.68	1.25, 2.25	<0.0001	1.46	1.19, 1.78	0.0003
No MI, no stroke, no PD, no hypertension, BMI ≤30, and age ≤70 years[d]	5,143	1.87	1.24, 2.84	1.83	1.09, 3.10	0.0004	1.86	1.33, 2.59	0.0002
No frequent snoring[d]	7,282	1.44	1.08, 1.92	1.47	0.99, 2.20	0.01	1.45	1.14, 1.84	0.002
No BPH/LUTS[d,e]	7,812	1.45	1.05, 2.00	1.31	0.85, 2.04	0.02	1.40	1.07, 1.82	0.01
No use of iron-specific supplements[d]	10,267	1.38	1.07, 1.78	1.48	1.09, 2.02	0.004	1.42	1.16, 1.73	0.0005
No diabetes or arthritis diagnosed during 2002–2008[d]	8,061	1.40	1.03, 1.91	1.48	1.004, 2.17	0.02	1.43	1.11, 1.83	0.005
No depressed mood/ antidepressant use during 2002–2008[d]	9,822	1.27	0.96, 1.68	1.54	1.12, 2.11	0.008	1.37	1.10, 1.69	0.004
RLS in 2002 and ED in 2008[b]	13,237	1.29	1.08, 1.54	1.49	1.23, 1.80	<0.0001	1.37	1.20, 2.00	<0.0001

Abbreviations: BMI, body mass index; BPH, benign prostatic hyperplasia; CI, confidence interval; ED, erectile dysfunction; LUTS, lower urinary tract symptoms; MI, myocardial infarction; PD, Parkinson's disease; RLS, restless legs syndrome; RR, relative risk.

[a] Adjusted for age (<60, 60–64, 65–69, 70–74, 75–79 or ≥70 years), race (Caucasian, African-American, or Asian and other), smoking status (never smoker, former smoker, or current smoker of 1–14 or ≥15 cigarettes/day), alcohol drinking (0, 0.1–9.9, 10.0–19.9, 20.0–29.9, or ≥30 g/day), BMI (<23, 23–24.9, 25–26.9, 27–29.9, or ≥30), physical activity (quintiles), level of phobic anxiety (0–1, 2, 3, or ≥4), use of antidepressant medication (yes/no), and history of stroke, hypertension, PD, or MI (yes/no for each).

[b] The method of generalized estimating equations with a log-binomial model was used to estimate the RRs and 95% CIs.

[c] Weight (kg)/height $(m)^2$.

[d] Generalized estimating equations log-Poisson models were used to estimate the RRs and 95% CIs because the log-binomial models did not converge.

[e] Men who had ever had surgery for an enlarged prostate, had moderate-to-severe LUTS, or reported use of medication for BPH were excluded.