



The Association of Restless Legs Syndrome to History of Gestational Diabetes in an Appalachian Primary Care Population

Kim E. Innes, MSPH, PhD^{1,2}; Sahiti Kandati, BDS, MPH¹; Kathryn L. Flack, BA^{1,3}; Parul Agarwal, MPH⁴; Terry Kit Selfe, DC, PhD^{1,2}

¹Department of Epidemiology, West Virginia University School of Public Health, Morgantown, WV; ²Center for the Study of Complementary and Alternative Therapies and Department of Physical Medicine and Rehabilitation, University of Virginia Health System, Charlottesville, VA; ³WV Focus: Reproductive Education & Equality, Charleston, WV; ⁴Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, Morgantown, WV

Objective: Restless legs syndrome (RLS) is a burdensome sensorimotor disorder that has been linked to diabetes and obesity. However, the relationship of RLS to gestational diabetes mellitus (GDM), a common pregnancy complication strongly associated with obesity and a harbinger of diabetes, remains unknown. In this study, we examined the association of RLS to history of GDM in a sample of older female primary care patients.

Methods: Participants were community-dwelling women aged ≥ 40 years drawn from an anonymous survey study of West Virginia adult primary care patients. Data gathered included detailed information on demographics, lifestyle factors, reproductive history, sleep patterns, and medical history; the survey also included an RLS diagnostic questionnaire. Women who were pregnant or had missing data on key variables were excluded from the analyses.

Results: Of the 498 participants included in the final analytic sample, 24.5% met diagnostic criteria for RLS (17.9% with symptoms at least once/week). After adjustment for

demographics, lifestyle characteristics, body mass index, diabetes and other comorbid conditions, parity, and other factors, those reporting history of GDM were almost three times as likely to meet criteria for RLS (odds ratio [OR] = 2.7, 95% confidence interval [CI] = 1.3, 5.3). This association increased in magnitude with increasing symptom frequency (adjusted OR for RLS symptoms ≥ 3 ×/week = 4.8, CI 2.1, 11.2, p for trend = 0.004).

Conclusions: History of GDM was strongly and positively related to RLS in this study of older female primary care patients, offering further support for a possible role of metabolic dysregulation in RLS development.

Keywords: gestational diabetes, metabolic syndrome, pregnancy complications, restless legs syndrome, sleep, Willis-Ekbom disease

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BRIEF SUMMARY

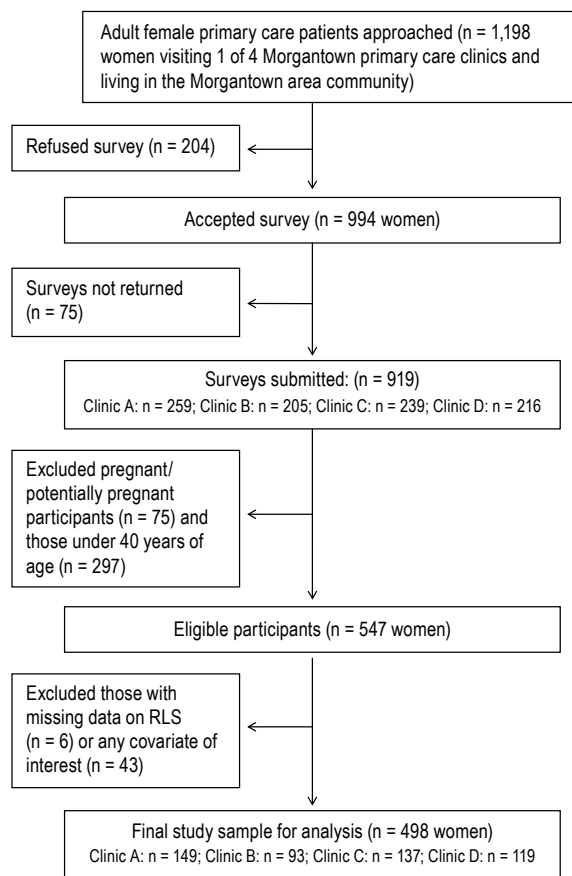
Current Knowledge/Study Rationale: Restless legs syndrome (RLS) is a burdensome sensorimotor disorder with prevalence rates that are higher in women and further elevated during pregnancy. Although the etiology of RLS remains unclear, RLS has been associated with diabetes, obesity, and related chronic conditions, suggesting a possible role of metabolic dysregulation. However, the relationship of RLS to history of gestational diabetes (GDM), a common pregnancy complication strongly linked to obesity and a harbinger of diabetes, remains unknown.

Study Impact: In this study of older female primary care patients, prior history of GDM was strongly and positively related to RLS, offering further support for a possible role of metabolic dysregulation in RLS development. Better understanding regarding the factors underlying the etiology and progression of RLS will aid in identifying cost-effective treatments for this challenging and still incurable condition.

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a burdensome sleep disorder affecting an estimated 10–15% of the general adult population, and up to 20% of primary care patients in the United States and Western Europe.^{1–3} RLS is characterized by an irresistible urge to move the legs that is typically accompanied by distressing, often painful sensations in the legs, begins or worsens during periods of inactivity, is worse during the evening and nighttime hours, and is partially or totally relieved by movement.⁴ Recently a fifth criterion has been added, stating that symptoms cannot be caused solely by another condition (e.g., leg cramps, positional discomfort).⁵ RLS can have profound negative effects on quality of life and daily functioning, comparable to those reported in other serious disorders, and is associated with significant economic, social, and health care burdens.^{6–10}

Although the etiology of RLS remains unclear, recent studies suggest that metabolic dysregulation may play an important role.² RLS has been significantly associated with diabetes, obesity, and other conditions characterized by insulin resistance and/or glucose intolerance and linked to the metabolic

syndrome,² although the direction of these relationships remains unclear. RLS is also more common in women and during pregnancy, and is positively associated with parity (a factor in turn linked to increased risk for obesity),^{11,12} insulin resistance, and glucose intolerance,¹³ suggesting that pregnancy-related

Figure 1—Study flow diagram.

metabolic changes may increase risk for RLS in women. One established gestational marker of metabolic dysfunction is gestational diabetes mellitus (GDM), a common complication of pregnancy that affects 2–14% of pregnancies in the United States, and that continues to increase in prevalence globally.^{14,15} GDM is a powerful predictor of the subsequent development of type 2 diabetes and the metabolic syndrome in women, and thus may be considered an early marker for these chronic insulin resistance conditions.^{16,17} For example, in a recent meta-analysis of 20 prospective studies, women with a history of GDM were at 7.5-fold increased risk overall for the development of type 2 diabetes.¹⁸ GDM has likewise been shown to be a strong predictor of the metabolic syndrome,^{17,19–21} with risk estimates ranging from threefold¹⁹ to more than fivefold.²⁰ However, although several studies have examined risk factors for RLS during pregnancy,^{22–26} as well as pregnancy-related risk factors for RLS in nonpregnant women,^{27–29} no studies to our knowledge have yet examined the relationship of RLS to history of GDM. In this study, we examined the association of RLS to history of GDM 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 adults visiting one of four Morgantown area primary care clinics affiliated with the West Virginia University (WVU) Health Sciences Center. We restricted our sample to women at least 40 years of age to reduce likelihood of including women with undetected pregnancy or early-onset RLS,^{30–32} which is thought by some to differ in etiology from late-onset RLS.^{30,32}

Survey methods are described elsewhere in detail.³ Briefly, surveys were offered to each adult patient in the clinic waiting area. Those who wished to participate but were unable to read were assisted by research staff. The survey was presented as a study regarding sleep habits in adults, including both those who slept well and those who did not. Over a period of 12 weeks, surveys were distributed during 3- to 4-hour time blocks. Survey administration times were systematically rotated in each clinic, to ensure similar coverage across clinics and reduce the probability of selection bias based on timing of survey administration. Overall survey response rates were excellent, with 919 of 1,198 women (76.7%) returning completed surveys to the drop box provided.³ The survey, consisting of 41 self-report items, required 5–10 minutes to complete. Detailed information was gathered regarding: demographic characteristics; lifestyle; current height and weight; history of physician diagnosed chronic mental and physical health conditions, current medications for these conditions; sleep duration and quality during the past 7 days; and reproductive history, including history of gestational diabetes. This anonymous survey study was approved by the West Virginia University Institutional Review Board.

As illustrated in **Figure 1**, excluding women who were pregnant ($n = 65$), unsure about their pregnancy status ($n = 10$), or aged less than 40 years ($n = 297$) left a sample of 547 eligible adult female primary care patients. Exclusion of those with missing data on RLS symptoms ($n = 6$, 1.1%) or on pregnancy history, demographics, lifestyle characteristics, and other covariates of interest ($n = 43$, 9.0%), yielded a final analytic sample of 498 female primary care patients. Participants with missing data were more likely to be older (62.9 ± 2.0 versus 56.9 ± 0.5 y, $p = 0.001$); they were less likely to: be college graduates (8% vs. 31%, $p = 0.0001$), be physically active at least 1 h/w (29.0% versus 48.7%, $p = 0.03$), and report an annual income over \$25,000 (31% versus 74%, $p < 0.001$) 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 health profiles, sleep patterns, reproductive history, prevalence of RLS, or other factors ($p > 0.1$).

Measurement of Outcomes, Indices of Burden, and Major Covariates

Ascertainment of RLS

RLS, the primary outcome of interest, was assessed using a previously validated seven item questionnaire³ adapted from the self-completed Cambridge-Hopkins diagnostic questionnaire (CH-RLSq)³³ and designed to capture the four International Restless Legs Syndrome Study Group's (IRLSSG) diagnostic criteria in effect at the time of the study,⁴ determine presence of accompanying unpleasant sensations, and exclude

common RLS mimics (e.g., positional discomfort, leg cramps). The seven questions were as follows: (1) “Do you ever have an urge to move your legs that is difficult to resist?”; If *YES*: (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?”; and (7) “Does the urge to move or the unpleasant sensations only occur or get worse in the evening or night?” An eighth item questioned RLS symptom frequency: “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). To be classified as RLS required an affirmative response to all four RLS diagnostic questions (#1, 5–7, above) and a negative response to questions 2 and 4. Because unpleasant sensations often accompany RLS symptoms, but are not an essential diagnostic criterion for RLS,⁴ we analyzed the prevalence and correlates of RLS with unpleasant sensations separately. Another section of the survey also asked participants if they had received a physician diagnosis of RLS and/or were taking medications for RLS.

Demographic and Lifestyle Characteristics

Information regarding demographic characteristics was collected via self-report survey questions, and included age, sex, race/ethnicity, education (< 12 years, high school graduate, some college, ≥ 4 years post high school [college graduate]), employment status (employed, unemployed/out of work, homemaker, retired, student, disabled), marital status (single, married or cohabiting, widowed, divorced), and annual household income (< \$25,000, \$25,000–50,000, \$50–75,000, > \$75,000). Lifestyle factors assessed included smoking history and current smoking status (five items), participation in physical activity (two items), and caffeine consumption (two items).

Reproductive History, Including GDM and Other Health-Related Factors

Reproductive history was assessed via self-report survey questions. History of GDM was scored as positive 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 diabetes?” Information was also gathered on menopausal status (one item), previous and current use of hormone replacement therapy (two items), current pregnancy status (one item), gestational hypertension/preeclampsia (one item), and parity (completed pregnancies, two items).

Obesity was defined as body mass index (BMI) ≥ 30, with BMI calculated as (weight in kg/height in m²). History of a specific chronic health disorder (including diabetes, anemia, hypertension, high cholesterol, heart disease, stroke, kidney disease, osteoarthritis, rheumatoid arthritis, and other serious conditions) was ascertained via self-report and defined as reported physician diagnosis of, and/or currently taking prescription medications for this disorder; depression and

sleep apnea were ascertained in a similar fashion. Metabolic syndrome was defined as the presence of at least three of the four following conditions: diabetes, hypertension, obesity, and high cholesterol. Sleep patterns were assessed using six questions adapted from items designed to evaluate sleep quality and duration and included in the 2005–2006 National Health and Nutrition Examination Survey (NHANES) cycle.^{3,34} Five survey items ascertained 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 five-item scale, as described in detail elsewhere, has been shown to be both reliable and useful.³ An additional, open-ended question was used to ascertain sleep duration (in hours and minutes) during the past week.

Analysis

All data were analyzed using IBM SPSS version 21. Potential differences between participants with and without missing data were evaluated using the Student t-test or Mann-Whitney *U* test for continuous or ordinal variables, and χ^2 test for categorical variables. We used multiple logistic regression to determine the independent association of RLS to history of GDM, and to assess the influence of potential confounders and effect modifiers; linear trends were assessed using polynomial contrasts. Unless stated otherwise, multivariable models were adjusted for demographic factors and lifestyle characteristics, as well as BMI, reproductive history (menopause, parity, use of hormone replacement therapy [HRT]) and comorbid conditions, including anemia, kidney disease, heart conditions, hypertension, high cholesterol, arthritis, stroke, and diabetes. Additional analyses also adjusted for cancer, sleep apnea, and depression. All p values presented are two-sided. We also assessed the joint effects of GDM and specific common chronic conditions associated with both RLS and GDM, including obesity, diabetes, and the metabolic syndrome.

In addition, we also conducted several sensitivity analyses to assess the robustness of the observed associations. We restricted RLS cases to those also reporting unpleasant sensations and examined the association of GDM to RLS severity, as indicated by frequency of reported symptoms (no RLS (referent category), RLS with symptoms less than once a week, RLS with symptoms one to two times a week, and RLS with symptoms at least three times a week). We also conducted analyses excluding participants with a history of kidney disease, anemia, stroke, neurological conditions, and diabetes and performed additional analyses excluding patients on medications that might influence RLS symptoms, including those for depression and high cholesterol.

RESULTS

Study population characteristics by RLS status are presented in **Table 1**. Participants were predominantly non-Hispanic white (92%), and married or cohabiting (67%). Only 31% had completed at least 4 years of college, and approximately 50% reported an annual household income of less than \$50,000. Almost 75% of the women were perimenopausal or postmenopausal, 23% reported taking HRT for more than 6

months at some point in their lives, and 9% were nulliparous. Seventy-five percent of participants reported at least one comorbid health condition, with over 52% reporting at least two comorbid conditions, and approximately one third reporting three or more comorbid disorders (**Table 1**). As indicated in **Table 2**, reported sleep impairment was high in this population, with 48% of women surveyed indicating sleep problems daily, and almost one-third reporting an average of less than 5 hours of sleep per night. Prevalence of several chronic conditions was also elevated in this sample, including obesity (43.8%), diabetes (20.8%), hypertension (48.7%), high cholesterol (40.7%), metabolic syndrome (23.6%), arthritis (26.5%), sleep apnea (9.1%), and depression (29.3%).

Of the 498 women included in this analysis, 45 (9%) reported a history of GDM. One hundred twenty-two participants (24.5%) met the four IRLSSG diagnostic criteria and did not report symptoms due to leg cramps or positional discomfort; of the 122 respondents with RLS, 73% (17.9% of total participants) reported experiencing symptoms at least once a week, and 24.6% (11.9% total participants) indicated symptoms three or more times a week. Of the 107 respondents with RLS who also reported unpleasant sensations, 64% indicated symptoms at least once a week, and 49.5% reported symptoms three or more times a week. Only 41 of those women meeting criteria for RLS (33.6%) had received a physician diagnosis, of whom 18 (14.8%) were on RLS medications.

Participants with RLS were more likely to be unemployed or disabled and less likely to be college-educated and from minority populations after adjustment for other demographic and lifestyle factors (**Table 1**). After adjustment for other factors, RLS also remained significantly and positively related to both parity and comorbidity, with likelihood of RLS rising with increasing number of completed pregnancies, and rising number of comorbid conditions. As indicated in **Table 2**, those with obesity, diabetes, or the metabolic syndrome were also more likely to meet criteria for RLS (adjusted ORs, respectively = 1.7, 95% confidence interval [CI] 1.1, 2.6; 2.0, CI 1.3, 3.3; and 1.7, CI 1.1, 2.8), as were women who indicated a history of sleep apnea or depression (adjusted ORs, respectively = 2.7, CI 1.4, 5.1 and 1.5, CI 1.0, 2.4). Relative to those without RLS, participants with RLS were significantly more likely to report sleeping less than 5 hours per night (adjusted OR = 1.7, CI 1.1, 2.7), and to indicate sleep problems at least 4 days per week (adjusted OR = 2.0, CI 1.1, 3.7), as well as daily sleep problems (adjusted OR = 1.6, CI 1.0, 2.4).

As illustrated in **Table 3**, reported history of GDM was associated with significantly increased likelihood of RLS in this population. Women who indicated a prior diagnosis of GDM were more than three times as likely to meet criteria for RLS (OR adjusted for demographic and lifestyle characteristics = 3.1, CI 1.6, 6.1). Further adjustment for BMI, reproductive history, and comorbid conditions including diabetes and anemia only slightly attenuated this association (OR = 2.7, CI 1.3, 5.3). The association of GDM to RLS increased in magnitude with rising RLS severity; GDM was associated with an approximately fivefold increase in risk for RLS with symptoms at least three times a week (OR = 4.8, CI 2.1, 11.8, p for trend = 0.004). As indicated in **Table 3**, restricting the analysis to RLS cases accompanied by unpleasant sensations ($n = 107$)

slightly strengthened the association of RLS to GDM (adjusted OR = 3.0, CI 1.5, 6.2; adjusted OR for symptoms three or more times a week = 5.0, CI 2.1, 11.8)).

Sensitivity analyses: Additional adjustment for depression and sleep apnea did not alter the relation with RLS (OR = 2.7, CI 1.4, 5.3), nor did inclusion of diagnosed cancer in the full model (OR = 2.8, CI 1.4, 5.5). Likewise, additional adjustment for sleep impairment or gestational hypertension/preeclampsia did not appreciably change the relation of GDM to RLS (ORs, respectively = 2.9, CI 1.5, 5.8 and 2.6, CI 1.2, 4.9). Excluding women with a history of kidney disease, anemia, stroke, neurological conditions, sleep apnea, or diabetes did not materially alter these findings, nor did including as RLS cases the seven 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 alter risk estimates (adjusted OR = 2.8, CI 1.4, 5.4), nor did specifically adjusting for antihypertensive and other medications in the model (adjusted OR = 2.7, CI 1.4, 5.2).

We found no evidence of significant interaction by obesity status, or by presence of diabetes, metabolic syndrome, hypertension, or high cholesterol ($p > 0.1$). As illustrated in **Table 4**, GDM remained strongly related to RLS even in the absence of obesity, diabetes, or the metabolic syndrome. However, the combination of prior GDM with any one of these conditions appeared to further increase the likelihood of RLS, suggesting these factors may have an additive effect on RLS risk.

DISCUSSION

Literature regarding RLS and pregnancy complications remains sparse. A recent cross-sectional study of 79 Peruvian women during the peripartum period documented a higher prevalence of preeclampsia in mothers with RLS,³⁵ although findings were based on small numbers and estimates were not adjusted for GDM, chronic hypertension, diabetes, or certain other conditions linked to increased risk for the development of RLS and/or preeclampsia.^{36–38} Moreover, the relation of chronic RLS to history of any pregnancy complication, including GDM, has not been explored in depth.

To our knowledge, this is the first study to examine the association of RLS to history of GDM. In brief, findings of this study in older female primary care patients suggest that prior history of GDM is strongly and positively related to RLS. In this population, women who reported a history of GDM were approximately three times as likely to meet criteria for RLS, and five times as likely to experience RLS symptoms at least three times per week. This relationship was not explained by demographic or lifestyle factors, parity and other reproductive characteristics, current BMI, or by reported history of diabetes, metabolic syndrome, apnea, or other comorbid conditions.

Consistent with our findings, most, although not all, prior studies assessing the association of RLS to diabetes have suggested a positive relationship between these conditions, with risk estimates ranging from 1.6 to 4.7.² In addition, two of the three studies evaluating the association of RLS to measures of glucose tolerance in adults without diabetes reported strongly increased likelihood of impaired glucose tolerance and elevated glycemia levels in those with RLS relative to those

Table 1—Demographic, lifestyle, reproductive, and health-related characteristics in 498 nonpregnant women ≥ 40 y of age attending 1 of 4 primary care clinics, stratified by RLS.

	All		No RLS (n = 376)		RLS (n = 122)		Adjusted OR (95% CI)*	p**
	n	%	n	%	n	%		
Demographic Characteristics								
Age (y)								0.55
40–49	150	30.12%	114	30.32%	36	29.51%	1.00 (Referent)	–
50–59	166	33.33%	121	32.18%	45	36.89%	1.20 (0.91,2.00)	0.25
60–69	117	23.49%	90	23.94%	27	22.13%	0.91 (0.50,1.66)	0.77
≥ 70	65	13.05%	51	13.56%	14	11.48%	0.79 (0.37,1.70)	0.54
Mean (SE)	56.96	(0.49)	57.07	(0.57)	56.37	(0.94)		0.65
Race/ethnicity								0.05
Non-Hispanic White	456	91.57%	339	90.16%	117	95.90%	1.00 (Referent)	
Minority	42	8.43%	37	9.84%	5	4.10%	0.37 (0.14,1.00)	
Marital status								0.22
Married/cohabiting	332	66.67%	249	66.22%	83	68.03%	1.00 (Referent)	–
Widowed/separated/divorced	141	28.31%	104	27.66%	37	30.33%	1.52 (0.83,2.78)	0.16
Single, never married	25	5.02%	23	6.12%	2	1.64%	0.35 (0.08,1.58)	0.17
Years of education								0.08
≤ 12 y	173	34.74%	122	32.45%	51	41.80%	1.00 (Referent)	–
Some college/technical school	170	34.14%	126	33.51%	44	36.07%	0.88 (0.54,1.43)	0.60
≥ 4 y college	155	31.12%	128	34.04%	27	22.13%	0.58 (0.33,1.00)	0.05
Current employment status								0.18
Employed/student	236	47.39%	183	48.67%	53	43.44%	1.00 (Referent)	–
Homemaker	48	9.64%	36	9.57%	12	9.84%	0.87 (0.40,1.91)	0.73
Retired	133	26.71%	105	27.93%	28	22.95%	0.89 (0.46,1.72)	0.74
Unemployed/laid off/disabled	81	16.27%	52	13.83%	29	23.77%	1.63 (0.95, 2.88)	0.07
Average household income								–
< \$25,000	118	23.69%	83	22.07%	35	28.69%	1.00 (Referent)	–
\$25,000–\$49,999	134	26.91%	100	26.60%	34	27.87%	0.91 (0.54,1.63)	0.76
\$50,000–\$74,999	100	20.08%	75	19.95%	25	20.49%	0.93 (0.48,1.77)	0.75
≥ \$75,000	107	21.49%	88	23.40%	19	15.57%	0.63 (0.31,1.19)	0.15
Don't know	39	7.83%	30	7.98%	9	7.38%	1.02 (0.46, 1.89)	0.75
<i>p for trend</i>								0.34
Lifestyle Characteristics								
Smoking Status								0.70
Never	284	57.03%	216	57.45%	68	55.74%	1.00 (Referent)	–
Former	134	26.91%	100	26.60%	34	27.87%	1.00 (0.61,1.65)	0.99
Current	77	15.46%	57	15.16%	20	16.39%	0.78 (0.40,1.45)	0.41
Unsure	3	0.60%	3	0.80%	0	0.00%	0.99 (0.37,1.98)	0.95
Exercise at least 1 h/w								0.91
Yes	212	42.57%	156	41.49%	56	45.90%	1.00 (Referent)	–
No	204	40.96%	158	42.02%	46	37.70%	0.93 (0.58, 1.48)	0.76
Unsure	82	16.47%	62	16.49%	20	16.39%	0.88 (0.48,1.62)	0.41
Drink at least five 8 oz caffeinated beverages/week								0.67
No	117	23.49%	90	23.94%	27	22.13%	1.00 (Referent)	–
Yes	381	76.51%	286	76.06%	95	77.87%	1.12 (0.67,1.86)	0.70
Reproductive History[†]								
Perrimenopause or postmenopause								–
No	122	24.50%	93	24.73%	29	23.77%	1.00 (Referent)	–
Yes	364	73.09%	275	73.14%	89	72.95%	1.25 (0.70,2.25)	0.46
Unsure	12	2.41%	8	2.13%	4	3.28%	1.10 (0.67,2.21)	0.52
Hormone Replacement Therapy								0.18
Current	28	5.62%	17	4.52%	11	9.02%	1.79 (0.76,4.22)	0.18
Ever (for > 6 mo)	114	22.89%	88	23.40%	26	21.31%	0.88 (0.49,1.59)	0.68
Number of completed pregnancies								0.25
None	46	9.24%	41	10.90%	5	4.10%	1.00 (Referent)	–
One or more	439	88.15%	324	86.17%	115	94.26%	0.56 (0.21,1.51)	0.25
Unsure	13	2.61%	11	2.93%	2	1.64%	0.88 (0.37,2.14)	0.45
Mean number (SE)			2.43	(0.97)	2.82	(0.14)		0.04
Per pregnancy increment							1.17 (1.02,1.35)	0.02
Comorbidity								
Comorbid Condition(s) [‡]								0.01
No	124	24.90%	103	27.39%	21	17.21%	1.00 (Referent)	–
Yes	374	75.10%	273	72.61%	101	82.79%	1.90 (1.07,3.39)	–
Number of comorbid conditions								0.13
None	124	24.90%	103	27.39%	21	17.21%	1.00 (Referent)	–
One	112	22.49%	84	22.34%	28	22.95%	1.68 (0.95,3.30)	0.13
Two	101	20.28%	76	20.21%	25	20.49%	1.70 (0.96,3.48)	0.09
Three or more	161	32.33%	113	30.05%	48	39.34%	2.30 (1.20,4.40)	0.01
<i>p for trend</i>								0.06
<i>Per single disorder increment</i>							1.20 (1.05,1.38)	0.007

*Adjusted for other sociodemographic and lifestyle factors in table. **All p values are two-sided. †Also adjusted for other reproductive characteristics. ‡Reported physician diagnosis of anemia, hypertension, high cholesterol, heart disease, stroke, kidney disease, diabetes, osteoarthritis, rheumatoid arthritis, lung disease, or other serious chronic condition. CI, confidence interval; OR, odds ratio; SE, standard error.

Table 2—Prevalence of sleep impairment and specific health conditions in 498 nonpregnant women ≥ 40 y of age attending 1 of 4 primary care clinics, stratified by restless legs syndrome status.

	Total %	No RLS % (n = 376)	RLS % (n = 122)	Odds Ratio*	95% CI Lower	95% CI Upper	p**
Sleep impairment							
Sleep disturbance at least 4 d/w [†]	75.46%	72.48%	84.43%	2.04	1.13	3.66	0.02
Sleep disturbance 7 d/w [†]	47.94%	44.78%	57.38%	1.56	1.00	2.43	0.05
Average sleep duration < 5 h/night	32.03%	28.61%	42.50%	1.74	1.11	2.73	0.02
Comorbid conditions							
Obesity (BMI ≥ 30)	43.78%	40.52%	53.39%	1.68	1.08	2.62	0.02
Diabetes	20.77%	17.62%	30.33%	2.04	1.25	3.34	0.005
Hypertension	48.68%	47.15%	53.28%	1.40	0.90	2.18	0.13
High cholesterol	40.73%	39.30%	45.08%	1.31	0.83	2.04	0.24
Metabolic syndrome	23.61%	20.98%	31.36%	1.73	1.05	2.83	0.03
Kidney disease	3.05%	2.44%	4.92%	2.02	0.68	5.98	0.21
Arthritis	26.48%	24.93%	31.15%	1.42	0.87	2.32	0.16
Stroke	2.85%	2.98%	2.46%	0.70	0.19	2.58	0.59
Anemia	14.05%	12.74%	18.03%	1.47	0.83	2.58	0.19
Parkinson disease or other neurological condition	6.11%	5.69%	7.38%	1.15	0.49	2.74	0.75
Sleep apnea	9.11%	6.61%	16.67%	2.66	1.39	5.07	0.003
Depression	29.33%	26.83%	36.89%	1.52	0.97	2.39	0.07

*Adjusted for demographics and lifestyle factors. **All p values are 2-sided. [†]Sleep disturbance defined as difficulty falling asleep, difficulty staying asleep, awakening too early, daytime sleepiness, and/or insufficient rest. CI, confidence interval.

without RLS,^{39–41} suggesting that RLS can precede the development of diabetes.²

The prevalence of RLS was high in this sample of older women, consistent with findings of our previously published study³ and likely at least in part reflecting the elevated rates of obesity, diabetes, and other chronic conditions characterizing this Appalachian population.^{2,3} Approximately 18% of participants met criteria for RLS and reported symptoms at least once a week, with 11.9% indicating symptoms at least three times a week. Unfortunately, direct comparisons of RLS prevalence across studies are challenging due to variation in RLS diagnostic criteria, definition of clinically significant RLS, and characteristics of target populations.^{1,2} Nonetheless, the prevalence of RLS observed in this study was higher than that reported in most,^{42–44} although not all^{41,45,46} prior studies of Western primary care and older adult populations that used similar criteria and/or clinical confirmation to define RLS.¹

Reported incidence of GDM was also elevated in this population, paralleling the high rates of obesity, inactivity, diabetes, and related chronic conditions in West Virginia adults.^{2,47–49} As has been repeatedly documented in previous studies,^{2,3,50,51} RLS was positively associated with both depression and sleep impairment in this sample of older women. Those with sleep apnea were also more likely to meet criteria for RLS, as has been reported in other populations.^{41,52,53}

Consistent with prior investigations, multiparity was significantly and positively associated with RLS in this study. Parity has been associated with RLS^{24,28,29,54–56} and with RLS symptom severity⁵⁷ in both pregnant^{24,54,55} and nonpregnant women.^{28,29,56} Although multiparity has also been related to increased risk for GDM⁵⁸ and for obesity,^{11,12} also a strong risk

factor for GDM, parity did not explain the association of RLS to GDM in this study. Similarly, although obesity, the metabolic syndrome, and diabetes are strongly linked to GDM,^{18,58} and were significantly associated with RLS in this population, adjustment for these factors only slightly attenuated the observed association of RLS to GDM.

Although underlying causal relationships cannot be determined in this cross-sectional study, the robust, independent positive association observed between RLS and history of GDM, coupled with previously published findings regarding glucose intolerance and RLS, provide further support for a role of metabolic dysregulation in the etiology of RLS. Glucose intolerance may in part reflect underlying activation of the hypothalamic pituitary adrenal (HPA) axis and contribute to the autonomic dysfunction documented in women with prior GDM.^{59,60} HPA axis and autonomic dysfunction have, in turn, been strongly linked to the pathogenesis of diabetes and related disorders, and more recently implicated in the development of RLS.² Unfortunately, we lacked information on the timing of GDM and RLS onset, and thus cannot preclude the possibility that in some women, RLS may have preceded the development of GDM. However, these participants are likely few, given that we excluded women younger than 40 years and that RLS generally develops later in life, with prevalence typically peaking in the sixth decade, as has been previously documented in this and other populations.^{1,3,61}

Strengths and Limitations

Strengths of this clinic-based survey study include the high study participation rates and the relatively large number of participants in our sample. Established international criteria to

Table 3—Association of history of gestational diabetes mellitus to restless legs syndrome and restless legs syndrome severity in 498 nonpregnant women ≥ 40 y of age attending 1 of 4 WVU primary care clinics.

Association of History of GDM to RLS*	Likelihood of Meeting Criteria for RLS	
	Odds Ratio (95% CI)	p**
Including all RLS cases (n = 122)		
Overall		
Crude	2.99 (1.60,5.59)	< 0.001
Adjusted for demographic, lifestyle factors [†]	3.14 (1.62,6.10)	< 0.001
Also adjusted for BMI, diabetes, and other comorbid conditions ^{††}	2.64 (1.34,5.20)	0.005
Also adjusted for reproductive characteristics ^{†††}	2.65 (1.32,5.32)	0.006
By frequency of RLS symptoms ^{***}		
Less than once/week	1.34 (0.36,5.00)	0.66
1–2 times/week	1.45 (0.37,5.57)	0.59
3 or more times/week	4.84 (2.08,11.22)	0.0002
<i>p for trend</i>		0.004
Including only RLS cases accompanied by unpleasant sensations (n = 107)		
Overall		
Crude	3.31 (1.75,6.26)	0.0002
Adjusted for demographic, lifestyle factors [†]	3.56 (1.79,7.06)	0.0003
Also adjusted for BMI, diabetes, and other comorbid conditions ^{††}	3.03 (1.51,6.09)	0.002
Also adjusted for reproductive characteristics ^{†††}	2.99 (1.45,6.16)	0.003
By frequency of RLS symptoms ^{***}		
Less than once/week	1.47 (0.39,4.59)	0.56
1–2 times/week	2.13 (0.54,8.44)	0.28
3 or more times/week	4.95 (2.08,11.77)	0.0003
<i>p for trend</i>		0.004

*Referent category is no reported history of GDM. **All p values are 2-sided. [†]Demographic characteristics include age, sex, race/ethnicity, marital status, education, occupation, and annual family income; lifestyle factors include smoking status, physical activity, and caffeine consumption. ^{††}Including reported physician diagnosis of anemia, hypertension, high cholesterol, heart disease, stroke, kidney disease, osteoarthritis, rheumatoid arthritis, lung disease, or other serious chronic condition. ^{†††}Including menopausal status, parity, and history of hormone replacement therapy. ***Adjusted for demographics, lifestyle factors, BMI, and comorbid conditions. BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; RLS, restless legs syndrome.

define RLS⁴ and validated questions based on an established diagnostic questionnaire³³ were used; we also collected information on symptom frequency, and asked specific questions regarding the presence of potential mimics to reduce risk of misclassification.⁶² Symptom frequency data allowed evaluation of potential dose-response associations. In addition, participants provided comprehensive self-report information on numerous potential correlates and confounders, including demographic and lifestyle characteristics, mood and sleep patterns, medical and reproductive history, and other health-related factors. The survey was presented as a study to examine typical sleep patterns and correlates in Morgantown area residents, with no mention of sleep deficits, pregnancy complications, or RLS; thus, participation bias associated with either RLS or pregnancy history, while possible, is unlikely.

Limitations of this pilot survey are also several. Our sample was restricted to older female primary care patients from a predominantly Appalachian community. Therefore, findings may not be generalizable to other populations. We did not collect data on alcohol consumption, which has been positively associated with RLS^{53,63} but inversely associated with GDM in some studies. We also lacked data on blood levels of hemoglobin, ferritin, and other analytes potentially related to

RLS, although we did have information on diagnosed anemia. However, iron-deficiency anemia has been negatively associated, and elevated serum levels of hemoglobin, ferritin, and related blood markers positively linked to GDM^{64,65}; thus, any undetected iron deficiency would be expected to attenuate the observed relationships. In addition, although we collected information on medication use for a number of specific chronic health conditions, including depression, anxiety, hypertension, dyslipidemia, and others, we did not gather data on specific medication types or on medication use for some uncommon but serious mental health conditions (e.g., schizophrenia or psychosis), which could potentially exacerbate (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, statins) or attenuate RLS symptoms (e.g., certain beta-blockers and alpha-2 agonists).^{2,62} However, excluding those on medication for high cholesterol or depression did not appreciably alter risk estimates, nor did specifically adjusting for antihypertensive, antidepressant, and other medications, suggesting that medication use is unlikely to explain the associations observed in this study. Finally, we did not have information on family history of RLS, an RLS risk factor that could potentially modify the association between RLS and prior history of GDM. We also lacked data on history of transient RLS in pregnancy, a

Table 4—Association of restless legs syndrome to history of gestational diabetes mellitus alone and in combination with diabetes, obesity, and the metabolic syndrome in 498 nonpregnant women ≥ 40 y of age attending 1 of 4 WVU primary care clinics.

Association of History of GDM to RLS (n = 122 RLS cases)	Likelihood of Meeting Criteria for RLS	
	Odds Ratio (95% CI) [†]	p*
History of GDM, by Diagnosis of Diabetes		0.001
No GDM, no diabetes	1.00 (referent)	
GDM only (no diabetes)	2.23 (0.92,5.41)	0.07
Diabetes only (no history of GDM)	1.66 (0.91,3.01)	0.09
History of both GDM and diabetes	4.65 (1.76,12.27)	0.002
<i>p for interaction</i>		0.55
History of GDM, by Obesity		0.003
No GDM, no obesity	1.00 (referent)	
GDM only (no obesity)	3.45 (1.27,9.35)	0.015
Obesity only (no history of GDM)	1.68 (1.03,2.72)	0.04
Both obesity and history of GDM	4.12 (1.39,12.18)	0.01
<i>p for interaction</i>		0.73
History of GDM, by Metabolic Syndrome		0.003
No GDM, no metabolic syndrome	1.00 (referent)	
GDM only (no metabolic syndrome)	3.05 (1.37,6.79)	0.006
Metabolic syndrome only (no history of GDM)	1.63 (0.95,2.80)	0.07
Both metabolic syndrome and history of GDM	4.42 (1.82,10.71)	0.001
<i>p for interaction</i>		0.72

[†]Adjusted for demographics, lifestyle characteristics, and BMI. *All p values are 2-sided. CI, confidence interval; GDM, gestational diabetes mellitus; RLS, restless legs syndrome.

factor recently linked to subsequent risk for chronic RLS.²⁷ If GDM predisposes to RLS during pregnancy, pregnancy-associated RLS may in part mediate the observed increased risk for chronic RLS associated with history of GDM.

Exclusion of participants with missing data on covariates may have introduced selection bias. Unmeasured confounding might also help explain our findings, although our ability to control for a large number of both known and potential factors linked to GDM and RLS renders this possibility less probable. Seven respondents reporting a physician diagnosis of RLS did not meet symptom criteria. Some of these participants may have experienced RLS, for example, only during pregnancy or in association with prior anemia, and others may have been misdiagnosed. One of the seven also reported taking RLS medications, which may have led to symptom relief. Although based on validated questions adapted from an established questionnaire³⁵ and incorporating questions designed to exclude common mimics, ascertainment of RLS was reliant on self-report; some measure of diagnostic error is thus possible. However, requiring an affirmative response to all four essential criteria, along with absence of discomfort due to leg cramps or positional discomfort, renders misdiagnosis less likely.^{62,66} Ascertainment of GDM and other medical diagnoses was based on self-report, potentially introducing bias. Although our target population comprised WVU primary care patients, who are more likely to seek and receive medical care and thus may be better informed about their health and medical conditions than a general West Virginia population, misclassification remains possible. A validation study of a broader Appalachian

population in the Ohio valley using medical records showed adequate concordance (74%) and excellent specificity (more than 95%) for self-reported diabetes, and very high concordance (> 99%) for self-reported cancers (unpublished data). Nonetheless, self-report of chronic illness has been shown to be vulnerable to misclassification,^{67–69} potentially influencing our findings.

As in most other epidemiological studies of RLS, our findings, while suggestive, are based on cross-sectional data, precluding determination of causality. Clearly, prospective studies are needed to confirm these findings, to investigate potential causal associations, and to explore possible underlying mechanisms.

CONCLUSIONS

Prior history of GDM was strongly and positively related to RLS in this study of older female primary care patients. This association remained robust after adjustment for demographic and lifestyle factors, parity and other reproductive characteristics, current BMI, and diabetes, anemia, and other comorbid conditions. Larger prospective studies are needed to further investigate the relationship of this common pregnancy complication to the development of RLS, and to determine possible causal pathways.

ABBREVIATIONS

BMI, body mass index
CH-RLSq, Cambridge-Hopkins diagnostic questionnaire
CI, confidence interval

GDM, gestational diabetes mellitus
 HRT, hormone replacement therapy
 IRLSSG, International Restless Legs Syndrome Study Group
 NHANES, National Health and Nutrition Examination Survey
 OR, odds ratio
 RLS, restless legs syndrome

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Address correspondence to: Kim E. Innes, MSPH, PhD, Department of Epidemiology, West Virginia University School of Public Health, PO Box 9190, Morgantown, WV 26506; Tel: (304) 293-5206; Fax: (304) 293-2700; Email: KInnes@hsc.wvu.edu

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