Restless Legs Syndrome and Hypertension in Middle-Aged Women

Salma Batool-Anwar, Atul Malhotra, John Forman, John Winkelman, Yanping Li, Xiang Gao

See Editorial Commentary, pp 763–764

Abstract—Limited research suggests a relationship between restless legs syndrome and hypertension. We, therefore, assessed the relationship between restless legs syndrome and hypertension among middle-aged women. This is a cross-sectional study including 65 544 women (aged 41–58 years) participating in Nurses’ Health Study II. The participants with diabetes mellitus and arthritis were excluded, because these conditions can mimic restless legs syndrome. Restless legs syndrome was assessed by a self-administered questionnaire based on the International Restless Legs Study Group criteria. Information on diagnosis of hypertension and blood pressure values were collected via questionnaires. Multivariable logistic regression models were used to analyze the relation between restless legs syndrome and hypertension, with adjustment for age, race, body mass index, physical activity, menopausal status, smoking, use of analgesics, and intake of alcohol, caffeine, folate, and iron. Compared with women with no restless legs symptoms, the multiple adjusted odds of having hypertension were 1.20 times (95% CI: 1.10–1.30; \( P \leq 0.0001 \)) higher among women with restless legs symptoms. The adjusted odds ratios for women who reported restless legs symptoms 5 to 14 times per month and \( \geq 15 \) times per month were 1.06 (95% CI: 0.94–1.18) and 1.41 (95% CI: 1.24–1.61) respectively, compared with those without the symptoms (\( P \) trend: <0.0001). Greater frequency of restless legs symptoms was associated with higher concurrent systolic and diastolic blood pressures (\( P \) trend: <0.0001 for both).

Women with restless legs syndrome have a higher prevalence of hypertension, and this prevalence increases with more frequent restless legs symptoms. (Hypertension. 2011;58:791-796.)

Key Words: restless legs syndrome ■ hypertension ■ sleep ■ cardiovascular disease ■ women

Restless legs syndrome (RLS) is a common yet underrecognized sensory motor disorder characterized by intense, unpleasant leg sensations and an irresistible urge to move the legs.1 The symptoms of RLS can impair sleep onset, sleep maintenance, and overall quality of life.2,3 Most studies have reported a prevalence of \( \approx 5\% \) to 15% of the adult population.4 RLS affects both men and women, with a female preponderance of \( \approx 2:1 \).5 Epidemiological studies have suggested a possible association between RLS and cardiovascular diseases7-9; however, the association between RLS and hypertension remains controversial. Previous studies have suggested that individuals with RLS are at increased risk of developing hypertension because of the presence of periodic limb movements of sleep (PLMS), seen in 80% of patients with RLS. The population-based studies have also suggested that hypertension may act as an intermediary risk factor leading to cardiovascular diseases9,10 in people with RLS. Despite improvements in awareness and treatment, the prevalence of hypertension has increased over the last decade.

According to the National Center for Health Statistics, 1 of 3 US adults experience hypertension, and it has been listed as a primary or contributing cause of death for 326 000 Americans in 2006.11,12 Because RLS may be associated with hypertension, further work into the possible clinical impact of RLS is required. We, therefore, sought to test the hypothesis that RLS would be associated with prevalence of hypertension in a large ongoing cohort of US middle-aged women.

Methods

Study Population

The Nurses’ Health Study II is a large prospective cohort of 116 430 female registered nurses who were 25 to 42 years old at the start of the study in 1989. Follow-up questionnaires are mailed to the participants every 2 years. The institutional review board at Brigham and Women’s Hospital approved this study, and completion of the questionnaires was considered participant’s consent.
Assessment of RLS
In 2005, we asked Nurses’ Health Study II participants (n = 97 642; mean age: 50.4 years) about RLS symptoms using questions based on the International Restless Legs Study Group Criteria.13 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 to 4 times per month, 5 to 14 times per month, and ≥15 times per month. The participants who answered yes were asked the following 2 questions: “Do these symptoms occur only at rest and does moving improve them?” and “Are these symptoms worse in the evening/night compared with the morning?”

A total of 79 992 women (82%) completed the questions regarding RLS. A probable diagnosis of RLS was thought to be present if participants answered “yes” to all of the above questions and if symptom frequency was ≥5 times per month.14 To reduce the misclassification of RLS, participants who had ever reported diabetest mellitus, had current arthritis, or who were currently pregnant were excluded, leaving 65 544 women in the primary analysis.

Assessment of Hypertension
Hypertension was self-reported by participants based on all of the biennial questionnaires; each questionnaire asked participants to report whether a clinician has made a new diagnosis of hypertension. Responses from the 2005 questionnaire, the same year as the questions regarding RLS, were used in this cross-sectional study to determine hypertension status. The 2005 questionnaire also inquired about the participant’s blood pressure during the preceding 2 years. Blood pressure assessment was done using predefined categories for systolic and diastolic blood pressures. The categories of systolic blood pressure responses (in millimeters of mercury) were <105, 105 to 114, 115 to 124, 125 to 134, 135 to 144, 145 to 154, 155 to 164, 165 to 174, 175+, and unknown or not checked within the past 2 years. The categories of diastolic pressure response were (in millimeters of mercury) <65, 65 to 74, 75 to 84, 85 to 94, 95 to 104, 105+, and unknown or not checked within the past 2 years. For the purpose of the present analyses, individual levels of blood pressure were assigned the midpoints of those ranges. Individuals who reported antihypertensive medication use were assigned to the highest category of blood pressure (SBP: 175 mm Hg; DBP: 105 mm Hg).

The validity of self-reported hypertension has been examined previously. Forman et al15 compared relevant medical charts from a subset of randomly selected nurses who reported a new diagnosis of hypertension on the 2005 biennial questionnaire with randomly selected participants who denied this diagnosis in 2005 and in every previous year. The sensitivity of self-reported hypertension was 94%, whereas the specificity was 85%.

Ascertainment of Covariates
Information on age, body mass index (BMI; weight in kilograms divided by height in meters squared), smoking status, physical activity, menopausal status, use of aspirin and other nonsteroidal antiinflammatory drugs, and presence of stroke or myocardial infarction were obtained from the 2005 questionnaire. Dietary intake was assessed based on a validated food frequency questionnaire.16,17 The reliability and validity of self-reported BMI and level of physical activity have been investigated previously.18,19 Self-reported weight and physical activity have suggested a correlation of 0.97 and 0.79, respectively.20 Alcohol consumption measured by questionnaires, administered 1 year apart, also provided highly reproducible results with a correlation of 0.90.21 Similarly, the validity of the food frequency questionnaire for measurement of folate intake has also been demonstrated in previous studies.22

Based on the diet prescribed in the Dietary Approaches to Stop Hypertension Trial,23 we constructed a Dietary Approaches to Stop Hypertension score focusing on 8 components, high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains and low intake of sodium, sweetened beverages, and red and processed meats.24

Statistical Analyses
Statistical analyses were completed using SAS version 9.1 (SAS Institute, Inc, Cary, NC). We categorized participants into 3 groups: no RLS, RLS symptoms 5 to 14 times per month, and RLS symptoms ≥15 times per month. Logistic regression models were used to calculate the prevalence odds ratios (ORs) and 95% CIs of having hypertension among participants with RLS compared with those without RLS. Means (eg, blood pressure) were compared using the general linear model procedure in SAS. The analyses were adjusted for age (in years), BMI (in kilograms per meter squared), BMI squared, race (white, black, or Asian and others), smoking (never smoked, former smoker, or current smoker: cigarettes per day: 1–14 or ≥15), physical activity (quintiles), alcohol intake (in grams per day: 0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥15.0), menopause status (premenopausal, no menstrual periods, or had menopause but now induced by hormones), analgesic use, oral contraceptive use, Dietary Approaches to Stop Hypertension score (quintile), and total folate intake (food and supplements, quintiles). In the Sensitivity analysis, we further adjusted for caffeine and iron intake, the Crown-Crisp phobic anxiety index, antidepressant use, sleep duration, and history of myocardial infarction or stroke. We examined potential interactions of the presence of RLS (no, 1–14, ≥15 times per month) with age (<50 or ≥50 years, median value), obesity status (BMI: <25, 25–29, and ≥30 kg/m²), and menopause status (yes or no), by including multiplicative terms in the logistic regression models, with adjustment for other potential confounders.

Results
The characteristics of women participating in Nurses’ Health Study II are shown in Table 1. Average age was 50.5 years. Greater intake of caffeine, analgesics, and tobacco was noted among women with RLS symptoms ≥15 times per month relative to those without RLS. Similarly, women with less physical activity and postmenopausal status reported more frequent RLS symptoms.

The prevalence of hypertension was 33.0% (576 of 1748) among the group with more frequent RLS symptoms (>15 times per month), 26.0% (643 of 2475) within the group with RLS symptoms 5 to 14 times per month, and 21.4% (13 104 of 61 321) within the group with no RLS symptoms (Table 2). The age-adjusted prevalence odds of hypertension were 1.43 times higher (95% CI: 1.33–1.53; P < 0.0001) among women with RLS symptoms. Significant associations between RLS and hypertension did not materially change (OR: 1.20 [95% CI: 1.10–1.30], after further adjustment for other potential covariates, such as BMI, BMI squared, menopausal status, Dietary Approaches to Stop Hypertension score, smoking, race, use of analgesics, oral contraceptives, alcohol, folate, and iron intake (a surrogate of iron deficiency). There was a significant relationship between hypertension and RLS severity as measured by symptom frequency: women experiencing RLS symptoms ≥15 times per month had higher odds of having hypertension compared with the group with less frequent symptoms (Table 2). The multivariate adjusted ORs for hypertension were 1.06 and 1.41 (95% CI: 0.94–1.18 and 1.24–1.61; P for trend: <0.0001) for women with RLS symptoms of 5 to 14 times per month and ≥15 times per month, respectively, relative to those without RLS (Table 2).

Subgroup analysis after stratifying age, BMI, and menopausal status suggested higher odds of having hypertension among women with RLS symptoms in all of the subgroups (Table 2). Women within the higher BMI category (≥30 kg/m²) and with RLS symptoms ≥15 times per month had higher odds of
having hypertension (OR: 1.57 [95% CI: 1.28–1.93]) compared with women with less frequent RLS symptoms (OR: 1.15 [95% CI: 0.96–1.37]). Similarly, women who reported sleeping <8 hours per day, along with more frequent RLS symptoms, had higher odds of having hypertension (Table 2). Women with RLS symptoms ≥15 times per month and who were sleeping <6 hours per day had an OR of 1.49 (95% CI: 1.19–1.87) for having hypertension compared with women without RLS symptoms and who reported similar sleep duration. In contrast, women with RLS symptoms ≥15 times per month who reported sleeping ≥8 hours per day or more had an OR of 1.24 (95% CI: 0.96–1.60) compared with women without RLS symptoms and with similar sleep duration. However, we did not find a significant interaction between the presence of RLS and age, obesity, menopause status, and sleep duration (P for interaction: >0.35 for all), in relation to the likelihood of having hypertension (Table 2).

We conducted several sensitivity analyses and obtained similar significant results. Multiple-adjusted ORs comparing women with RLS symptoms ≥15 times per month with those without RLS were 1.41 (95% CI: 1.24–1.61) after excluding participants with stroke or myocardial infarction and 1.35 (95% CI: 1.15–1.60) after excluding antidepressant users. Further adjustment for intake of caffeine and iron, the Crown-Crisp phobic anxiety index, antidepressant use, sleep duration, and history of myocardial infarction or stroke did not materially change the association between RLS and HTN: adjusted OR comparing the women with RLS symptoms ≥15 times per month with those without RLS was 1.31 (95% CI: 1.15–1.50). We did another sensitivity analysis to exclude the current antihypertensive users. The multiple-adjusted OR comparing women with RLS symptoms ≥15 times per month with those without the symptoms was 1.84 (95% CI: 1.48–2.27) after excluding the antihypertensive users.

We also observed a significant relationship between RLS severity, as assessed by frequency of the symptoms, and blood pressure. The multivariate adjusted mean systolic blood pressure was 130 mm Hg among the group with no RLS, 131 among the group with RLS symptoms 5 to 14 times per month, and 133 mm Hg among the group with symptoms ≥15 times per month (P trend: <0.0001; Figure A). The adjusted mean diastolic blood pressures were 80, 81, and 82 mm Hg, respectively, across 3 RLS categories (P trend: <0.0001; Figure B).

### Discussion

Our results demonstrate increased prevalence of hypertension among women with RLS symptoms. The association was independent of age, BMI, smoking status, and presence of stroke or myocardial infarction. Similar associations were observed in the subgroup analyses. These findings are consistent with the previous literature suggesting a possible role for RLS in the pathogenesis of hypertension. In a survey including 4000 men selected from the general population in central Sweden, participants with RLS symptoms were more likely to report hypertension (OR: 1.5 [95% CI: 0.9–2.4]), after adjusting for age, smoking, and alcohol consumption. However, this study did not include women. Moreover, the study failed to exclude RLS mimics, such as peripheral neuropathy, and anxiety. Because patients with RLS mimics meet all of the essential diagnostic criteria and do not actually have RLS, it is extremely important to exclude these RLS mimics. Another cross-sectional study of 18 980 participants found a significant association between RLS and hypertension (OR: 1.36 [95% CI: 1.14–1.61]), as did the telephone survey, which ascertained these 2 diseases and found a direct relation (P<0.05).

A number of possible biological mechanisms could account for the increased risk of hypertension in those with RLS. Roughly 80% of patients with RLS have periodic limb movements (PLMs) during sleep. PLMs are rhythmic extensions of the big toe and dorsiflexion of the ankle, lasting 0.5 to 5.0 seconds, which occur 200 to 300 times per night. Such leg movements are associated with sympathetically mediated elevations in both heart rate and blood pressure, which may be responsible for the increased cardiovascular diseases seen in patients with RLS. It is postulated that these repetitive blood pressure elevations at night lead to the development of daytime hypertension. Electroencephalographic arousals resulting from PLMSs may represent another risk factor for hypertension in persons affected by RLS. Interestingly, the arousals from sleep have also been shown to increase blood pressure through elevated peripheral sympathetic tone, even in individuals without PLMS. Increased...
daytime pulse rate and blood pressure has also been shown to be associated with higher arousal rate in individuals without PLMS. It is, therefore, possible that arousals associated with RLS with or without PLMSs are responsible for hypertension. Moreover, the prevalence of PLMSs in patients with grade III hypertension has been shown to be twice as frequent as in patients with grades I and II hypertension together (36.4% versus 13.0%, respectively; $P<0.02$). PLMSs are also concomitantly identified in patients with obstructive sleep apnea, an independent risk factor for hypertension.

In a large US sample, subjects with low sleep efficiency and average sleep duration of $\leq 5$ hours per night were found to have increased risk of developing hypertension. In addition, insufficient sleep may be responsible for increased risk of cardiovascular disease as a result of increased blood pressure. In the current study, when we adjusted for sleep duration, the association between RLS and hypertension was attenuated but remained significant, suggesting that RLS was not merely leading to hypertension through an effect on sleep duration.

Our results represent an important addition to the literature, because our sample size is considerably greater than previously published studies, and we were able to control rigorously for potential covariates and exclude patients in which misclassification is likely to occur. We acknowledge a number of limitations. First, the cross-sectional nature of the study design prevents us from drawing conclusions about temporality or causality in the RLS-hypertension association. RLS can lead to hypertension because of its effect on sleep quality and duration or the coexisting PLMS. Alternatively hypertension can also cause RLS through vascular changes or secondary to effects of medications used to treat hypertension. However, we obtained similar positive associations between RLS and hypertension when we excluded participants who reported the use of antihypertensive medicines. Residual confounding is impossible to exclude because of the observational nature of our study. Thus, conducting a prospective study to clarify whether individuals with RLS have an increased risk of developing hypertension is important in this context.

As discussed earlier, increased frequencies of patients with RLS have PLMSs, which are also identified in patients with obstructive sleep apnea, an independent risk factor for hypertension. Although we controlled for snoring, a surrogate of obstructive sleep apnea, an independent risk factor for both RLS and hypertension, was not collected in our cohort. It remains possible that confounding by renal failure played a role in our results, although the effects would be modest because of the low prevalence of chronic renal failure in the general populations. The status of iron deficiency, yet another risk factor for RLS, was not available for our cohort. However, further adjusting for the use of iron specific supplements, a surrogate for iron deficiency did not alter the observed association between RLS and hypertension.

Table 2. Association Between Restless Legs Syndrome and Hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>No RLS</th>
<th>RLS $\leq 14$ Times per mo</th>
<th>RLS $\geq 15$ Times per mo</th>
<th>$P$ for Trend</th>
<th>$P$ for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension cases, n</td>
<td>13104</td>
<td>643</td>
<td>576</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension prevalence (%)</td>
<td>21.4</td>
<td>26.0</td>
<td>33.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted OR (95% CI)</td>
<td>1</td>
<td>1.24 (1.13–1.36)</td>
<td>1.73 (1.56–1.92)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted OR*</td>
<td>1</td>
<td>1.06 (0.94–1.18)</td>
<td>1.41 (1.24–1.61)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>&lt;50 y</td>
<td>1.0</td>
<td>1.06 (0.87–1.30)</td>
<td>1.52 (1.21–1.91)</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 50 y</td>
<td>1.0</td>
<td>1.05 (0.91–1.21)</td>
<td>1.37 (1.17–1.60)</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Body mass index*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>$&lt;25$ kg/m$^2$</td>
<td>1.0</td>
<td>0.93 (0.75–1.17)</td>
<td>1.31 (1.02–1.68)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>25–29 kg/m$^2$</td>
<td>1.0</td>
<td>1.06 (0.87–1.29)</td>
<td>1.33 (1.06–1.67)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>$\geq 30$ kg/m$^2$</td>
<td>1.0</td>
<td>1.15 (0.96–1.37)</td>
<td>1.57 (1.28–1.93)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Menopause status†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Before</td>
<td>1.0</td>
<td>0.96 (0.79–1.18)</td>
<td>1.33 (1.06–1.67)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>1.0</td>
<td>1.13 (0.98–1.30)</td>
<td>1.42 (1.21–1.67)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Sleep duration, h/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>$\leq$ 6</td>
<td>1.0</td>
<td>1.003 (0.81–1.24)</td>
<td>1.49 (1.19–1.87)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>1.17 (0.98–1.39)</td>
<td>1.47 (1.18–1.81)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 8</td>
<td>1.0</td>
<td>1.05 (0.83–1.33)</td>
<td>1.24 (0.96–1.60)</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; RLS, restless leg syndrome.
†Data were adjusted for the above variables except menopause status.

P<0.0001

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diagnostic criteria used in the present study. Our study lacks the information on RLS treatment; therefore, it is unclear whether the association between RLS and hypertension would change after adequate treatment of RLS. However, there are limited studies on long-term efficacy of RLS treatment, and studies have reported underrecognition and undertreatment of RLS.

In conclusion, in this large-scale cross-sectional study, we found that women with RLS had a higher risk of having hypertension than those without RLS, independent of several known risk factors for hypertension. Future prospective studies are needed to confirm this observation.

Perspectives
The prevalence of hypertension continues to rise despite increased awareness and improved treatments. Therefore, there is an increasing need to better understand the potential risk factors leading to hypertension. The current study used a large cohort of women to examine the association between RLS and hypertension after adjusting for potential covariates. The results show that the prevalence of hypertension is higher among women with RLS symptoms. Moreover, there was a significant relationship between RLS severity, as measured by symptom frequency, and hypertension.

Because of the cross-sectional nature of this study, it is difficult to determine causality. Therefore, future prospective studies are required to confirm these findings.

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References
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