Prospective study of restless legs syndrome and mortality among men

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ABSTRACT

Objective: To prospectively examine whether men with restless legs syndrome (RLS) had an increased risk of mortality.

Method: This was a prospective cohort study of 18,425 US men free of diabetes, arthritis, and renal failure in the Health Professionals Follow-up Study (HPFS). In 2002, RLS was assessed using a set of standardized questions. Deaths were identified from state vital statistics records, the National Death Index, family reports, and the postal system.

Results: During 8 years of follow-up (2002–2010), we documented 2,765 deaths. In an age-adjusted model, RLS was associated with a 39% increased risk of mortality (hazard ratio [HR] = 1.39; 95% confidence interval [CI] 1.19–1.62; $p < 0.0001$). The association between RLS and mortality was slightly attenuated after further adjustment for body mass index, lifestyle factors, chronic conditions, sleep duration, and other sleep-related disorders (adjusted HR = 1.30; 95% CI 1.11–1.52; $p = 0.003$). When we further excluded those with major chronic conditions (e.g., cancer, high blood pressure, cardiovascular disease, and other comorbidities), the adjusted HR was 1.92 (95% CI 1.03–3.56; $p = 0.04$). The interactions between RLS and other risk factors (older age, overweight, short sleep duration, smoking, low physical activity, and unhealthy diet) in relation to total mortality risk were not significant (p for interaction >0.2 for all).

Conclusion: We observed that men with RLS had a higher overall mortality and this association was independent of known risk factors. The increased mortality in RLS was more frequently associated with respiratory disease, endocrine disease, nutritional/metabolic disease, and immunologic disorders. Future research exploring the pathophysiologic relationship between these disorders and RLS is warranted. *Neurology*® 2013;81:52–59

GLOSSARY

AHEI = Alternate Healthy Eating Index; **BMI** = body mass index; **CI** = confidence interval; **CVD** = cardiovascular disease; **HPFS** = Health Professionals Follow-up Study; **HR** = hazard ratio; **ICD-8** = *International Classification of Diseases*, eighth revision; **IRLSSG** = International RLS Study Group; **MS** = multiple sclerosis; **PD** = Parkinson disease; **PLMS** = periodic limb movements of sleep; **RLS** = restless legs syndrome.

Restless legs syndrome (RLS) is a bothersome chronic condition, characterized by an almost irresistible urge to move the legs and usually occurring with leg sensations of burning, creeping, tugging, or “like insects crawling inside the legs,” which are worse in the evening and night with significant relief in the morning.^{1–3} This sensorimotor disorder was described in the late 17th century by Sir Thomas Willis and was coined RLS by Karl Ekbom in the 1940s.² RLS affects 5%–10% of adults in the general population,^{4–8} and is associated with various chronic conditions.⁹

A notable high mortality associated with RLS has been observed among men and women with renal disease.^{10,11} In the general population, 3 previous studies^{12–14} examined the association between RLS symptoms and mortality and reported inconsistent results. However, these studies are limited by small sample size, failure to employ standard questions to assess RLS,^{12,13} or lack of information on RLS frequency.^{12,14} Further, the association between RLS and cause-specific death was not examined in these studies.^{12–14} The primary aim of the current study was to prospectively examine

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whether men with RLS have an increased risk of mortality, with and without adjustment for known risk factors for mortality, in 18,425 men participating in an ongoing US prospective cohort, the Health Professionals Follow-up Study (HPFS). In a secondary analysis, we also explored the association between RLS and mortality among an apparently healthy population, who were free of common chronic conditions.

METHODS Study population. 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 were mailed to participants every 2 years to update information on potential risk factors and to ascertain newly diagnosed diseases.

In 2002, 31,722 men who were still alive and actively participating in the study completed RLS questions,⁵ which were developed based on the International RLS Study Group (IRLSSG) criteria (appendix e-1 on the *Neurology*[®] Web site at www.neurology.org).¹⁵ A participant who had symptoms ≥ 5 times per month and answered yes to the subsequent questions was considered to have RLS; others (including men with symptoms 1–4 times per month) were classified as no RLS. To reduce possible misclassification of RLS, we excluded participants with diabetes, arthritis, and renal failure through the follow-up period, leaving 18,423 men in our primary analyses. In a sensitivity analysis, we further examined the association between RLS and mortality including all participants with RLS information.

Standard protocol approvals, registrations, and patient consents. The institutional review board at Brigham and Women's Hospital and Harvard School of Public Health reviewed and approved this study, and receipt of each questionnaire implied participant's consent.

Ascertainment of deaths. Deaths were identified from state vital statistics records, the National Death Index, family reports, and the postal system.¹⁶ The follow-up for death in the HPFS is at least 98% complete. Cause of death was identified from death certificates or review of medical records. For this analysis, we separately evaluated all-cause mortality, death from cardiovascular disease (CVD) (*ICD-8* codes 390 through 458), cancer (*ICD-8* codes 140 through 207), and other conditions.

Assessment of other covariates. Information on potential confounders, such as age, ethnicity, smoking status, weight, height, physical activity, multiple vitamin supplement, iron-specific supplement, medication use (e.g., aspirin, antidepressants, and antihypertensive drugs), and history of major chronic diseases (e.g., cancer, elevated total cholesterol, hypertension, Parkinson disease [PD], emphysema or chronic bronchitis, chronic obstructive pulmonary disease, pneumonia, asthma, pernicious anemia, ulcerative colitis or Crohn disease, and renal failure) was collected via biennial questionnaires throughout the follow-up period. Body mass index (BMI) was calculated as weight (kg)/height (m)². High blood pressure was recorded as either hypertension or use of antihypertensive medications. The CVD events included myocardial infarction, stroke, coronary bypass, coronary angioplasty, and angina pectoris.¹⁷ Information on sleep duration and snoring frequency was also collected in the 2000 questionnaire. In 2004, we asked questions regarding insomnia symptoms and excessive daytime sleepiness¹⁸ (appendix e-1).

Information on food and alcohol consumption was collected every 4 years via a validated, semiquantitative food frequency questionnaire.¹⁹ Diet quality was assessed by the Alternate Healthy Eating Index (AHEI), which has been shown to be associated with a lower risk of major chronic diseases, including death, in our cohort.²⁰

Statistical analyses. Person-years for each participant were calculated from the date the 2002 questionnaire was returned to the date of death; January 30, 2010; or the date of return of their last questionnaire, whichever came first.

We categorized participants into 3 groups: no RLS, RLS with symptoms 5–14 times/month, and RLS with symptoms 15+ times/month. We used time-dependent Cox proportional hazard models to assess the hazard ratio (HR) of all-cause mortality and RLS status during follow-up. In addition, we analyzed CVD mortality and cancer mortality separately.

We adjusted for the potential risk factors of mortality, including age, BMI, physical activity, AHEI, ethnicity, smoking, alcohol consumption, multiple vitamin supplement, dietary iron intake and iron-specific supplement, use of medications and history of major chronic diseases, snoring, sleep duration, and presence of insomnia with daytime sleepiness. All covariables were updated time-dependent except ethnicity, sleep duration, and frequent snoring. We examined potential factors (appendix e-1) that may modify the association between RLS and all-cause mortality.

We examined the joint associations of RLS and the potential biologic intermediates (CVD, high blood pressure, and insomnia with daytime sleepiness) with risk of total mortality. We also examined the joint association of RLS and cancer because we found some suggestive evidence that RLS tended to be associated with a higher cancer mortality (see Results for details). As the insomnia and daytime sleepiness information was collected in 2004, we analyzed the joint effect between RLS and insomnia with daytime sleepiness based on 6 years of follow-up (2004–2010).

We did a secondary analysis among an apparently healthy population, who were free of cancer, high blood pressure, CVD, PD, diabetes, arthritis, obesity, snoring every night, cancer, emphysema or chronic bronchitis, chronic obstructive pulmonary disease, pneumonia, asthma, pernicious anemia, ulcerative colitis or Crohn disease, and renal failure. We also did several sensitivity analyses. First, we excluded men with PD, which can co-occur with RLS.²¹ Second, we excluded men using iron-specific supplement, having inadequate dietary intakes of iron, magnesium, folate, and vitamin B₁₂ (i.e., less than the estimated average requirement for each nutrient²²), regularly using benzodiazepines, and reporting physician-diagnosed multiple sclerosis (MS). Third, we examined the relationship between RLS and mortality based on the whole cohort adding back all excluded samples (i.e., individuals with diabetes, arthritis, and renal failure). Finally, we did the lag analysis by excluding deaths during the first 4 years of follow-up (i.e., 2002–2006).

RESULTS Among the 18,425 participants, 690 (3.7%) men met the criteria of RLS at baseline. Compared to men without RLS, those with RLS were more likely to use antidepressant drugs, had more frequent insomnia complaints, and had a higher prevalence of high blood pressure, CVD, and PD (table 1).

With up to 8 years of follow-up, we documented 2,765 deaths. In an age-adjusted analysis, men with RLS had an increased risk of total mortality compared to men without RLS, with a positive linear trend between frequent RLS symptoms and total mortality (table 2). These associations were slightly attenuated in the multivariable analyses controlling for age, BMI, lifestyle risk

Table 1 Baseline characteristics according to restless legs syndrome status in 2002 in the Health Professionals Follow-Up Study^a

	HPFS (n = 18,425)	
	No RLS	RLS
No.	17,735	690
Age, ^b y	67.1	67.1
Current smokers, %	4.1	5.5
Past smokers, %	51.6	55.9
Caucasian, %	96.0	98.2
Body mass index, kg/m ²	25.7	26.0
Physical activity, ^c METs/week	36.6	35.3
Alternate Healthy Eating Index score	48.1	46.9
Alcohol, g/day	12.6	12.8
Use of aspirin, %	54.5	55.4
Multiple vitamin supplement, %	32.5	33.7
Sleep duration, hours per 24 hours	7.1	7.0
Insomnia with daytime sleepiness, %	41.3	51.3
Frequent snoring, %	31.5	32.3
Use of iron-specific supplement, %	1.4	1.4
Use of antidepressant, %	4.4	9.1
Presence of (in or prior to 2002, %)		
High blood pressure	45.8	49.7
Elevated total cholesterol	52.6	56.6
Cardiovascular diseases ^d	13.4	16.2
Cancer	17.7	19.3
Parkinson disease	0.7	1.4

Abbreviations: HPFS = Health Professionals Follow-Up Study; RLS = restless legs syndrome.

^a Values were standardized to the age distribution of the overall cohort.

^b Value is not age-adjusted.

^c Metabolic equivalents from recreational and leisure-time activities.

^d Cardiovascular diseases: myocardial infarction, stroke, angina, and coronary revascularization in current study.

factors, presence of common chronic conditions, and sleep performance. The multivariable adjusted mortality hazard was 1.30 (95% confidence interval [CI] 1.11–1.52) comparing men with RLS and men without RLS. Further adjusting for the dietary intakes of iron, magnesium, folate, and vitamin B₁₂, regular use of benzodiazepine, and having MS attenuated the association slightly (adjusted HR 1.25; 95% CI 1.07–1.47).

We observed no significant interactions between RLS and known risk factors for mortality (older age, overweight, short sleep duration, smoking, low physical activity, and low dietary quality; *p* for interaction >0.2 for all). The association between RLS and total mortality also persisted in subgroup analyses stratified by these variables (table 3). Although men with hypertension, CVD, cancer, or insomnia with daytime sleepiness had statistically significant high risk of all-cause mortality,

having any of these 4 conditions/diseases plus RLS pre-disposed men to a higher risk (figure 1).

When evaluating the cause-specific mortality, we found a significant association between RLS and other cause mortality (table e-1), which was mainly derived by death due to respiratory disease (HR 1.73; 95% CI 1.03–2.89, *p* = 0.04), endocrine, nutrition/metabolic diseases, and immunity disorders (HR 4.97; 95% CI 1.26–19.5, *p* = 0.02), and diseases of the blood and blood-forming organs (HR 5.85; 95% CI 1.34–25.5, *p* = 0.02). We also observed a positive trend between RLS and increased risk of CVD mortality or cancer mortality, though the associations were not statistically significant (table e-2).

The multivariable adjusted HR of total mortality was 1.92 (95% CI 1.03–3.56) among a relatively healthy group, after we excluded men with cancer, PD, high blood pressure, CVD, diabetes, arthritis, obesity, snoring every night, cancer, emphysema or chronic bronchitis, chronic obstructive pulmonary disease, pneumonia, asthma, pernicious anemia, ulcerative colitis or Crohn disease, and renal failure. Among this chronic disease-free population, we also observed a dose-response relationship between RLS severity, as assessed by the symptom frequency, and increased risk of total mortality (*p* trend = 0.03; figure 2).

We conducted several sensitivity analyses to test the robustness of our observations. We first excluded individuals with PD, a condition that is associated with RLS¹⁹; the multivariable adjusted HR of total mortality comparing men with and without RLS was 1.31 (95% CI 1.12–1.54). Excluding the individuals with inadequate dietary intakes of iron, magnesium, folate, or vitamin B₁₂ (i.e., less than the estimated average requirement for each nutrient²²), regular use of benzodiazepine, or physician-diagnosed MS did not materially change our results (HR 1.31; 95% CI 1.09–1.58). We then excluded fatal cases occurring during the first 4 years of follow-up; the multivariable adjusted HR of total mortality was 1.29 (95% CI 1.04–1.61). Finally, we conducted analysis based on the whole cohort by taking back all excluded samples and observed a multivariable adjusted HR of 1.16 (95% CI 1.04–1.29).

DISCUSSION In this large prospective cohort, we observed that men with RLS had a higher risk of total mortality, which was independent of age, BMI, smoking status, physical activity, diet quality, antidepressant use, and sleep duration. The combination of RLS further increases the risk of total mortality in individuals with high blood pressure, CVD, cancer, or insomnia.

The mechanisms that underlie the association between RLS and mortality are not understood. RLS may increase risk of mortality through insufficient and disturbed sleep, which has been noted among most RLS sufferers, even in nonclinical populations. Short

Table 2 Risk of total mortality according to baseline restless legs syndrome status

	Restless legs syndrome status in 2002			p Trends	RLS vs no RLS, HR (95% CI), p value
	No RLS	RLS 5-14 times/mo	RLS 15+ times/mo		
Person-years	128,914	2,764	1,939		4,703/128,914
No. of cases	2,594	91	80		171/2,594
Incident rate (per 10 ⁵ person-years)	2,012	3,293	4,126		2,012/3,636
Age-adjusted HR	1 (reference)	1.33 (1.08, 1.64)	1.46 (1.17, 1.83)	<0.0001	1.39 (1.19, 1.62), <0.0001
Multivariable adjusted model 1 ^a	1 (reference)	1.38 (1.12, 1.71)	1.36 (1.09, 1.71)	0.0002	1.37 (1.17, 1.61), <0.0001
Multivariable adjusted model 2 ^b	1 (reference)	1.34 (1.09, 1.66)	1.35 (1.07, 1.69)	0.0005	1.34 (1.15, 1.57), 0.0002
Multivariable adjusted model 3 ^c	1 (reference)	1.32 (1.07, 1.63)	1.28 (1.02, 1.60)	0.003	1.30 (1.11, 1.52), 0.001

Abbreviations: CI = confidence interval; HR = hazard ratio; RLS = restless legs syndrome.

^aEstimated from Cox proportional hazards models and adjusted for age (months), ethnicity (Caucasian, yes/no), smoking status (never smoker, former smoker, or current smoker: 1-14 or ≥ 15 cigarettes/day), alcohol drinking (g/day: 0, 0.1-9.9, 10.0-19.9, 20.0-29.9, and ≥ 30), body mass index (continuous), physical activity (quintiles), multiple vitamin supplement (yes/no), regular use of aspirin (yes/no), iron-specific supplement (yes/no), Alternate Healthy Eating Index (quintile), use of antidepressant drugs (yes/no), presence of cancer, elevated total cholesterol, and Parkinson disease. All were treated as time-varying covariates except ethnicity.

^bFurther adjusted for presence of high blood pressure and cardiovascular disease (yes/no), treated as time-varying covariates.

^cFurther adjusted for sleep duration (hours: ≤ 5 , 6, 7, 8, ≥ 9), frequent snoring (yes/no), and presence of insomnia with daytime sleepiness (yes/no or missing).

sleep duration has been consistently associated with total mortality, with a pooled HR of 1.12 (95% CI 1.06–1.18) compared to the reference groups in a recently published meta-analysis.²³ Increased risk of total mortality¹² and coronary artery disease mortality²⁴ had also been found in men with insomnia complaints. Causative mechanisms relating short sleep duration and sleep disturbance to adverse health include reciprocal changes of circulating levels of leptin and ghrelin,^{25,26} which facilitate the development of obesity, diabetes, and CVD by positive energy balance. However, in the present study, the association between RLS and mortality was independent of sleep duration, frequent snoring, and insomnia complaints, which implies that the association could not be completely explained by these sleep factors.

Another potential pathway between RLS and mortality is through the unfavorable effect of RLS on blood pressure and cardiovascular risk. RLS may lead to nocturnal hypertension through the influence of periodic limb movements of sleep (PLMS).²⁷ One recent study showed that the nondipping pattern of nocturnal blood pressure is more common in patients with RLS compared to controls,²⁸ which has been suggested to be an independent risk factor for cardiovascular events.²⁹ Positive associations between RLS and CVD had also been consistently observed in cross-sectional studies with ORs ranging from 1.4 to 2.9.⁹ In one prospective study, a significantly higher risk of coronary heart diseases (HR 1.7; 95% CI 1.1–2.6) was found among people with RLS for >3 years relative to those without RLS.³⁰ In the present study, we observed that the combination of RLS with hypertension or CVD is associated with increased mortality. Although there was no meaningful attenuation of the RLS–mortality association with further adjustment for high blood pressure and CVD, it

remains possible that the nocturnal blood pressure variations associated with RLS could be among potential underlying mechanisms for the observed association between RLS and mortality. RLS may also reflect an underlying neurodegenerative disorder. Though excluding individuals with PD did not materially change the results, we still could not rule out the possibility that RLS could be a preclinical symptom of PD or other neurodegenerative disorders. A previous study suggested that physician occupation was associated with a higher risk of PD and incidental Lewy body disease.³¹ However, as a large proportion of patients with PD (~60%–90%) do not have RLS symptoms,^{21,32} this could only explain a part of the observed RLS–mortality association.

Presence of other common risk factors for mortality in patients with RLS may also increase the risk of mortality.^{5,10,33} However, controlling for those variables in the main analyses or subgroup analysis based on status of those factors did not materially change the association between RLS and mortality. Further, we found that RLS was significantly associated with a higher risk of death primarily caused by respiratory disorders, diseases of blood and blood-forming organs, and endocrine, nutritional, or immunity disorders. This is consistent with previous observations that RLS may co-occur with chronic obstructive pulmonary disease³⁴ and iron-deficiency anemia.³⁵ Further, previous studies have also reported a relationship between RLS and several autoimmune diseases (e.g., MS, Crohn disease, and celiac disease).^{36,37} However, we are unable to examine the association between RLS and death due to each of these disorders individually because of small numbers. When we excluded men ever reported as having major chronic conditions, such as CVD, obesity, obstructive pulmonary disease, pernicious anemia, ulcerative colitis

Table 3 Stratified analysis of the association between RLS and total mortality

	No. of cases (incident rate, per 10 ⁵ person-years)		Multivariable adjusted HR (95% CI), ^a <i>p</i>		
Stratification factors	No RLS	RLS	No RLS	RLS	<i>p</i> for interaction ^a
Age, y					
<80	1,570 (1,339)	88 (2,227)	1 (reference)	1.50 (1.21-1.86), <i>p</i> = 0.0002	0.26
≥80	1,024 (8,800)	83 (11,035)	1 (reference)	1.20 (0.95-1.51), <i>p</i> = 0.12	
Body mass index, kg/m ²					
<25	1,411 (2,518)	91 (4,496)	1 (reference)	1.29 (1.04-1.61), <i>p</i> = 0.02	0.41
≥25	1,183 (1,623)	80 (2,987)	1 (reference)	1.31 (1.03-1.65), <i>p</i> = 0.03	
Sleep duration (per 24 hours)					
<7	603 (1,790)	43 (3,394)	1 (reference)	1.23 (0.88-1.71), <i>p</i> = 0.22	0.94
≥7	1,964 (2,090)	128 (3,782)	1 (reference)	1.27 (1.06-1.52), <i>p</i> = 0.01	
Current smoking					
No	2,421 (1,954)	161 (3,611)	1 (reference)	1.29 (1.10-1.52), <i>p</i> = 0.002	0.87
Yes	173 (3,442)	10 (4,103)	1 (reference)	1.53 (0.70-3.33), <i>p</i> = 0.29	
Alternate Healthy Eating Index score ^b					
High	1,081 (1,711)	62 (2,946)	1 (reference)	1.30 (1.00-1.70) <i>p</i> = 0.05	0.99
Low	1,326 (2,157)	94 (3,847)	1 (reference)	1.26 (1.02-1.56), <i>p</i> = 0.03	
Physical activity level ^b					
High	911 (1,382)	53 (2,331)	1 (reference)	1.20 (0.89-1.61) <i>p</i> = 0.22	0.54
Low	1,651 (2,645)	112 (4,692)	1 (reference)	1.29 (1.06-1.57), <i>p</i> = 0.01	

Abbreviations: CI = confidence interval; HR = hazard ratio; RLS = restless legs syndrome.

^a Estimated from Cox proportional hazards models and adjusted for age (months), ethnicity (Caucasian, yes/no), smoking status (never smoker, former smoker, or current smoker: 1–14 or ≥15 cigarettes/day), alcohol drinking (g/day: 0, 0.1–9.9, 10.0–19.9, 20.0–29.9, and ≥30), body mass index (continuous), physical activity (quintiles), multiple vitamin supplement (yes/no), regular use of aspirin (yes/no), iron-specific supplement (yes/no), Alternate Healthy Eating Index (quintile), sleep duration (hours: ≤5, 6, 7, 8, ≥9), frequent snoring (yes/no), presence of insomnia with daytime sleepiness (yes/no or missing), use of antidepressant drugs (yes/no), presence of cancer, elevated total cholesterol, Parkinson disease, high blood pressure, and cardiovascular disease (all yes/no), except the stratified variable. All were treated as time-varying covariates except ethnicity, sleep duration, snoring, and insomnia with daytime sleepiness.

^b Cutoff points are the median value of the sample.

or Crohn disease, MS, and snoring every night, the association between RLS and total mortality remained significant, suggesting RLS could be a novel risk factor for total mortality, independent of these morbidities.

Strengths of the present study include a large sample size and use of the standard IRLSSG diagnostic criteria, which has shown a relatively good sensitivity and specificity of RLS diagnosis.¹⁵ In 2 previous studies of RLS and mortality in general populations, the total sample sizes were rather small (<6,000 for both) and the RLS was assessed using a single question.^{12,13} We also excluded 2 common mimics of RLS, diabetes and arthritis, in our primary analysis. In a recent study based on 4 cohorts from the United States and Germany,¹⁴ RLS was not significantly associated with increased risks of all-cause mortality. However, the authors did not exclude individuals with diabetes and arthritis from their analysis and failed to consider the frequency of RLS symptoms in their main analysis. The discrepancy between our study and this published study¹⁴ implies that adjustment for the diabetes

and arthritis in the analysis as covariate may not be the best way to rule out the relevant misclassification. It would be of importance to consider frequency of RLS symptoms (i.e., severity) when we attempt to understand potential clinical implications of presence of RLS. Although we are not able to exclude 2 other common RLS mimics,³⁸ positional discomfort and leg cramps, there has been no reported evidence that these 2 conditions are associated with a higher total mortality. Other strengths of our study include detailed and repeated assessments of lifestyle risk factors and common chronic diseases over the course of follow-up. Another important strength is the high follow-up rate. In each 2- or 4-year cycle of the HPFS survey, follow-up rates have averaged 94%.³⁹ The follow-up for death in the HPFS is at least 98% complete.

Several limitations of the present study warrant consideration. Although the significant association between RLS and total mortality is consistently observed in the primary analysis and several sensitivity analyses, it must be emphasized that observational studies cannot prove

Figure 1 Joint effect of restless legs syndrome with high blood pressure, cardiovascular disease, cancer, and insomnia with daytime sleepiness on risk of mortality

Up to 8 years of follow-up (2002–2010) for joint effect on mortality between restless legs syndrome (RLS) and high blood pressure (A), cardiovascular disease (B), and cancer (C), and up to 6 years of follow-up of mortality (2004–2010) for joint effect between RLS and insomnia with daytime sleepiness (D). Multivariable adjusted hazard ratio estimated from Cox proportional hazards models and adjusted for age (months), ethnicity (Caucasian, yes/no), smoking status (never smoker, former smoker, or current smoker), alcohol drinking (g/day: 0, 0.1–9.9, 10.0–19.9, 20.0–29.9, and ≥ 30), body mass index (continuous), physical activity (quintiles), multiple vitamin supplement (yes/no), regular use of aspirin (yes/no), iron-specific supplement (yes/no), Alternate Healthy Eating Index (quintile), sleep duration (hours: ≤ 5 , 6, 7, 8, ≥ 9), frequent snoring (yes/no), presence of insomnia with daytime sleepiness (yes/no or missing), use of antidepressant drugs (yes/no), presence of cancer, elevated total cholesterol, Parkinson disease, high blood pressure, and cardiovascular disease (all yes/no), except the joint variable. All were treated as time-varying covariates except ethnicity, sleep duration, snoring, and presence of insomnia with daytime sleepiness; p for interaction >0.2 for all. CI = confidence interval.

causality, and residual confounding cannot be ruled out, although we controlled known risk factors in the analyses. To minimize potential residual confounding due to comorbidities of RLS, we conducted a secondary analysis by excluding participants with major chronic conditions and found that the RLS–mortality association was even stronger in this apparently health population.

Secondly, we did not collect information on RLS medications except for benzodiazepines. However, because RLS is a highly underdiagnosed disease, with only 6%–10% of RLS cases having been diagnosed in

Western counties,⁴⁰ we infer that few individuals in this sample were treated. The observed association between RLS and mortality did not materially change after excluding men using benzodiazepines. In this context, although we cannot rule out the possibility of residual confounding due to medications, it is unlikely to be a major source of bias.

Another limitation is that our cohort represents a relatively healthy group of mostly Caucasian men, and findings from this analysis might not be generalizable to other populations. However, the estimated 3.7% prevalence of

Figure 2 Association between restless legs syndrome severity and mortality among relatively healthy men

Relatively healthy men in the present study means men who were free of cancer, Parkinson disease, high blood pressure, cardiovascular disease, diabetes, arthritis, obesity, snoring every night, cancer, emphysema or chronic bronchitis, chronic obstructive pulmonary disease, pernicious anemia, ulcerative colitis or Crohn disease, pneumonia, asthma, and renal failure. Estimated from Cox proportional hazards models and adjusted for age (months), ethnicity (Caucasian, yes/no), smoking status (never smoker, former smoker, or current smoker), alcohol drinking (g/day: women 0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥ 15 ; men 0, 0.1–9.9, 10.0–19.9, 20.0–29.9, and ≥ 30), body mass index (continuous), physical activity (quintiles), multiple vitamin supplement (yes/no), regular use of aspirin (yes/no), iron-specific supplement (yes/no), Alternate Healthy Eating Index, sleep duration (hours: <7, 7, >7), frequent snoring (yes/no), presence of insomnia with daytime sleepiness (yes/no or missing), use of antidepressant drugs (yes/no), and presence of elevated total cholesterol (yes/no). CI = confidence interval; RLS = restless legs syndrome.

RLS in the present sample is comparable to the general population (around 3% to 8% in men).^{4,6–8} The homogeneous socioeconomic background in our cohort may minimize potential confounding due to educational attainment or differential access to health care. Our study is also limited by lack of objective measurements of iron deficiency, which has been shown to be associated with RLS.³⁵ In the current analyses, we thus employed use of iron-specific supplement and inadequate iron intake as surrogates of iron deficiency. Adjustment for these variables did not materially change the observed significant association between RLS and mortality.

The results of this study indicate that men with RLS had a higher overall mortality, which highlights the clinical importance of RLS, a common but underrecognized disorder. Increasing awareness of RLS, especially training for health professions, should be encouraged if our findings are confirmed by future studies.

AUTHOR CONTRIBUTIONS

Conception and design: Y. Li, X. Gao; analysis and interpretation of the data: Y. Li, W. Wang, X. Gao; drafting of the article: Y. Li; critical revision of the article for important intellectual content: Y. Li, W. Wang, J.W. Winkelman, A. Malhotra, J. Ma, X. Gao; final approval of the article: Y. Li, W. Wang, J.

W. Winkelman, A. Malhotra, J. Ma, X. Gao; provision of study materials or patients: J. Ma, X. Gao; statistical expertise: Y. Li, X. Gao; collection and assembly of data: J. Ma, X. Gao; obtaining of funding: X. Gao.

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