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The Relationship of Restless Legs Syndrome to History of Pregnancy-Induced Hypertension

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Abstract

Background: Restless legs syndrome (RLS), a burdensome sleep disorder, has been associated with cardiovascular disease (CVD), hypertension, diabetes, and related disorders. However, the relationship of RLS to history of pregnancy-induced hypertension (PIH), a predictor of subsequent CVD, diabetes, and associated conditions, remains little explored. In this study, we investigated the relationship of RLS to history of PIH in a sample of primary care patients.

Methods: Participants were women aged ≥40 years drawn from an anonymous survey study of West Virginia primary care patients. Data collected included detailed information on demographics, lifestyle factors, sleep patterns, and reproductive/medical history; the survey also included an RLS diagnostic questionnaire. Women who were pregnant or unsure about their pregnancy status were excluded from the analyses.

Results: Of the 498 participants in the final analytic sample, 24.5% met diagnostic criteria for RLS (17.9% with symptoms ≥once/week, 11.9% with symptoms ≥3 times/week); 73 (16.5% of parous women) reported a history of PIH, defined as physician-diagnosed preeclampsia or gestational hypertension. After adjustment for demographics, lifestyle characteristics, obesity, reproductive history, health conditions, and other factors, those reporting a history of PIH were approximately twice as likely to meet criteria for RLS (odds ratio [OR] = 1.9; 95% confidence interval [CI] = 1.1, 3.6). These associations increased in magnitude with increasing symptom frequency (adjusted OR for RLS with symptoms ≥3 times/week = 3.8; CI 1.9, 7.6; p for trend = 0.003).

Conclusions: History of PIH was strongly and positively related to current RLS in this study of primary care patients; these findings further support a possible role for metabolic dysregulation in RLS etiology.

Introduction

Restless legs syndrome (RLS), also known as Willis–Ekbom disease, is a burdensome sleep disorder affecting a significant percentage of adults, with estimates in the United States and Europe ranging from 4% to 29%, depending on the criteria and population.[1–3] RLS is characterized by a compelling urge to move the legs that begins or worsens during periods of inactivity, is worse during the evening and at night, is at least partially relieved by movement, and is frequently accompanied by uncomfortable, often painful sensations in the legs.[4] In addition, these symptoms cannot be due to another condition, such as leg cramps or positional discomfort.[5]

A major cause of chronic sleep loss,[3,6] RLS leads to significant impairment of daily functioning and quality of life, increased health-related costs, and declines in productivity that are comparable to those reported in other serious chronic disorders, including diabetes, hypertension, Parkinson's disease, and stroke.[7–11] While data regarding the overall financial burden of RLS in the United States remain limited, a comprehensive cost study conducted in Australia estimated the economic impacts of RLS to total $11.1 billion in 2004.[12] Collectively, these studies suggest that RLS is a serious chronic condition of major public health import, affecting a large proportion of the adult population and exacting a significant toll in terms of health, quality of life, and economic cost.

The etiology of RLS remains poorly understood.[13–15] Currently, the primary underlying causes of RLS are thought to be genetic predisposition, dopaminergic dysfunction, and deficiencies in iron metabolism,[13–19] although these factors

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have to date offered only a partial explanation.[2] Recent research suggests that metabolic and autonomic factors may also play an important role in the development of RLS.[2] RLS has been strongly associated with cardiovascular disease (CVD), hypertension, diabetes, obesity, and other conditions characterized by metabolic and autonomic dysfunction.[2] While most studies linking RLS to these disorders have been cross-sectional, limiting causal inference,[2] recent prospective studies in German adults have shown history of myocardial infarction, along with key components of the metabolic syndrome to be significant predictors of incident RLS,[20,21] supporting a possible etiologic link. The prevalence of RLS is also elevated in women, is increased up to threefold during pregnancy,[22] and is positively associated with number of births or parity[23]; parity has, in turn, been shown to predict early-onset hypertension,[24] obesity,[25–27] dyslipidemia,[28] diabetes,[29–31] the metabolic syndrome,[32] atherosclerosis, and cardiovascular events.[28,33] Pregnancy is accompanied by profound physiological alterations paralleling those characterizing the metabolic syndrome; these include increased insulin resistance and reduced glucose tolerance, weight gain and fat accumulation, dyslipidemia, inflammation, and sympathetic activation,[32,34] in addition to significant hemodynamic changes and vascular remodeling.[35] Pregnancy-related metabolic and autonomic perturbations can persist postpregnancy,[32,35–37] and may explain, in part, the relationship between parity and the development of conditions related to CVD and the metabolic syndrome.[32,35] Given the growing evidence for an association between these conditions and RLS, pregnancy-related metabolic and hemodynamic changes may also underlie both the marked increase in RLS prevalence and severity observed during pregnancy and the positive association of RLS to parity. One common complication of pregnancy that is increasingly recognized as a gestational marker of metabolic and hemodynamic dysfunction and future chronic disease risk is pregnancy-induced hypertension (PIH).[38,39]

PIH is characterized by *de novo* hypertension in pregnancy and encompasses both nonproteinuric (gestational) hypertension and proteinuric hypertension (preeclampsia).[40] The second leading global cause of maternal mortality,[41] PIH affects at least 5%–10% of pregnancies, with prevalence continuing to rise both in the United States and elsewhere.[42–44] Women who experience PIH are at least two to four times more likely to develop hypertension, the metabolic syndrome, type 2 diabetes, CVD, and stroke,[38,39,45–50] with the increased risk evident within 1–3 years following delivery.[38,49] PIH may thus be viewed as an early risk marker for these disorders,[45,50] conditions which have also been associated with RLS.[2,21,51,52] However, while several studies have examined risk factors for RLS during pregnancy as well as pregnancy-related risk factors for RLS in nonpregnant women, the association of RLS to common physiological complications of pregnancy, including PIH, remains little explored. One cross-sectional study of pregnant Peruvian women reported elevated prevalence of preeclampsia among those with RLS,[53] although findings were based on small numbers, estimates were not adjusted for several potentially confounding factors, and it is unknown if RLS persisted beyond pregnancy. To our knowledge, no studies have yet investigated the relationship of chronic RLS in nonpregnant women to history of PIH, a strong predictor of several chronic conditions associated with RLS. In this investigation, we examined the association of RLS to prior PIH in a sample of older female primary care patients.

Methods

Study population and survey administration

Participants for this study were nonpregnant women 40 years of age and older, drawn from an anonymous survey study of ambulatory, community-dwelling, English-speaking West Virginia (WV) residents visiting 1 of 4 Morgantown area primary care clinics affiliated with the WV University (WVU) Health Sciences Center.[3] We restricted our sample to women 40 years of age and older ($\sim$45% of all respondents and 65% of female respondents) to reduce the probability of including women with undetected pregnancy or early onset RLS,[13,54,55] which is thought by some to more strongly reflect genetic and other factors.[13,54]

Survey methods have been described in detail elsewhere.[3] Written survey questionnaires were offered to each adult patient seated in the clinic waiting area. The survey was presented to potential participants as an investigation regarding sleep patterns in Morgantown area adults, including both those who slept well and those who did not. Surveys were administered during 3- to 4-hour time blocks over the course of 12 weeks; survey distribution times and days of the week were rotated systematically in each clinic to ensure similar coverage across clinics and to reduce the probability of selection bias based on timing of survey administration. Survey response rates were excellent overall, with 76.7% of women contacted returning completed surveys.[3] The survey instrument included 41 self-report items and required 5–10 minutes to complete. Data gathered included detailed information on the following: demographic and lifestyle factors; current height and weight; history of physician-diagnosed health conditions and current medications for these conditions; sleep duration and quality during the past 7 days; and, in women, reproductive history, including history of PIH. This anonymous survey study was approved by the WVU Institutional Review Board.

A total of 553 adult female primary care patients aged 40 years and older submitted completed surveys. Pregnant women and those unsure about their pregnancy status ($n=6$) were excluded from the analytic sample as were those with missing data on RLS symptoms ($n=6$, 1.1%) or on pregnancy history, demographics, lifestyle factors, and other covariates of interest ($n=43$, 9.0%), yielding a final analytic sample of 498 female primary care patients. Participants with missing data were more likely to be older (62.9 ± 2.0 vs. 56.9 ± 0.5 years, $p=0.001$), and less likely to be college graduates (8% vs. 31%, $p=0.0001$), to indicate an annual income over $25,000 (31% vs. 74%, $p<0.001$), or to report exercising at least 1 hour per week (29.0% vs. 48.7%, $p=0.03$) than those without missing data. Relative to those included in the analysis, participants with incomplete data did not differ in other demographic or lifestyle characteristics, or in sleep patterns, health profiles, reproductive history, prevalence of RLS, or other factors ($p>0.1$).

Measurement of RLS, PIH, and major covariates

Ascertainment of RLS. RLS, the primary outcome of interest, was ascertained *via* responses to a previously

Table 1. Questions Used to Ascertain Presence of Restless Legs Syndrome

1. Do you ever have an urge to move your legs that is difficult to resist? If YES, proceed to questions 2–8:
2. Will simply changing leg position by itself once without continuing to move usually relieve these feelings?
3. Is this urge to move usually accompanied by unpleasant sensations in the legs?
4. Are the unpleasant sensations due to leg cramping?
5. Does the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting?
6. Is the urge to move or the unpleasant sensations partially or totally relieved by movement, such as walking or stretching?
7. Does the urge to move or the unpleasant sensations only occur or get worse in the evening or night?
RLS symptom frequency was ascertained *via* an 8th question
8. How often do you experience these symptoms?(Circle one: less than once/month, 1–3 days/month, 1–2 days/week, and 3 or more days/week)

RLS, restless legs syndrome.

validated seven-item questionnaire[3] adapted from the self-completed Cambridge-Hopkins diagnostic questionnaire[56] (CH-RLSq) and designed to capture the four International Restless Legs Syndrome Study Group's (IRLSSG) diagnostic criteria in effect at the time,[4] exclude common RLS mimics (leg cramps and positional discomfort),[5] and determine presence of accompanying unpleasant sensations (Table 1).

RLS was defined as an affirmative response to all four RLS diagnostic questions (1, 5–7, above) along with a negative response to questions 2 and 4. Since the presence of unpleasant sensations is not an essential diagnostic criterion for RLS, but rather an often associated characteristic,[4] the prevalence and correlates of RLS with unpleasant sensations were assessed in separate analyses. Participants were also asked, in a separate section of the survey, if they had received a physician diagnosis of RLS and/or were taking medications for RLS.

Demographic and lifestyle characteristics. Demographic characteristics were ascertained *via* self-report survey questions and included age, sex, race/ethnicity, education, employment status, marital status, and annual household income. Lifestyle factors measured included smoking history and current smoking status (five items), caffeine consumption (two items), and participation in physical activity (two items).

Reproductive history, including PIH and other health-related factors. Reproductive history was also assessed *via* self-report survey questions. History of PIH was scored as positive (one) if the participant answered ''yes'' to the following two questions (1) ''Have you ever been pregnant?'' and (2) ''If yes, were you ever told by a doctor that you had gestational hypertension or preeclampsia?'' If the participant answered ''no'' to either question, history of PIH was scored as negative (zero). Information was also gathered on menopausal status (one item), previous and current use of hormone replacement therapy (HRT) (two items), parity (completed pregnancies, two items), history of gestational diabetes (GDM) (two items), and current pregnancy status (one item).

History of a specific chronic health disorder (including hypertension, high cholesterol, heart disease, stroke, diabetes, kidney disease, anemia, sleep apnea, depression, and other serious conditions) was likewise determined *via* self-report, and defined as physician diagnosis of, and/or currently taking prescription medications for this disorder. Metabolic syndrome was defined as the presence of at least three of the four following conditions: hypertension, obesity, diabetes, and high cholesterol. Body mass index (BMI) was calculated as weight in kg/height in m^2, with obesity defined as BMI $\geq$30. Five survey items were used to determine the number of days (0–7) during the past week that the participant experienced specific sleep problems (difficulty falling asleep, difficulty staying asleep, early awakening, insufficient rest, and daytime fatigue/somnolence); the composite 5-item scale has been shown to be both reliable and useful and is described in detail elsewhere.[3] A sixth open-ended question was used to ascertain average sleep duration per night (in hours and minutes) during the past week.

Statistical analyses

Analyses were performed using SPSS v. 21. Possible differences between participants with and without missing data were assessed using the Student's *t*-test or Mann–Whitney *U* test for continuous or ordinal variables and chi square test for categorical variables. Multiple logistic regression was used to determine the independent associations of RLS to history of PIH and evaluate the influence of potential confounders and effect modifiers; linear trends were assessed using polynomial contrasts. Factors known or suspected to be related to RLS were selected for inclusion as covariates in the multivariate models.[1–3,57,58] Unless indicated otherwise, multivariable models were adjusted for demographic and lifestyle characteristics, reproductive history (menopause, parity, use of HRT), BMI, and number of comorbid conditions, including heart conditions/CVD, hypertension, high cholesterol, arthritis, stroke, diabetes, anemia, and kidney disease. Additional analyses also adjusted for GDM, sleep apnea, depression, sleep impairment, and cancer. All *p*-values given are two sided. We also assessed the potential modifying effects of age, obesity, and specific common chronic disorders, including diabetes, hypertension, CVD, and the metabolic syndrome.

In addition, we conducted several sensitivity analyses to evaluate the robustness of the observed associations. We examined the association of PIH to RLS severity, as indicated by frequency of reported symptoms (no RLS [referent category], RLS with symptoms less than once/week, RLS with symptoms once or twice/week, and RLS with symptoms or more times/week); we also restricted RLS cases to those with accompanying unpleasant sensations. To determine the potential influence of specific chronic conditions (diabetes, kidney disease, anemia, stroke, CVD, hypertension, arthritis, and high cholesterol) on the relationship of PIH and RLS, we also adjusted for each disorder both separately and combined in our multivariate analyses. In addition, we conducted analyses excluding participants with a history of kidney disease, anemia, stroke, neurological conditions, CVD, and diabetes and performed additional analyses excluding patients on

Table 2. Demographic, Lifestyle, Reproductive, and Health-Related Characteristics of 498 Nonpregnant Women ≥40 Years of Age Attending Four Primary Care Clinics, Stratified by Restless Legs Syndrome Status

		RLS	
	Total	*No*	*Yes*
Demographic characteristics			
Age: mean in years (SE)	56.96 (0.49)	57.07 (0.57)	56.37 (0.94)
Race/ethnicity			
Non-Hispanic White	91.6%	90.2%	95.9%
Minority	8.4%	9.8%	4.1%
Marital status			
Married/cohabiting	66.7%	66.2%	68.0%
Widowed/separated/divorced	28.3%	27.7%	30.3%
Single, never married	5.0%	6.1%	1.6%
Years of education			
≤12 years	34.7%	32.4%	41.8%
Some college/technical school	34.1%	33.5%	36.1%
4+ years college	31.1%	34.0%	22.1%
Current employment status			
Employed/student	47.4%	48.7%	43.4%
Homemaker	9.6%	9.6%	9.8%
Retired	26.7%	27.9%	23.0%
Unemployed/laid off/disabled	16.3%	13.8%	23.8%
Average household income			
<$25,000	23.7%	22.1%	28.7%
$25,000–$49,999	26.9%	26.6%	27.9%
$50,000–$74,999	20.1%	19.9%	20.5%
≥$75,000	21.5%	23.4%	15.6%
Don't know	2.8%	2.7%	3.3%
p for trend			
Lifestyle characteristics			
Smoking status			
Never	57.0%	57.4%	55.7%
Former	26.9%	26.6%	27.9%
Current	15.5%	15.2%	16.4%
Unsure	0.6%	0.8%	0.0%
Exercise less than 1 hour/week	41.0%	42.0%	37.7%
Drink at least five 8 oz caffeinated beverages/week	76.5%	76.1%	77.9%
Reproductive history			
Peri- or postmenopausal	73.1%	73.1%	73.0%
HRT			
Current	5.6%	4.5%	9.0%
Ever (for >6 months)	22.9%	23.4%	21.3%
Number of completed pregnancies			
One or more	88.6%	86.4%	95.1%
Mean number (SE)	2.53 (0.08)	2.43 (0.97)	2.82 (0.14)
Comorbidity			
History of serious chronic health condition(s)[a]			
No	24.9%	27.4%	17.2%
Yes	75.1%	72.6%	82.8%
Number of serious chronic health conditions			
None	24.9%	27.4%	17.2%
One	22.5%	22.3%	23.0%
Two	20.3%	20.2%	20.5%
Three or more	32.3%	30.1%	39.3%

(*continued*)

TABLE 2. (CONTINUED)

	Total	RLS	
		No	Yes
History of chronic health conditions			
Obesity (BMI ≥30)	43.78%	40.52%	53.39%
Diabetes	20.77%	17.62%	30.33%
CVD	11.41%	10.30%	14.75%
Hypertension	48.68%	47.15%	53.28%
High cholesterol	40.73%	39.30%	45.08%
Metabolic syndrome	23.61%	20.98%	31.36%
Kidney disease	3.05%	2.44%	4.92%
Arthritis	26.48%	24.93%	31.15%
Stroke	2.85%	2.98%	2.46%
Anemia	14.05%	12.74%	18.03%
Parkinson's disease/other neurological condition	6.11%	5.69%	7.38%
Sleep apnea	9.11%	6.61%	16.67%
Depression	29.33%	26.83%	36.89%
Sleep impairment			
Sleep disturbance[b] at least 4 days/week	75.46%	72.48%	84.43%
Sleep disturbance[b] 7 days/week	47.94%	44.78%	57.38%
Average sleep duration <5 hours/night	32.03%	28.61%	42.50%

$n = 122$ with RLS, 376 without RLS.
[a]Reported physician diagnosis of anemia, hypertension, high cholesterol, heart disease, stroke, kidney disease, diabetes, osteoarthritis, rheumatoid arthritis, lung disease, or other serious chronic condition.
[b]Defined as difficulty falling asleep, difficulty staying asleep, awakening too early, daytime sleepiness, or insufficient rest.
BMI, body mass index; CVD, cardiovascular disease; HRT, hormone replacement therapy.

medications that might influence RLS symptoms, including those for depression, hypertension, and high cholesterol.

Results

Study population characteristics by RLS status are given in Table 2. Participants were predominantly non-Hispanic white (92%) and married or cohabiting (67%). Less than a third had completed 4 years of college, and ~50% reported an annual household income of under $50,000. Almost 75% of respondents were perimenopausal or postmenopausal, 23% reported taking HRT for more than 6 months at some point in their lives, and 87% had completed at least one pregnancy. Forty-four percent of the women in this study were obese and 75% reported at least one serious health condition, with more than 50% reporting at least two and approximately one-third reporting ≥3 comorbid disorders (Table 2). Reflecting the high comorbidity rates in this population, prevalence of several common chronic disorders was elevated, including hypertension (48.7%), high cholesterol (40.7%), metabolic syndrome (23.6%), diabetes (20.7%), arthritis (26.5%), and depression (29.3%). Reported sleep impairment was also high in this population, with almost 50% of women surveyed indicating sleep problems daily and almost one-third reporting an average of less than 5 hours sleep per night (Table 2).

Of the 498 women included in this analysis, 122 (24.5%) met the current IRLSSG diagnostic criteria; 17.9% of respondents (73% of those with RLS) reported experiencing symptoms at least once per week and 11.9% (24.6% of those with RLS) indicated symptoms at least thrice per week. One hundred and seven respondents with RLS (21.5%) also reported unpleasant sensations; of those, 64% indicated symptoms at least once per week and 49.5% reported symptoms at least thrice per week. Only one-third ($n = 41$) of the women meeting diagnostic criteria for RLS had ever received a physician diagnosis, of whom 18 (14.8% of those meeting criteria for RLS) were taking RLS medications. Of the 441 women reporting at least one pregnancy, 73 (16.5%) indicated receiving a diagnosis of PIH.

As illustrated in Table 3, reported history of PIH was associated with significantly higher odds of RLS in this population. Women who indicated a prior diagnosis of PIH were approximately twice as likely to meet criteria for RLS (odds ratio [OR] adjusted for demographic and lifestyle characteristics = 1.8; 95% confidence interval [CI]: 1.0, 3.2). Further adjustment for BMI, reproductive history, and comorbid conditions, including hypertension, diabetes, anemia, CVD, and other major disorders, slightly strengthened this association (OR = 1.9; CI: 1.1, 3.6). Likewise, restricting the analysis to RLS cases accompanied by unpleasant sensations ($n = 107$) modestly strengthened this relationship of PIH to RLS (fully adjusted OR = 2.0; CI: 1.0, 3.8). Additional adjustment for depression and sleep apnea did not materially alter these associations (fully adjusted ORs for all RLS and RLS with unpleasant sensations, respectively, = 2.0 [CI: 1.0, 3.6] and 1.9 [CI: 1.1, 3.7]) nor did inclusion of diagnosed cancer in the full model (ORs, respectively = 2.0; CI: 1.1, 3.6 and 2.0; 1.2, 3.6). Similarly, additional adjustment for sleep impairment did not appreciably change the relationship of PIH to RLS (fully adjusted OR = 1.9; CI: 1.0, 3.4). Controlling for prior history of GDM, a strong predictor of PIH,[59–61] and recently linked to chronic RLS[52] only slightly attenuated this association (adjusted OR = 1.8; CI: 1.0, 3.2).

The association of PIH to RLS increased in magnitude with rising RLS severity, with PIH associated with an approximately fourfold increase in odds for RLS with

Table 3. Association of History of Pregnancy-Induced Hypertension to Restless Legs Syndrome and Restless Legs Syndrome Severity in 498 Nonpregnant Women ≥40 Years of Age Attending Four West Virginia University Primary Care Clinics

	Likelihood of meeting criteria for RLS	
Association of history of PIH to RLS	*OR (95% CI)*	p
Including as cases all those meeting criteria for RLS (n = *122*)		
Overall		
Crude	1.73 (1.01, 2.95)	0.045
Adjusted for demographic, lifestyle factors[a]	1.81 (1.03, 3.17)	0.04
Also adjusted for BMI, diabetes, and other comorbid conditions[b]	1.89 (1.04, 3.45)	0.04
Also adjusted for reproductive characteristics[c]	1.94 (1.06.3.59)	0.03
By frequency of RLS symptoms[d]		
Less than once/week	0.79 (0.27, 2.76)	0.71
1–2 times/week	1.13 (0.36, 3.54)	0.84
3 or more times/week	3.75 (1.85, 7.60)	0.00025
p for trend		*0.003*
Including as RLS cases only those with RLS accompanied by unpleasant sensations (n = *107*)		
Overall		
Crude	1.73 (0.99, 3.03)	0.054
Adjusted for demographic, lifestyle factors[a]	1.83 (1.01, 3.31)	0.05
Also adjusted for BMI, diabetes, and other comorbid conditions[b]	1.98 (1.05, 3.74)	0.03
Also adjusted for reproductive characteristics[c]	1.97 (1.03, 3.79)	0.04
By frequency of RLS symptoms[d]		
Less than once/week	0.92 (0.26, 3.26)	0.89
1–2 times/week	1.57 (0.50, 5.10)	0.45
3 or more times/week	3.25 (1.53, 6.90)	0.002
p for trend		*0.02*

n = 122 with RLS, 376 without RLS. All *p*-values are two-sided. Referent category is no reported history of PIH.

[a]Demographic characteristics include age, race/ethnicity, marital status, education, occupation, and annual family income; lifestyle factors include smoking status, physical activity, and caffeine consumption.

[b]Including reported physician diagnosis of anemia, hypertension, high cholesterol, heart disease, stroke, kidney disease, osteoarthritis, rheumatoid arthritis, lung disease, or other serious chronic condition.

[c]Including menopausal status, parity, and history of HRT.

[d]Adjusted for demographics, lifestyle factors, BMI, and comorbid conditions.

CI, confidence intervals; OR, odds ratio; PIH, pregnancy-induced hypertension.

symptoms at least 3 times per week (OR = 3.8; CI: 1.9, 7.6; *p* for trend = 0.005). Excluding women with a history of kidney disease, anemia, stroke, neurological conditions, sleep apnea, or diabetes did not appreciably alter these findings nor did including as RLS cases the 7 women who indicated receiving a diagnosis of RLS, but did not meet RLS criteria. In addition, excluding those on medication for high cholesterol or depression did not appreciably alter risk estimates (adjusted OR = 2.2; CI: 0.9, 5.1) nor did specifically adjusting for antihypertensive, lipid-lowering, and antidepressant medication in the model (adjusted OR = 1.8; CI: 1.0, 3.4).

We found no evidence of significant interaction by obesity status, history of GDM, or by presence of diabetes, metabolic syndrome, hypertension, or high cholesterol ($p > 0.1$). As illustrated in Table 4, PIH remained strongly related to RLS even in the absence of obesity, CVD, diabetes, or GDM. However, the combination of prior PIH with diabetes and CVD appeared to markedly increase the likelihood of RLS (adjusted ORs for history of PIH in combination with CVD and diabetes, respectively = 4.7; CI: 1.1, 20.1 and 5.7; CI: 2.0, 16.7), suggesting at least an additive effect of these factors on RLS risk.

Discussion

While a growing number of studies suggest an association between RLS and chronic conditions characterized by metabolic dysregulation, the relationship of RLS to PIH and other gestational markers of metabolic dysfunction remains little explored. A recent cross-sectional study of 79 Peruvian peripartum women documented a greater prevalence of preeclampsia in mothers with RLS, suggesting a potential association.[53] However, these findings were based on small numbers (8 women with preeclampsia) and, although women were matched on age and BMI, estimates were not adjusted for GDM, chronic hypertension, diabetes, or other conditions associated with increased risk for both RLS and preeclampsia. It is also unknown if this association persisted beyond pregnancy. In our recent companion study,[52] we documented a strong positive association between previous history of GDM and RLS that was independent of demographic and lifestyle factors, BMI, comorbid conditions, and reproductive history, including history of PIH.

To our knowledge, this is the first study to examine the association of current chronic RLS to history of PIH and among the first to investigate the relationship of RLS to any complication of pregnancy. Briefly, findings of this study in older female primary care patients suggest that history of PIH is significantly and positively related to RLS; in this population, women who reported a history of PIH were approximately twice as likely to meet criteria for RLS and nearly four times as likely to experience RLS symptoms at least thrice per week. This relationship was not explained by demographic or

Table 4. Association of Restless Legs Syndrome to History of Pregnancy-Induced Hypertension Alone and in Combination with Obesity, Diabetes, Cardiovascular Disease, and Gestational Diabetes

Association of history of GDM to RLS (n = *122 RLS cases*)	*Likelihood of meeting criteria for RLS*	
	OR (95% CI)[a]	p
History of PIH, by obesity		0.01
No PIH, no obesity	1.00 (referent)	
PIH only (no obesity)	2.91 (1.25, 6.8)	0.01
Obesity only (no history of PIH)	1.80 (1.1, 2.93)	0.02
Both obesity and history of PIH	2.63 (1.20, 5.77)	0.02
p for interaction		NS
History of PIH, by diagnosis of CVD		0.003
No PIH, no CVD	1.00 (referent)	
PIH only (no CVD)	1.72 (0.95, 3.18)	0.08
CVD only (no history of PIH)	1.29 (0.67, 4.83)	0.43
History of both PIH and CVD	4.71 (1.12, 20.07)	0.04
p for interaction		NS
History of PIH, by diagnosis of diabetes		0.007
No PIH, no diabetes	1.00 (referent)	
PIH only (no diabetes)	1.70 (0.94, 3.05)	0.07
Diabetes only (no history of PIH)	1.54 (0.80, 3.10)	0.20
Both history of PIH and diabetes	5.71 (1.95, 16.72	0.001
p for interaction		NS
History of PIH, by history of GDM		0.003
No PIH, no GDM	1.00 (referent)	
PIH only (no GDM)	2.11 (1.09, 4.09)	0.03
GDM only (no history of PIH)	3.49 (1.56, 7.83)	0.002
History of both PIH and GDM	2.73 (0.95, 7.89)	0.06
p for interaction		NS

$n = 498$ nonpregnant women ≥40 years of age attending four WVU primary care clinics. All *p*-values are two sided. NS ($p \geq 0.1$).
[a]Adjusted for demographics, lifestyle characteristics, and BMI.
GDM, gestational diabetes; WVU, West Virginia University.

lifestyle factors, parity, history of GDM, or other reproductive characteristics, current BMI, or reported diagnosis of hypertension, diabetes, CVD, metabolic syndrome, apnea, or other chronic conditions associated with both RLS and PIH.

Consistent with the findings of our previous studies in Appalachian adults,[1,52] the prevalence of RLS in this study was high, likely at least, in part, reflecting the elevated rates of obesity, hypertension, diabetes, and other chronic conditions that characterize this population.[1,52] Over 24% of participants met criteria for RLS, with ~12% reporting symptoms three or more times per week. Similarly elevated prevalence rates in women have been reported in some,[62–64] but not other[65–67] U.S. and Western European studies targeting primary care and/or older adult populations and using comparable criteria.[1]

Reported incidence of PIH was also elevated in this sample, with over 16% of parous women indicating a physician diagnosis of preeclampsia or gestational hypertension in at least one pregnancy. The high observed rate of PIH may, in part, reflect the elevated prevalence of major PIH risk factors in WV women, including those comprising our sample. For example, WV mothers, who have among the highest rates of PIH, also have the highest prevalence of prepregnancy obesity, diabetes, and hypertension in the country,[68,69] and among the highest rates of GDM.[70] In addition, West Virginians suffer the highest rates of depression in the nation.[71] These common conditions significantly increase risk for the development of hypertensive disorders of pregnancy.[61,72–76] For example, in three recent large European population-based cohort studies, obesity was associated with a four to over sixfold increase in risk for PIH after adjusting for multiple potential confounders, including glucose tolerance[76,77] and maternal weight gain[27,77]; in one of these investigations, a Spanish cohort study of 9,270 pregnant women, investigators found elevated BMI (>26.1 kg/m^2) to account for 50% of incident PIH.[76]

While underlying causal relationships cannot be ascertained in this cross-sectional study, the positive independent association between RLS and history of PIH observed in this study, along with previously published findings regarding the relationship of RLS to hypertension, glucose intolerance, obesity, and related conditions provide further support for a role of metabolic dysregulation in the etiology of RLS. While hypertensive disorders of pregnancy have been strongly and bidirectionally linked to diabetes, chronic hypertension, CVD, and related disorders,[50,78,79] conditions which are also associated with RLS,[2] controlling for these factors did not materially alter the relationship of PIH history to chronic RLS, suggesting that the observed association of PIH to RLS was not mediated or confounded by these conditions. Similarly, while GDM significantly increases risk for PIH,[59,60] and we recently showed history of GDM to be strongly and positively associated with chronic RLS,[52] adjusting for GDM only slightly attenuated the observed relationship of PIH to RLS in this study. However, other related shared risk factors

could help explain the positive association between PIH and RLS noted in our study. For example, hypertension in pregnancy and the risk factors that often precede it may, in part, reflect underlying sympathetic overactivity and activation of the hypothalamic pituitary adrenal (HPA) axis[80] and, in turn, contribute to the autonomic dysfunction documented in women with prior PIH.[80–82] Autonomic and HPA axis dysfunction have been strongly linked to the pathogenesis of hypertension, diabetes, and related disorders, and more recently implicated in the development of RLS.[2] Other, related metabolic perturbations may also play a role, including elevated oxidative stress, systemic inflammation, subclinical reduction in glucose tolerance, and factors implicated in the pathogenesis of both PIH[45,60,83–85] and, more recently, RLS.[86–89]

Unfortunately, lacking information on the timing of PIH and RLS onset, we cannot rule out the possibility that the onset of RLS may have preceded the development of PIH in some women. However, given that RLS generally develops later in life, with prevalence typically peaking in the 6th decade,[1,3,90] we excluded women under the age of 40, these participants are likely few; moreover, in a recent prospective study of 209 pregnant women, RLS was unrelated to the subsequent development of gestational hypertension,[91] suggesting that reverse causality is unlikely.

Strengths and limitations

Strengths of this survey study include the relatively large number of respondents and the high participation rate in our clinic-based sample. We used well-established international criteria to define RLS[4] and validated questions based on an established diagnostic questionnaire,[56] assessed symptom frequency, and asked specific questions regarding the presence of potential mimics to decrease the risk of misclassification.[6] Information on symptom frequency allowed evaluation of potential dose–response relationships. In addition, comprehensive self-report information was available regarding numerous potential confounding, mediating, and/or modifying factors, including demographic and lifestyle characteristics, mood and sleep patterns, reproductive history, BMI, and multiple health conditions. The survey was presented to potential participants as a study to assess typical sleep patterns and correlates in Morgantown area residents, with no mention of pregnancy complications, RLS, or sleep deficits; thus, participation bias associated with either RLS or pregnancy history, while possible, is not likely.

Limitations of this preliminary survey are also several. The study sample was restricted to older female primary care patients from an Appalachian community, and findings may thus not be generalizable to other populations, including women less likely to make planned healthcare appointments. However, targeting primary care waiting-room populations may also carry certain advantages versus, for example, using a stratified random sample of the general population; these include likely greater response rates and higher health literacy among potential participants, thus potentially reducing the likelihood of selection and misclassification bias.

We did not collect information separately on preeclampsia and gestational hypertension and thus were unable to assess potential differences in the association of RLS to these two hypertensive complications of pregnancy. Moreover, we did not collect data specifically on prepregnancy hypertension; thus, some cases of PIH may include other hypertensive disorders of pregnancy. In addition, given that this was an anonymous survey study, ascertainment of PIH and other medical diagnoses was based on self-report, potentially introducing bias. In particular, some misclassification of PIH is possible. Medical record validation studies in United States, European, and Taiwanese populations have demonstrated high specificity of maternal recall for both preeclampsia (96%–100%) and gestational hypertension (92%–100%), but suggest variable sensitivity for these two hypertensive complications of pregnancy (52%–100% for gestational hypertension; 57%–100% for preeclampsia),[92–94] with estimates appearing unrelated to the length of recall.[92] Thus, while the documented high specificity of maternal recall renders overascertainment of these conditions unlikely in our study, reduced sensitivity could have resulted in underascertainment of PIH, leading to attenuation of the observed associations.

Misclassification of chronic health conditions is also a possibility, although our target population comprised WVU primary care patients, who are more likely to seek and receive medical care and thus to be better informed about their health and medical conditions than a general WV population. While a validation study using medical records showed adequate concordance (74%) and excellent specificity (over 95%) for self-reported diabetes and very high concordance (>99%) for self-reported cancers in a broader Appalachian population in the Ohio valley (unpublished data), self-report of chronic illness has been shown to be vulnerable to misclassification,[95–97] potentially affecting our findings.

We lacked data on certain lifestyle characteristics, including alcohol consumption, which has been positively associated with RLS,[98,99] but inversely associated with PIH[72,100,101] in some studies; omission of this factor from our models may thus have biased the observed estimates toward the null. Although we did have information on diagnosed anemia, we lacked data on blood levels of iron, ferritin, and other analytes potentially related to RLS. However, given that serum levels of iron, ferritin, and related blood markers have been inversely associated with risk for PIH,[102,103] any undetected iron deficiency would be expected to attenuate the observed relationships.

In addition, while we collected general information on medication use for each of multiple specific chronic health conditions, including dyslipidemia, hypertension, depression, and diabetes, we did not collect data on specific medication types or medication use for other serious mental health conditions (*e.g.*, psychosis), which could potentially attenuate (*e.g.*, certain alpha-2 agonists and beta-blockers) or exacerbate (*e.g.*, statins, tricyclic antidepressants, selective serotonin reuptake inhibitors) RLS symptoms.[2,6] However, excluding those taking medication for depression or high cholesterol did not appreciably alter risk estimates nor did adjusting in the models for antihypertensives and other medications, suggesting that the associations observed in this study are not likely explained by medication use. We also lacked data on family history of RLS, an RLS risk factor, which could potentially modify the association between RLS and prior history of PIH. We did not have information on history of transient RLS in pregnancy, a factor recently linked to subsequent risk for chronic RLS.[104] If PIH predisposes to RLS during pregnancy, as suggested in a recent study of Peruvian women,[53] the observed increased risk for chronic

RLS associated with history of PIH may be partially mediated by pregnancy-associated RLS.

Selection bias may have been introduced by exclusion of participants with missing data on covariates. Our findings might also be affected by unmeasured confounding, although this possibility is lessened by our ability to control for a large number of both known and potential confounders. Seven respondents not meeting RLS symptom criteria reported having been diagnosed with RLS. One of the 7 reported taking RLS medications, which may have led to symptom relief. Others may have experienced transient RLS (*e.g.*, associated with pregnancy or prior anemia) or received a diagnosis of RLS in error. Although our study was based on validated questions adapted from an established questionnaire[56] and incorporating questions designed to exclude common mimics, determination of RLS was reliant on self-report of symptoms, and a degree of diagnostic error is thus possible. However, the requirement for positive scores on all four essential criteria, coupled with the absence of discomfort due to leg cramps or positional discomfort, renders misdiagnosis less probable.[6,105]

Similar to most epidemiological investigations of RLS, our findings are based on data gathered during a single time period; therefore, no determination of causality can be made. Prospective studies are needed to confirm these findings and to explore possible causal pathways.

Conclusions

Reported history of PIH was significantly and positively associated with current RLS in this study of older female primary care patients. This relationship remained robust after adjustment for demographic and lifestyle factors, parity, GDM and other reproductive characteristics, BMI, and multiple chronic health conditions. Larger prospective studies are needed to further examine the association of this common pregnancy complication to the development of RLS, to determine potential causal relationships, and to investigate possible underlying mechanisms.

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Author Disclosure Statement

No competing financial interests exist.

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