



## Original Contribution

# Prospective Study of Restless Legs Syndrome and Risk of Depression in Women

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Most research on the association between restless legs syndrome (RLS) and depression has involved cross-sectional data. The objective of the present study was to evaluate this issue prospectively among Nurses' Health Study participants. A total of 56,399 women (mean age = 68 years) who were free of depression symptoms at baseline (2002) were followed until 2008. Physician-diagnosed RLS was self-reported. During 300,155 person-years of follow-up, the authors identified 1,268 incident cases of clinical depression (regular use of antidepressant medication and physician-diagnosed depression). Women with RLS at baseline were more likely to develop clinical depression (multivariate-adjusted relative risk (RR) = 1.5, 95% confidence interval (CI): 1.1, 2.1;  $P = 0.02$ ) than those without RLS. The presence of RLS at baseline was also associated with higher scores on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10) and the 15-item Geriatric Depression Scale (GDS-15) thereafter. Multivariable-adjusted mean differences were 1.00 (standard error, 0.12) for CESD-10 score and 0.47 (standard error, 0.07) for GDS-15 score between women with RLS and those without RLS ( $P < 0.0001$ ). In conclusion, women with physician-diagnosed RLS had an increased risk of developing clinical depression and clinically relevant depression symptoms. Further prospective studies using refined approaches to ascertainment of RLS and depression are warranted.

depression; meta-analysis; prospective studies; restless legs syndrome

Abbreviations: CESD-10, 10-item version of the Center for Epidemiologic Studies Depression Scale; CI, confidence interval; GDS-15, 15-item version of the Geriatric Depression Scale; RLS, restless legs syndrome; SE, standard error.

Restless legs syndrome (RLS), also known as Ekbom syndrome, is a common, bothersome sensorimotor disorder that is characterized by an almost irresistible urge to move the legs, accompanied by an unpleasant sensation in the legs and a worsening of the symptoms in the evening or during the night (1). These symptoms can result in severe sleep disturbance and may be associated with the emergence of depression symptoms (2–4). To date, 17 population-based cross-sectional studies (5–21) and 5 clinic-based case-control studies (22–26) of RLS and depression have been conducted, and most of them have found a high co-occurrence of RLS and depression. However, to our knowledge, the association between RLS and depression has not been examined in a prospective study to date.

Interestingly, the association between RLS and depression appears to be inconsistent among women in these published studies. In 2000, Rothdach et al. (5) reported that men, but not women, with RLS had a higher likelihood of having depression, as compared with controls. This similar difference between men and women was observed in a subsequent Japanese study based on 1,008 men and 1,015 women (8). However, in a women-only Swedish study (15), women with RLS had approximately double the likelihood of self-reported depressed mood. Further, in a clinic-based German study including 519 women with RLS (27), 52.7% of them had abnormal anxiety/depression scores as evaluated by means of a 5-item quality-of-life scale called the EQ-5D (EuroQol Group, Rotterdam, the Netherlands),

relative to approximately 4.9% in the general population (28). Given the inconsistent results on the association between RLS and depression in women, larger, better-controlled studies among women are needed.

Our purpose in the present study was to examine prospectively whether women with RLS had an elevated risk of developing depression during 6 years of follow-up, using data from the Nurses' Health Study. In a secondary analysis, we also examined the association between RLS and risk of clinically relevant depression symptoms.

## MATERIALS AND METHODS

The Nurses' Health Study cohort was established in 1976, when 121,700 female registered nurses aged 30–55 years residing in 11 US states responded to a mailed questionnaire regarding their medical history and health practices. The cohort has been followed every 2 years with mailed questionnaires that update exposure information and inquire about newly diagnosed medical illnesses (29).

On the 2002 questionnaire, we asked 82,160 participants who were still alive and actively participating in the Nurses' Health Study whether they had ever been diagnosed with RLS by a physician. We therefore used 2002 as the baseline date in the present analysis and excluded women who reported having physician-diagnosed depression during or prior to 2002 ( $n = 9,054$ ) or reported it after 2002 with an unknown start date ( $n = 89$ ), those who reported regular use of antidepressant medication during or prior to 2002 ( $n = 6,059$ ), and those who had a Mental Health Inventory score of 52 or less (i.e., depressive symptoms) at any of the study contacts made in 1992, 1996, and 2000 ( $n = 3,405$ ) (see Web Figure 1, which appears on the *Journal's* website (<http://aje.oxfordjournals.org/>)). The Mental Health Inventory is a 5-item subscale of the Short Form 36 health status survey (30, 31), and a lower score ( $\leq 52$ ) has been found to have high sensitivity and specificity for major depressive disorder (32). After further excluding women who did not have complete information on physician-diagnosed depression or regular use of antidepressant medication ( $n = 7,154$ ), 56,399 women were included in the present analysis. Participants who were included had a similar age (mean age = 68.1 years vs. 67.7 years) and body mass index (26.5 vs. 27.3) as those who were excluded from the present analysis. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard School of Public Health.

Information on potential confounders, including age, body weight, menopausal status and estrogen hormone therapy, smoking status, physical activity, use of aspirin and multiple vitamin supplements, and history of major chronic conditions, including hypertension, elevated cholesterol concentration, diabetes, arthritis, heart diseases (myocardial infarction and/or angina), stroke, and cancer, was collected via biennial questionnaires throughout the follow-up period. Body mass index was calculated from self-reported weight and height as weight in kilograms divided by height in meters squared. Information on alcohol consumption was collected using validated food frequency questionnaires every 4 years. In 2002,

we also collected information on sleep duration and snoring frequency.

## Case ascertainment

A participant was considered clinically depressed if she reported both physician-diagnosed depression and regular use of antidepressant medication. The questions on regular antidepressant medication use and physician-diagnosed depression were asked in 2002, and data were updated biennially through 2008.

Depression symptoms were evaluated by means of 2 commonly used self-report measures: the 10-item version of the Center for Epidemiologic Studies Depression Scale (CESD-10) in 2004 and the 15-item version of the Geriatric Depression Scale (GDS-15) in 2008. The CESD-10 is a short-form scale with 10 items that is designed to identify depressive symptoms in the general population (33). The CESD-10 has shown good predictive accuracy when compared with the full-length 20-item version of the Center for Epidemiologic Studies Depression Scale, with a kappa index of 0.97 (33). Responses are recorded using a 4-point Likert scale ranging from rarely (scored 0) to all of the time (scored 3), and points are summed across the 10 items to provide a total CESD-10 score ranging from 0 to 30. Respondents who provided data on at least 9 of the CESD-10 items were included in the analyses, with mean imputation used to replace the missing items. The optimum cutoff point for the CESD-10 scores was 10 (33). The GDS-15 is a 15-item short version of the Geriatric Depression Scale. Giving 1 point for each matching answer and summing the points results in the GDS-15 score (34). Respondents who provided data on all 15 items of the GDS-15 were included in the analyses. The GDS-15 has excellent properties in screening for major depression (35) as assessed by the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (36). The optimum cutoff point for the GDS-15 is 5, yielding a sensitivity of 92% and a specificity of 85% in predicting major depression (35).

Clinically relevant depressive symptoms were defined as either CESD-10 score  $\geq 10$  or GDS-15 score  $\geq 5$ .

## Statistical methods

Person-years for each participant were calculated from the date on which the 2002 questionnaire was returned to the diagnosed date of depression or death; June 1, 2008; or the date of return of the last questionnaire, whichever came first. Time-dependent Cox proportional hazards models were used to estimate age- and multivariate-adjusted relative risks (and 95% confidence intervals) of clinical depression and clinically relevant depression symptoms for women with RLS compared with women without RLS. The age-adjusted mean values for the CESD-10 score and GDS-15 score and multivariate-adjusted mean differences in scores between women with RLS and women without RLS were compared using a generalized linear model.

The basic Cox model adjusted for age (continuous, in years), ethnicity (Caucasian, African-American, or Asian/

other), smoking status (never smoker, former smoker, or current smoker), alcohol drinking (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or  $\geq 15$  g/day of alcohol), body mass index ( $< 23$ , 23–24.9, 25–29.9, 30–34.9, or  $\geq 35$ ), physical activity (quintiles), marital status (married/in a partnership, widowed, or separated/divorced/single), living status (alone or with others; binary), regular involvement in a social or community group (yes or no; binary), menopausal status, use of estrogen hormone therapy (no use, past use, or current use), and the presence of hypertension, elevated cholesterol level, diabetes, arthritis, myocardial infarction/angina, stroke, Parkinson's disease, and cancer (yes/no). In the final Cox and generalized linear models, we also adjusted for use of iron-specific supplements (yes/no), sleep duration ( $\leq 5$ , 6, 7, 8, or  $\geq 9$  hours per 24-hour period), and snoring frequency (every night, most nights, a few nights per week, occasionally, or almost never), because iron deficiency has been shown to be associated with both RLS and neurocognitive function (1). Because we did not collect information on iron deficiency, we employed use of iron-specific supplements as a surrogate measure for iron deficiency in the current analysis.

In a secondary analysis, we also examined the association between RLS and depression based on different definitions: 1) physician-diagnosed depression; 2) either physician-diagnosed depression or regular use of antidepressant medication; 3) physician-diagnosed depression, CESD-10 score  $\geq 10$ , or GDS-15 score  $\geq 5$ ; and 4) physician-diagnosed depression, regular antidepressant medication use, CESD-10 score  $\geq 10$ , or GDS-15 score  $\geq 5$ .

In order to test the robustness of our observations, we conducted several sensitivity analyses by 1) excluding the women who had ever been diagnosed with diabetes or arthritis; 2) excluding women who had ever had confirmed Parkinson's disease; 3) excluding women who had ever been diagnosed with myocardial infarction/angina or stroke by the end of follow-up; and 4) excluding the incident depression cases diagnosed during the period 2002–2004 in case these were subclinical cases preceding the diagnosis of RLS.

Finally, we conducted a meta-analysis of the published data on RLS and depression. We identified relevant studies by searching the MEDLINE, PubMed, Embase (Excerpta Medica Database), and OMIM (Online Medelian Inheritance in Man) databases using the keyword combination "restless legs syndrome or RLS or Ekbom syndrome and depression" for all studies published in English from 1966 through August 2011. Studies without control participants were not considered in the analysis. In addition, the reference lists from the relevant publications were used to identify additional studies. Four clinic-based studies and 14 community-based studies met the inclusion criteria and were included in the meta-analysis (5–8, 11–19, 21, 22, 24–26) (Web Table 1). We used the  $Q$  statistic to examine heterogeneity among the studies, and the significance level was set at 0.1. We used random-effects models to calculate the pooled odds ratio because significant heterogeneity was observed. Publication bias was assessed using Begg's test.

We used the SAS statistical package (version 9; SAS Institute Inc., Cary, North Carolina) for the cohort analyses and

STATA (version 9.0; StataCorp LP, College Station, Texas) for the meta-analysis. All  $P$  values were 2-tailed ( $P < 0.05$ ).

## RESULTS

At baseline, 928 out of 56,399 women reported having ever been diagnosed with RLS. Compared with women without RLS, those with RLS were more likely to be older, to frequently snore, and to have a higher prevalence of major chronic conditions, such as hypertension, elevated cholesterol concentration, stroke, heart diseases, Parkinson's disease, arthritis, and diabetes (Table 1).

During the 300,155 person-years of follow-up, we identified 1,268 incident cases of clinical depression. The age-adjusted relative risk of clinical depression was 1.66 (95% confidence interval (CI): 1.18, 2.35) for women with RLS versus those without RLS (Table 2). Adjustment for lifestyle factors, the presence of chronic conditions, sleep duration, and frequent snoring attenuated the association (adjusted relative risk = 1.5, 95% CI: 1.1, 2.1). The interactions between RLS and the covariates (age, obesity, sleep duration, and frequent snoring) were not significant ( $P$ -interaction  $> 0.3$  for all), and the association between RLS and clinical depression persisted in subgroup analyses stratified according to these variables (data not shown).

Women with physician-diagnosed RLS also had a significantly higher CESD-10 score in 2004 and a significantly higher GDS-15 score in 2008 (Table 3). The multivariable-adjusted mean differences were 1.00 (standard error (SE), 0.12) for CESD-10 score and 0.47 (SE, 0.07) for GDS-15 score among women with RLS versus those without RLS ( $P < 0.0001$ ). Women with RLS had a higher risk of developing clinically relevant depression symptoms (CESD-10  $\geq 10$  or GDS-15  $\geq 5$ )—the multivariate-adjusted relative risk of clinically relevant depression symptoms was 1.53 (95% CI: 1.33, 1.76). Considering that 1 item on the CESD-10 ("My sleep was restless") was sleep-related and may have confounded the association between RLS and CESD-10 score, we excluded this item and recalculated the score based on the other 9 items, yielding relatively lower mean scores (4.08 (SE, 0.01) among women with RLS and 4.73 (SE, 0.11) among women without RLS) and a significant multivariate-adjusted mean difference (0.64 (SE, 0.11);  $P < 0.0001$ ).

We conducted several sensitivity analyses and obtained similar results. The multivariable-adjusted relative risk was 1.48 (95% CI: 0.99, 2.23) for clinical depression and 1.52 (95% CI: 1.29, 1.79) for clinically relevant depression symptoms after excluding women with histories of diabetes and arthritis, two common conditions that mimic RLS. The multivariable-adjusted relative risk was 1.53 (95% CI: 1.08, 2.16) for clinical depression and 1.54 (95% CI: 1.34, 1.76) for clinically relevant depression symptoms after excluding women who had ever been diagnosed with Parkinson's disease, and relative risks were 1.51 (95% CI: 1.02, 2.23) and 1.53 (95% CI: 1.30, 1.80), respectively, after excluding women who had ever been diagnosed with cardiovascular diseases prior to the endpoint. When we excluded the incident depression cases diagnosed during the period 2002–2004, the multivariable-adjusted relative risk was 1.40

**Table 1.** Characteristics of Participants According to Restless Legs Syndrome Status at Baseline, Nurses' Health Study, 2002<sup>a</sup>

	Physician-diagnosed RLS Status in 2002			
	No RLS (n= 55,471)		RLS (n= 928)	
	%	Mean (SD)	%	Mean (SD)
Age, years		68.0 (6.9)		69.6 (6.9)
Smoking status				
Never smoker	46.4		45.8	
Current smoker	7.2		5.6	
Former smoker	46.4		48.6	
Caucasian race	97.5		98.5	
Premenopausal	0.4		0.2	
Current menopausal hormone use	34.4		36.9	
Body mass index <sup>b</sup>		26.5 (5.3)		26.9 (5.3)
Physical activity, METs/week		18.5 (22.8)		18.3 (22.7)
Alcohol intake, g/day		6.1 (10.7)		5.5 (10.8)
Sleep duration, hours/day		7.13 (0.98)		6.96 (0.99)
Frequent snoring	20.7		26.2	
Marital status				
Married/in a partnership	76.1		77.8	
Widowed	17.1		15.5	
Separated/divorced/single	6.8		6.7	
Living alone	18.2		17.0	
Not involved in any social or community groups	30.8		30.1	
Presence of chronic conditions during or prior to 2002				
Arthritis	10.2		15.5	
Diabetes	8.8		11.7	
Hypertension	52.7		59.7	
Hypercholesterolemia	63.4		71.9	
Stroke	2.0		3.9	
Cancer	16.9		18.6	
Parkinson's disease	0.3		0.7	
Myocardial infarction/angina	9.9		14.4	

Abbreviations: MET, metabolic equivalent task; RLS, restless legs syndrome; SD, standard deviation.

<sup>a</sup> All data were standardized to the age distribution of the overall cohort.

<sup>b</sup> Weight (kg)/height (m)<sup>2</sup>.

(95% CI: 0.83, 2.33) for clinical depression and 1.70 (95% CI: 1.34, 2.15) for GDS-15 score  $\geq 5$ .

When different definitions of depression were applied, the statistical significance of the association between RLS and depression was unchanged. The multivariable-adjusted relative risks ranged from 1.47 to 1.88 ( $P < 0.0001$  for all) (Table 4) after adjustment for age, lifestyle factors, chronic conditions, sleep duration, and other covariates.

Finally, we conducted a meta-analysis including all published case-control and cross-sectional studies of associations between RLS and clinical depression and/or depressive symptoms. Comparing women with RLS with those without RLS, the pooled odds ratio was 2.32 (95% CI: 2.01, 2.69;  $P$ -heterogeneity = 0.04) without inclusion of the present

study and 2.25 (95% CI: 1.94, 2.60;  $P$ -heterogeneity = 0.02) with the present study included (Figure 1). The pooled odds ratios were similar for community-based and clinical studies (data not shown). To the best of our knowledge, our study provides the first evidence that the presence of RLS is associated with the future risk of developing depression. The funnel plot (Web Figure 2) and results based on Begg's test did not support the existence of publication bias ( $P = 0.6$ ).

## DISCUSSION

In this prospective study, we observed that women with RLS had a higher risk of developing both clinical depression and clinically relevant depressive symptoms. This

**Table 2.** Adjusted Relative Risk of Clinical Depression<sup>a</sup> According to Baseline Restless Legs Syndrome Status, Nurses' Health Study, 2002–2008

	No RLS	RLS		P Value
		RR	95% CI	
No. of cases	1,235	33		
Person-years of follow-up	295,493	4,662		
Crude incidence (per 100,000 person-years)	418	708		
Age-adjusted RR	1	1.66	1.18, 2.35	0.004
Multivariate RR <sup>b</sup>	1	1.58	1.11, 2.23	0.01
Multivariate RR <sup>c</sup>	1	1.51	1.07, 2.14	0.02
Multivariate RR <sup>d</sup>	1	1.49	1.06, 2.10	0.02

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

<sup>a</sup> Clinical depression was defined as reported regular use of antidepressant medication *and* physician-diagnosed depression.

<sup>b</sup> Adjusted for age (years), body mass index (weight (kg)/height (m)<sup>2</sup>; continuous), ethnicity (Caucasian or other), smoking status (never, past, or current smoker), marital status (married/in a partnership, widowed, or separated/divorced/single), solitary living status (yes/no; binary), regular involvement in a social or community group (yes/no; binary), menopausal status (premenopausal or postmenopausal), menopausal hormone use (never, past, or current user), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15 g/day), and physical activity (quintiles).

<sup>c</sup> Further adjusted for the presence of diabetes, arthritis, stroke, myocardial infarction, angina, cancer, hypertension, high cholesterol level, or Parkinson's disease (yes/no).

<sup>d</sup> Further adjusted for use of iron-specific supplements, sleep duration (≤5, 6, 7, 8, or ≥9 hours per 24-hour period), and snoring frequency (every night, most nights, a few nights per week, occasionally, or almost never).

association appeared to be independent of age, smoking status, physical activity, body mass index, history of several chronic conditions, sleep duration, and snoring.

There are several potential mechanisms that may underlie the association between RLS and risk of depression. Firstly, dopaminergic hypofunction is a common pathophysiologic thread linking RLS and depression, as well as the more severe hypodopaminergic condition of Parkinson's disease. RLS may be related to postsynaptic desensitization that overcompensates during the circadian low point of dopaminergic activity in the evening and night (1). Dopaminergic mesolimbic and mesocortical systems are involved in anhedonia and lack of motivation, two core symptoms of depression (37). In addition, RLS may increase risk of Parkinson's disease (38), and depression is a common nonmotor Parkinson's disease symptom that can antedate the diagnosis of Parkinson's disease (39); thus, a subset of participants with RLS and incident depression may be on an ultimate path toward Parkinson's disease. However, the hypothesized role of the dopaminergic system in the observed RLS-depression relation is complex and remains to be elucidated. Secondly, a common genetic cause for both RLS and depression could be a potential reason. In one recent study, Puschmann et al. (40) observed a family of 5 generations; the 43 individuals displayed signs and symptoms of Parkinson's disease, RLS, essential tremor, or depression, and a considerable number of the affected persons had features of more than 1 of these disorders, implying a potential genetic cause within the family.

The third potential mechanistic link between RLS and depression may be the presence of clinical or subclinical

vascular disease: RLS has been related to increased cardiovascular disease risk (11, 41, 42), and vascular factors are associated with clinical presentations of depression in older persons (43). However, our results were unaffected by adjustment for these conditions, making this explanation unlikely. The fourth potential explanation is that because RLS is a bothersome chronic condition (44), persons with RLS may have a distinctly impaired quality of life (1, 2). For example, it is common for persons with RLS to complain of fatigue, disturbed sleep, diminished concentration, and psychomotor agitation (4). Thus, symptoms accompanying RLS may in turn lead to depressive symptoms and/or clinical depression in RLS sufferers. Furthermore, insomnia itself has been well established as a risk factor for incident depression (45), and the sleep disruption common in RLS may predispose RLS patients to depression. In our study, adjustment for sleep duration and frequent snoring did attenuate the association between RLS and depression, implying that the RLS-depression association could be partly explained by the sleep disturbance. We cannot exclude the possibility that women who have been diagnosed with RLS may visit physicians more frequently than others and thus are more likely to have their depression ascertained. Persons with RLS may also be more likely to be diagnosed with depression by physicians attentive to the mental health consequences of chronic illnesses. However, we observed a similar significant association between RLS and increased depression risk in secondary analyses in which different diagnostic criteria for depression were used. Further, when we used the self-reported CESD-10 or GDS-15 score as the outcome, a similar result was seen. The similar significant results obtained using different

**Table 3.** Adjusted Relative Risk of Clinically Relevant Depression Symptoms<sup>a</sup> According to Baseline Restless Legs Syndrome Status, Nurses' Health Study, 2002–2008

	No RLS				RLS			
	No.	Score	RR	95% CI	No.	Score	RR	95% CI
Clinically relevant depression symptoms (CESD-10 score $\geq 10$ or GDS-15 score $\geq 5$ )								
No. of cases	7,292				212			
Person-years of follow-up	299,386				4,791			
Crude incidence (per 100,000 person-years)	2,436				4,425			
Age-adjusted RR			1	Reference			1.71*	1.49, 1.96
Multivariate RR <sup>b</sup>			1	Reference			1.53*	1.33, 1.76
CESD-10 score								
Age-adjusted mean score		4.97		4.94, 5.00		6.21*		5.98, 6.44
No. of cases with CESD-10 score $\geq 10$	5,775				172			
Age-adjusted RR			1	Reference			1.73*	1.49, 2.02
Multivariate RR <sup>b</sup>			1	Reference			1.52*	1.30, 1.77
GDS-15 score								
Age-adjusted mean score		1.36		1.34, 1.38		1.91		1.78, 2.04
No. of cases with GDS-15 score $\geq 5$	2,323				71			
Age-adjusted RR			1	Reference			1.82*	1.44, 2.30
Multivariate RR <sup>b</sup>			1	Reference			1.70*	1.34, 2.15

Abbreviations: CESD-10, 10-item version of the Center for Epidemiologic Studies Depression Scale; CI, confidence interval; GDS-15, 15-item version of the Geriatric Depression Scale; RLS, restless legs syndrome; RR, relative risk.

\*  $P < 0.0001$ .

<sup>a</sup> Depression symptoms were evaluated with the CESD-10 in 2004 and the GDS-15 in 2008. Clinically relevant depression symptoms were defined as CESD-10 score  $\geq 10$  or GDS-15 score  $\geq 5$ .

<sup>b</sup> Adjusted for age (years), body mass index (weight (kg)/height (m)<sup>2</sup>; continuous), ethnicity (Caucasian or other), smoking status (never, past, or current smoker), marital status (married/in a partnership, widowed, or separated/divorced/single), solitary living status (yes/no; binary), regular involvement in a social or community group (yes/no; binary), menopausal status (premenopausal or postmenopausal), menopausal hormone use (never, past, or current user), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or  $\geq 15$  g/day), physical activity (quintiles), the presence of diabetes, arthritis, stroke, myocardial infarction, angina, cancer, hypertension, high cholesterol level, or Parkinson's disease (yes/no), use of iron-specific supplements, sleep duration ( $\leq 5$ , 6, 7, 8, or  $\geq 9$  hours per 24-hour period), and snoring frequency (every night, most nights, a few nights per week, occasionally, or almost never).

definitions of depression suggest that our findings were robust. In order to reduce the bias of possible reverse causation, we reexamined the association between RLS and depression after excluding the incident cases occurring between 2002 and 2004, and found similar results.

Our findings are consistent with previous retrospective and cross-sectional observations (5–26). However, the magnitude of the association between RLS and risk of depression observed in the current prospective analysis was smaller than the concurrent odds ratios in previous cross-sectional or retrospective studies, as was shown in the meta-analysis (relative risk = 1.5 vs. odds ratio = 2.3). This is consistent with the notion that retrospective studies and cross-sectional observations could lead to overestimation of the association (46). It has been suggested that depression or antidepressant medication use may increase the risk of RLS (22, 47). Using the prospective study design, we minimized the potential for reverse causation, although we cannot dismiss its existence altogether.

To our knowledge, this was the first prospective study to investigate the association between RLS and risk of incident

depression. A key strength of our prospective approach is the ability to avoid recall and selection biases. Another strength is that we collected detailed information on lifestyle and chronic conditions using validated questionnaires, which enabled us to control for the potential confounders that may be associated with both RLS and depression, such as obesity, physical activity, and chronic diseases. However, because of the observational nature of our study design, we cannot exclude the possibility of residual confounding. Thus, we support interventional studies to assess whether treated RLS patients develop less depression than placebo-treated controls.

One limitation is that the RLS assessment in the current study was based on established physician diagnoses. The prevalence of RLS in US women ranges from 6.4% to 11.2%, based on the International RLS Study Group criteria (10, 11, 48, 49). Thus, the RLS prevalence in this study (2.4% before excluding women with depression or depression symptoms at baseline and 1.7% in the current sample) demonstrates the underdiagnosis of RLS. In a large-scale US study published in 2005 that included 16,202 adults

**Table 4.** Adjusted Relative Risk of Depression According to Baseline Restless Legs Syndrome Status, Using Different Definitions of Depression, Nurses' Health Study, 2002–2008

Definition of Depression	No RLS				RLS			
	No.	Incidence	RR	95% CI	No.	Incidence	RR	95% CI
Physician-diagnosed depression								
No. of cases	1,626				44			
Person-years of follow-up	297,704				4,747			
Crude incidence (per 100,000 person-years)		546				927		
Age-adjusted RR			1	Reference			1.65**	1.22, 2.23
Multivariate-adjusted RR <sup>a</sup>			1	Reference			1.47*	1.09, 1.99
Either physician-diagnosed depression or regular use of antidepressant medication								
No. of cases	3,860				131			
Person-years of follow-up	295,493				4,662			
Crude incidence (per 100,000 person-years)		1,306				2,810		
Age-adjusted RR			1	Reference			2.13***	1.79, 2.53
Multivariate-adjusted RR <sup>a</sup>			1	Reference			1.88***	1.57, 2.23
Physician-diagnosed depression, CESD-10 score $\geq 10$ , or GDS-15 score $\geq 5$								
No. of cases	8,469				239			
Person-years of follow-up	295,993				4,676			
Crude incidence (per 100,000 person-years)		2,861				5,111		
Age-adjusted RR			1	Reference			1.71***	1.50, 1.94
Multivariate-adjusted RR <sup>a</sup>			1	Reference			1.55***	1.36, 1.76
Physician-diagnosed depression, regular antidepressant medication use, CESD-10 score $\geq 10$ , or GDS-15 score $\geq 5$								
No. of cases	10,057				299			
Person-years of follow-up	295,993				4,676			
Crude incidence (per 100,000 person-years)		3,398				6,394		
Age-adjusted RR			1	Reference			1.83***	1.63, 2.05
Multivariate-adjusted RR <sup>a</sup>			1	Reference			1.65***	1.47, 1.85

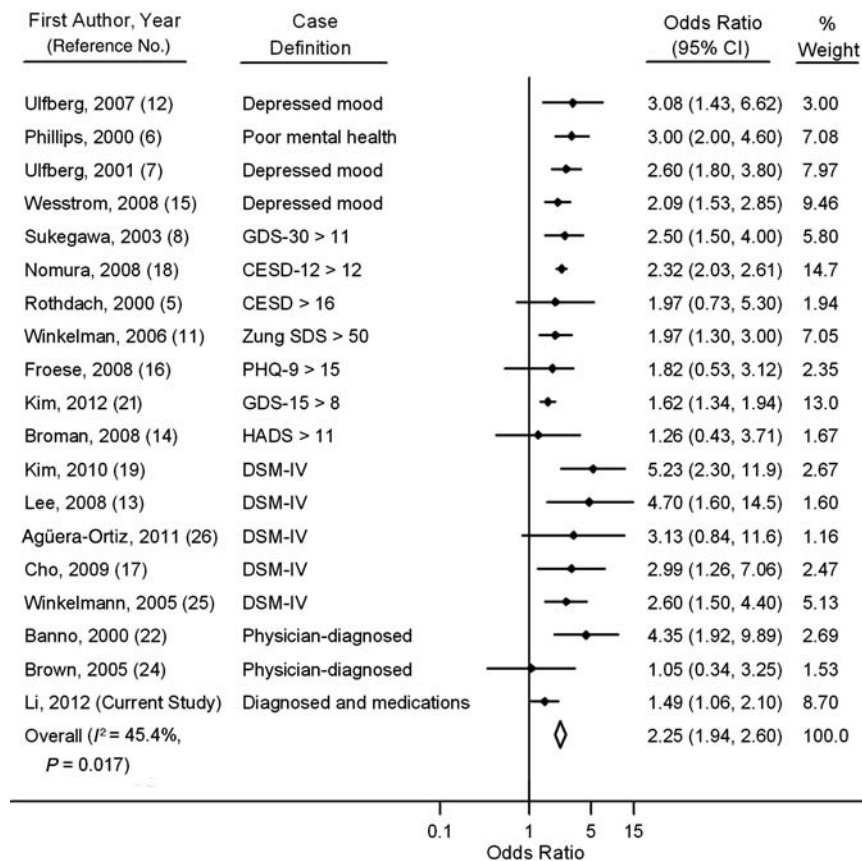
Abbreviations: CI, confidence interval; RLS, restless legs syndrome; RR, relative risk.

\*  $P < 0.01$ ; \*\*  $P < 0.001$ ; \*\*\*  $P < 0.0001$ .

<sup>a</sup> Adjusted for age (years), body mass index (weight (kg)/height (m)<sup>2</sup>; continuous), ethnicity (Caucasian or other), smoking status (never, past, or current smoker), marital status (married/in a partnership, widowed, or separated/divorced/single), solitary living status (yes/no; binary), regular involvement in a social or community group (yes/no; binary), menopausal status (premenopausal or postmenopausal), menopausal hormone use (never, past, or current user), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or  $\geq 15$  g/day), physical activity (quintiles), the presence of diabetes, arthritis, stroke, myocardial infarction, angina, cancer, hypertension, high cholesterol level, or Parkinson's disease (yes/no), use of iron-specific supplements, sleep duration ( $\leq 5$ , 6, 7, 8, or  $\geq 9$  hours per 24-hour period), and snoring frequency (every night, most nights, a few nights per week, occasionally, or almost never).

aged  $\geq 18$  years, only 6.2% of the RLS sufferers ( $n = 337$ ) reported having received a diagnosis of RLS (49). Similar results were seen in another survey conducted among 6 Western European countries: Only 9% of RLS cases ( $n = 365$ ) had been diagnosed previously (50). Thus, although RLS was probably underreported in the present study, we could not interview individual patients, because that approach would have been unrealistic given our sample size. Misclassification of depression is another concern because of the possibility of low recognition of depression by physicians, undertreatment of depression, and use of antidepressant medication for indications other than depression.

We tried to maximize the specificity of the case definition, accepting as incident cases of depression only women who reported both a diagnosis of depression and the use of antidepressants. This approach increased the specificity of diagnoses but decreased the sensitivity, which would have been more likely to weaken the observed associations. However, as long as the probability of correctly classifying women with an incident case of depression is independent of their diagnosis of RLS (nondifferential misclassification of outcome between women with RLS and women without RLS), the low sensitivity of this strict case definition should not bias relative risk estimates (51).



**Figure 1.** Associations between restless legs syndrome and depression in previously published studies, in the Nurses' Health Study cohort (current study; 2002–2008), and in a pooled meta-analysis of Nurses' Health Study participants (diamond; 2002–2008). Only crude odds ratios were available from the studies by Sukegawa et al. (8), Ulfberg et al. (12), Kim et al. (19), Banno et al. (22), Brown et al. (24), and Agüera-Ortiz et al. (26), and only pooled odds ratios were available from the studies by Winkelman et al. (11) and Broman et al. (14), who reported odds ratios for depression according to the severity of restless legs syndrome. Case definitions of depression included 1) self-reported symptoms of depression (depressed mood or poor mental health) assessed by means of a single question or with an unclear justification for the cutoff score; 2) self-reported symptoms of depression on a scale with a validated cutoff score, such as the 15- or 30-item version of the geriatric depression scale (GDS), the regular or 12-item Center for Epidemiologic Studies Depression scale (CESD), the Zung Self-rating Depression Scale (Zung SDS), the 9-item version of the Personal Health Questionnaire (PHQ), or the Hospital Anxiety and Depression Scale (HADS); 3) depression diagnosed according to the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV); 4) physician- or clinician-diagnosed depression; and 5) physician- or clinician-diagnosed depression and use of antidepressant medication. Based on the  $Q$  statistic,  $P$ -heterogeneity = 0.017. Bars, 95% confidence interval (CI).

In conclusion, in this large-scale prospective study, we found that the presence of physician-diagnosed RLS was associated with a higher risk of developing depression in women during 6 years of follow-up. Further studies using more precise diagnostic strategies for identifying RLS and depression in the community are warranted.

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