



Physical activity, sedentary behavior, and restless legs syndrome in persons with multiple sclerosis

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ABSTRACT

The present study examined the relationships among parameters (i.e., volume and pattern) of physical activity and sedentary behavior with the presence and severity of restless legs syndrome (RLS) in adults with multiple sclerosis (MS). Participants with MS ($N = 253$) wore an accelerometer for a 7-day period and completed the Cambridge-Hopkins Restless Legs Syndrome Questionnaire, the International Restless Legs Syndrome Study Group Scale (IRLS), and the Patient Determined Disease Steps scale. Sixty-six (26%) persons with MS had RLS (MS + RLS). There were no differences between the MS + RLS and MS group for parameters of physical activity or sedentary behavior. Among participants with IRLS scores in the mild range ($n = 26$), more time spent in light physical activity ($r_s = -0.39$), fewer sedentary bouts per day ($r_s = 0.55$), less time in sedentary bouts per day ($r_s = 0.51$), and fewer breaks in sedentary time per day ($r_s = 0.57$) were associated with lower RLS severity. This study represents the first step toward recognizing a relationship between physical activity, patterns of sedentary behavior, and RLS severity in MS and these results suggest that light physical activity and the pattern of sedentary behavior may be important targets for prospective behavioral interventions that target the management of RLS in persons with MS who have mild RLS severity.

1. Introduction

Restless legs syndrome (RLS) is an idiopathic sensorimotor disorder characterized by uncomfortable sensations and the uncontrollable urge to move the affected extremities, most commonly the legs. RLS occurs in upwards of 15% of the general population [1] and the prevalence exceeds 25% of persons with multiple sclerosis (MS) [2]. This presents RLS as one of the most common sleep disorders among persons with MS [3]. Although the pathology underlying RLS is currently unknown, a recent review suggested that symptoms of RLS may result from central dopaminergic dysfunction causing spinal circuitry hyper-excitability [4] and the presence of RLS seemingly is associated with decreased

myelin integrity in the cervical spinal cord of persons with MS [5].

There are many consequences of RLS for persons with MS. Persons with MS and RLS report greater excessive daytime sleepiness [6,7], reduced sleep quality, worse clinical disability [7,8], and reduced quality of life [9] than persons with MS who do not have RLS. Nevertheless, there currently is no evidence-based method of managing RLS and its symptoms in persons with MS. Pharmacological treatment may be a useful option for the management of RLS in persons with MS, yet comorbidities, side effects, and potential drug interactions exist in MS that may undermine tolerance, adherence, and efficacy of some pharmacological treatments. This underscores the importance of identifying a non-pharmacological approach that can be used independently, or in

Abbreviations: CH-RLSq, Cambridge-Hopkins Questionnaire; DMT, disease modifying therapy; IRLS, International Restless Legs Syndrome Study Group Scale; IQR, interquartile range; LPA, light physical activity; MS, multiple sclerosis; MVPA, moderate-to-vigorous physical activity; NARCOMS, North American Research Committee on Multiple Sclerosis; PDDS, Patient Determined Disease Steps; PPMS, primary progressive multiple sclerosis; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; UAB, University of Alabama at Birmingham; USPS, United States Postal Service

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combination with pharmacology, for managing symptoms of RLS in MS.

Physical activity may represent a behavioral correlate of RLS and could be targeted as an approach for its management in persons with MS [10]. To date, physical activity has demonstrated substantial benefits for managing many consequences of MS [11,12], including mobility [13,14], balance [15], cognition [16], fatigue [17], and quality of life [18] in adults with MS. Physical activity may further improve sleep quality in adults with MS [19], yet there is no evidence on RLS as an outcome. Such a focus on physical activity and RLS in MS is predicated on previous research supporting exercise as a promising non-pharmacological approach for managing symptoms of RLS in the general population and other clinical populations [10,20,21]. We further note that movement of the effected extremities -one of the characteristic features of RLS- could translate into chronic behavior change paradigms for ongoing management.

The focus on physical activity, based on an activity continuum perspective [22], might further consider the relationship between sedentary behavior and RLS symptoms in persons with MS. Sedentary behavior, representing the other end of the activity continuum, is highly prevalent in MS [23], and people with MS engage in sedentary behavior as an energy conservation approach for the management of MS-related symptoms (e.g., fatigue) [24,25]. Sedentary behavior may exacerbate or contribute to the worsening of RLS symptoms in MS, as increased severity of symptoms while resting is a defining feature of RLS. This further underscores the importance of understanding sedentary behavior and RLS in MS.

The present study explored the relationships among parameters of physical activity and sedentary behaviors with the presence and severity of RLS in MS. To provide a more nuanced understanding of the activity continuum and RLS in MS, the volume (i.e., total amount of behaviors over the day) and pattern (e.g., number of breaks in behaviors over the day) of physical activity and sedentary behavior were studied as correlates of RLS features in MS. We expected that physical activity parameters (e.g., more time spent in moderate-to-vigorous physical activity [MVPA] and light physical activity [LPA], more active bouts per day) would be associated with lower RLS symptom severity, whereas sedentary behavior parameters (e.g., more time spent sedentary and more sedentary bouts per day) would be associated with greater symptom severity.

2. Materials and methods

2.1. Participants

Participants were recruited through the North American Research Committee on Multiple Sclerosis (NARCOMS) patient registry. The NARCOMS registry is a voluntary, self-report registry developed by the Consortium of MS Centers, wherein participants with MS complete an enrollment questionnaire and surveys biannually. The NARCOMS registry staff distributed flyer advertisements among a randomly selected sample of 1000 persons with MS who had completed the most recent biannual survey, and those who were interested in participating contacted the University of Alabama at Birmingham (UAB) research team. Participants who contacted the research team were included in the study based on the following criteria: (1) age 18 years or older; (2) diagnosis of MS; and (3) member of the NARCOMS registry. Of the 1000 persons recruited through NARCOMS, 296 contacted the research team and were screened for eligibility. One person declined participation following screening, and 295 persons were enrolled in the study. Twenty people did not complete the study for numerous reasons including not signing the consent form ($n = 8$), not wanting to wear the accelerometer ($n = 1$), and not returning study materials ($n = 11$). Of note, no one was excluded from the study. This resulted in a sample of 275 persons with MS with a final sample of 253 persons who completed all measures.

2.2. Restless legs syndrome

2.2.1. Diagnosis

Participants were considered to have a positive diagnosis of RLS based on the Cambridge-Hopkins Questionnaire (CH-RLSq). The CH-RLSq has demonstrated validity and sensitivity for diagnosing RLS via telephone and in survey form [26]. The CH-RLSq requires that participants fulfill the five criteria for a positive diagnosis of RLS (i.e., (1) the desire to move the legs in association with uncomfortable sensations; (2) the need to move the legs in response to these sensations; (3) the worsening of sensations at rest; (4) the partial or complete relief of the urge with movement; and (5) the sensations occurring most frequently during the evening or early part of the night). The CH-RLSq also includes other items for excluding common mimics of RLS, namely leg cramps and positional discomfort.

2.2.2. Symptom Severity

RLS symptom severity was assessed using the International Restless Legs Syndrome Study Group (IRLS) Scale. The IRLS is a validated 10-question survey that provides a global score commonly used to assess the overall severity of symptoms as well as the frequency and impact of symptoms on daily life with regard to the previous seven days [27]. Overall symptom severity was determined by combining the sum of the scores on the questionnaire, for a maximum score of 40. Participants were categorized as having mild (scores 1–10), moderate (scores 11–20), severe (scores 21–30) or very severe (scores 31–40) RLS symptoms based on total IRLS scores [27]. The IRLS has demonstrated validity, reliability, and responsiveness in clinical trial settings [28]. Additionally, the IRLS has demonstrated correlations with the Clinical Global Impression item 1 (i.e., clinical judgment of RLS severity) and the RLS-Quality of Life questionnaire [29]. Thus, the IRLS allows for measuring the degree of symptoms and understanding factors and treatments that influence RLS by physicians and researchers.

2.3. Perceived sleep quality

Perceived sleep quality during the past month was assessed with the Pittsburgh Sleep Quality Index (PSQI) [30]. The PSQI includes 19 items to form seven component scores: (1) subjective sleep quality; (2) sleep latency; (3) sleep duration; (4) habitual sleep efficiency; (5) frequency of sleep disturbances; (6) frequency of sleep medication use; and (7) daytime dysfunction. The seven component scores were calculated to be equally weighted on a scale that ranged between 0 (not during the past month) and 3 (three or more times a week) and then summed into a global PSQI score that ranged between 0 and 21; higher scores reflected worse perceived sleep quality. There is evidence of internal consistency, reliability, and validity of scores from the PSQI in a number of populations including MS [30–32].

2.4. Physical activity and sedentary behavior

Participants wore an ActiGraph GT3X+ accelerometer on a belt around the waist during waking hours over a 7-day period. The model of ActiGraph accelerometer has acceptable accuracy in MS across a range of walking speed and levels of neurological disability, including persons who walk with canes or rollators [33]. Participants recorded wear time in a diary on a daily basis, and further were instructed not to wear the device while sleeping. Wear time was estimated based on the Troiano algorithm from ActiLife and compared with the wear time diary for consistency in judging a day of data as valid for inclusion in the analysis. All participants included in analyses had 1 or more days of valid data (i.e., 10 h of wear time). Raw data from the accelerometers were reintegrated as a 60 s epoch file and processed using ActiLife software for examining wear time and quantifying physical activity and sedentary behavior parameters. Physical activity was quantified into average time spent in LPA and MVPA (min/day), average number of

Table 1
Characteristics of overall sample and the subsamples based on presence of restless legs syndrome.

	All Participants (N = 253)	MS + RLS (n = 66)	MS (n = 187)	p-Value	d
Demographic and Clinical Characteristics					
Age (years)	59.4 (10.0)	59.1 (9.7)	59.5 (10.1)	0.758 ^a	–
Gender (n (%))	204 (80.6%) F/49 (19.4%) M	54 (81.8%) F/12 (18.2%) M	150 (80.2%) F/37 (19.8%) M	0.998 ^b	–
Race (n (%))				0.422 ^b	–
Black/African American	4 (1.6%)	0 (0.0%)	4 (2.1%)	–	–
Caucasian	239 (94.5%)	65 (100.0%)	174 (93.0%)	–	–
Latino/Latina	5 (2.0%)	0 (0.0%)	5 (2.7%)	–	–
Other	4 (1.6%)	0 (0.0%)	3 (1.6%)	–	–
MS Type (n (%))				0.731 ^b	–
Relapsing-Remitting MS	170 (67.2%)	43 (65.2%)	127 (67.9%)	–	–
Secondary Progressive MS	51 (20.2%)	14 (21.2%)	37 (19.8%)	–	–
Primary Progressive MS	29 (11.5%)	9 (13.6%)	20 (10.7%)	–	–
Benign	3 (1.2%)	0 (0.0%)	3 (1.6%)	–	–
Disease Duration (years)	20.3 (9.7)	19.9 (10.1)	20.4 (9.6)	0.566 ^a	–
MS-specific DMT (n (%)) Yes	184 (72.7%)	47 (71.2%)	137 (73.3%)	0.676 ^b	–
PDDS (median [IQR])	3.0 [8.0]	3.0 [7.0]	3.0 [8.0]	0.300 ^a	–
IRLS	–	11.4 (7.6)	–	–	–
PSQI	7.2 (3.5)	7.6 (4.0)	7.1 (3.3)	0.562 ^a	0.136
Accelerometer Wear Time (min/day)	807.3 (86.6)	803.0 (83.1)	808.8 (88.0)	0.641	0.068
Valid Days (number of days)	5.9 (1.7)	5.8 (1.8)	5.9 (1.6)	0.877 ^a	0.059
Physical Activity Behavior					
LPA (min/day)	243.9 (86.3)	248.5 (79.9)	242.3 (88.6)	0.437 ^a	0.073
MVPA (min/day)	14.9 (20.8)	14.9 (18.2)	14.9 (21.6)	0.742 ^a	0.000
Active Bouts (#/day)	0.3 (0.5)	0.3 (0.6)	0.2 (0.5)	0.231 ^a	0.181
Average Active Bout Length (min)	4.2 (8.7)	4.7 (8.1)	4.0 (8.9)	0.261 ^a	0.082
Total time of Active Bouts (min/day)	6.0 (13.9)	6.3 (10.8)	5.9 (14.9)	0.287 ^a	0.031
Sedentary Behavior					
Sedentary Behavior (min/day)	548.5 (90.4)	539.6 (78.6)	551.6 (94.2)	0.357	0.138
Breaks in Sedentary Time (#/day)	6.9 (1.9)	6.8 (2.0)	6.9 (1.9)	0.857	0.051
Average Sedentary Bout Length (min)	49.7 (13.8)	49.7 (11.7)	49.7 (14.6)	0.920 ^a	0.000
Sedentary Bouts (#/day)	6.1 (2.0)	6.0 (2.0)	6.1 (2.0)	0.670	0.050
Total time of Sedentary Bouts (min/day)	304.4 (127.7)	296.3 (120.1)	307.2 (130.4)	0.612 ^a	0.087

Note: Data are presented in mean \pm standard deviation unless otherwise specified. MS multiple sclerosis; RLS restless legs syndrome; DMT Disease Modifying Therapies; PDDS Patient Determined Disease Status; IQR interquartile range; IRLS International Restless Legs Syndrome Study Group Scale; PSQI Pittsburgh Sleep Quality Index; LPA Light Physical Activity; MVPA Moderate-to-Vigorous Physical Activity.

^a Mann-Whitney *U* Test.

^b Chi Square Analysis.

active bouts per day, average active bout length, and total time spent in active bouts per day. Parameters of sedentary behavior included time spent sedentary (min/day), average number of breaks in sedentary time per day, average sedentary bout length, average number of sedentary bouts per day, and total time of sedentary bouts (min/day). We quantified MVPA based on a MS-specific cut-point of 1584 cpm [34], and the value of 100 cpm was a cut-point for delineating data into either LPA or sedentary behavior.

2.5. Demographics and clinical characteristics

Participants completed a demographic and clinical characteristics questionnaire for information regarding age, gender, race, MS type, disease onset, and disease duration. Participants were also asked to provide a list of current use of over-the-counter and/or prescription medications. Participants also completed the Patient Determined Disease Steps (PDDS) as a measure of patient reported disability status [35]. Importantly, the PDDS has demonstrated evidence for validity and strong correlations with the Expanded Disability Status Scale, pyramidal and cerebellar functional scores, and walking ability in persons with MS [36].

2.6. Procedures

This study was approved by the University's Institutional Review Board and participants provided written informed consent. Upon enrollment into the study, participants were sent all study materials via the United States Postal Service (USPS), including two copies of the

informed consent document (one for them to sign and return and one of them to sign and keep), an overview of the study along with instructions, an accelerometer and belt with instructions, the questionnaire packet, a \$10 gift card, and a pre-stamped, pre-addressed envelope for return service of all materials. Participants were asked to wear the accelerometer during waking hours for a period of seven days and completed the battery of questionnaires during the one-week period. Participants returned all materials through the USPS.

2.7. Statistical analysis

All data were analyzed in SPSS Statistics, Version 25 (IBM Corporation, Armonk, NY), and descriptive statistics are reported as mean and standard deviation (SD), unless otherwise noted (e.g., median and interquartile range [IQR] or number and percentage). All analyses were interpreted with an a priori *p*-value of 0.05. We examined frequency distributions and conducted Shapiro-Wilks analysis for establishing normality of the variables, whereby a *p*-value $>$.05 was indicative of a normal distribution. We compared mean scores between MS + RLS and MS groups, and between RLS severity subgroups (i.e., mild vs. moderate-to-very severe) with independent samples *t*-test for continuous and/or normally distributed variables, Mann-Whitney *U* Test for ordinal and/or non-normally distributed variables, and Chi Square analysis for nominal variables. The difference in mean scores between RLS diagnosis groups was estimated with Cohen's *d* whereby effect sizes of 0.2, 0.5, and 0.8 were interpreted as small, moderate, and large, respectively [37]. We further examined Spearman correlations (r_s) within the subgroup of participants with MS and RLS among

physical activity parameters, sedentary behavior parameters, perceived sleep quality, and RLS severity. Additionally, we explored Spearman correlations (r_s) within RLS severity subgroups among physical activity parameters, sedentary behavior parameters, perceived sleep quality, and RLS severity to assess differences in these relationships between persons who have mild RLS severity and moderate-to-very severe RLS severity. Correlation coefficients of 0.1, 0.3, and 0.5 were interpreted as small, moderate, and large, respectively [37].

3. Results

3.1. Overall sample characteristics

Demographic and clinical characteristics as well as physical activity and sedentary behavior parameters for the overall sample of participants ($N = 253$) are presented in Table 1. The sample was largely female (81%) and Caucasian (95%) with a mean (SD) age of 59.4 (10.0) years. Participants mostly had relapsing-remitting MS (RRMS) (67%) followed by secondary progressive MS (SPMS; 20%) and primary progressive MS (PPMS; 12%) with moderate disability (median [IQR] PDDS score: 3.0 [8.0]). The sample had an average (SD) disease duration of 20 (9.7) years and most participants were using an MS-specific disease modifying therapy (DMT; 73%).

Of note, 144 participants (57%) acquired the minimum wear time for all seven days, 43 (17%) for six days, 25 (10%) for five days, 13 (5%) for four days, and 28 (11%) for one to three days of valid wear time and were included in analyses. Participants spent an average of 243.9 (86.3) min/day in LPA and 14.9 (20.8) min/day in MVPA with an average of 0.3 (0.5) bouts of activity per day at an average length of 4.2 (8.7) min for a total of 6.0 (13.9) min/day in active bouts. Regarding sedentary behavior parameters, the sample engaged in an average of 548.5 (90.4) min/day in sedentary behavior with an average of 6.9 (90.4) breaks in sedentary time per day and an average bout length of 49.7 (13.8) min, 6.1 (2.0) average sedentary bouts per day, and a total time of 304.4 (127.7) min/day of sedentary bouts.

3.2. Restless legs syndrome in multiple sclerosis

Demographic and clinical characteristics as well as physical activity and sedentary behavior parameters for the subsamples of MS + RLS ($n = 66$) and MS only ($n = 187$) are presented in Table 1. Approximately 26% of our sample fit the criteria for a positive diagnosis of RLS based on the CH-RLSq diagnostic questionnaire with a mean (SD) IRLS score of 11.4 (7.6) indicating moderate RLS severity on average. Within the MS + RLS group, 9 (14%) individuals reported no symptoms, 26 (39%) mild symptoms, 24 (36%) moderate symptoms, 6 (9%) severe symptoms, and 1 (2%) reported very severe symptoms of RLS. There were no significant differences between groups for age, gender, race, MS type, disease duration, disability status, MS-specific DMTs, or perceived sleep quality. There further were no significant differences between the MS and MS + RLS group for parameters of physical activity or sedentary behavior.

3.3. Restless legs syndrome severity and activity

Sample characteristics as well as parameters of physical activity and sedentary behavior as a function of RLS severity in the MS + RLS group ($n = 57$) are presented in Table 2. Of note, participants categorized as having no RLS severity ($n = 9$) were not included and those categorized as having moderate, severe, and very severe symptoms of RLS were collapsed into a single group (i.e., moderate-to-very severe) considering sample size restrictions. There were no significant difference between RLS severity groups for any of the demographic or clinical characteristics and there were, further, no differences between RLS severity groups for parameters of physical activity or sedentary behavior. However, persons with moderate-to-very severe RLS reported

Table 2

Characteristics of persons with multiple sclerosis and restless legs syndrome based on symptom severity.

	Mild ($n = 26$)	Moderate-Very Severe ($n = 31$)	<i>p</i> -Value
Demographic and Clinical Characteristics			
Age (years)	56.9 (8.6)	59.4 (11.3)	0.242 [#]
Gender (n (%))	19 (73.1) F/7 (26.9) M	27 (87.1) F/4 (12.9) M	0.182 ⁺
MS Type (n (%))			0.939 ⁺
Relapsing-Remitting MS	17 (65.4)	21 (67.7)	
Secondary Progressive MS	6 (23.1)	6 (19.4)	
Primary Progressive MS	3 (11.5)	4 (12.9)	
Disease Duration (years)	18.8 (9.2)	19.6 (10.7)	0.860 [#]
Years since symptom onset	23.7 (10.1)	26.3 (11.4)	0.418 [#]
PDDS (median [IQR])	3.0 [6.0]	4.0 [7.0]	0.093 [#]
MS-specific DMT (n (%)) Yes	19 (73.1)	24 (77.4)	0.704 ⁺
IRLS	6.6 (2.6)	16.7 (4.8)	0.000 [#]
PSQI	6.0 (3.7)	9.2 (4.1)	0.003 [#]
Accelerometer Wear Time (min/day)	819.6 (83.3)	799.8 (82.3)	0.285 [#]
Physical Activity Parameters			
LPA (min/day)	271.9 (66.8)	240.6 (77.4)	0.116 [#]
MVPA (min/day)	18.6 (19.0)	13.6 (19.0)	0.200 [#]
Active Bouts (#/day)	0.4 (0.6)	0.3 (0.7)	0.299 [#]
Average Active Bout Length (min)	5.9 (9.8)	4.2 (7.5)	0.267 [#]
Total time of Active Bouts (min/day)	7.9 (12.4)	5.8 (10.7)	0.241 [#]
Sedentary Behavior Parameters			
Sedentary Behavior (min/day)	529.1 (58.7)	545.6 (88.2)	0.207 [#]
Breaks in Sedentary Time (#/day)	6.5 (1.8)	7.0 (2.1)	0.439 [#]
Average Sedentary Bout Length (min)	46.0 (6.6)	50.8 (11.6)	0.059 [#]
Sedentary Bouts (#/day)	5.6 (1.9)	6.2 (2.1)	0.423 [#]
Total time of Sedentary Bouts (min/day)	258.1 (84.4)	309.6 (123.4)	0.120 [#]

Notes: Nine (12.2%) participants screened positive for RLS and reported no symptoms (IRLS = 0) for the previous seven day period that were not included in this table; values are reported as mean (standard deviation) unless otherwise specified. MS Multiple Sclerosis; bold text indicates significant differences between groups. PDDS Patient Determined Disease Status; DMT Disease Modifying Therapy; IRLS International Restless Legs Syndrome Study Group Scale; PSQI Pittsburgh Sleep Quality Index; LPA Light Physical Activity; MVPA Moderate-to-vigorous Physical Activity.

⁺ Chi Square Analysis.

[#] Mann-Whitney *U* Test.

significantly worse perceived sleep quality compared with persons with mild RLS severity ($p < .01$).

3.4. Relationships among restless legs syndrome severity and activity

The summary of Spearman correlations (r_s) within the MS + RLS group and RLS severity subgroups among RLS severity and parameters of physical activity and sedentary behavior are presented in Table 3. Perceived sleep quality had a moderate, positive association with RLS severity ($r_s = 0.31$) in the sample of persons with MS who had RLS. Regarding physical activity parameters, There was a moderate, negative association between time spent in LPA ($r_s = -0.39$) and RLS severity for persons with mild RLS severity. There were no significant associations among RLS severity and parameters of physical activity in the MS + RLS group as a whole nor in the moderate-to-severe subgroup.

Regarding sedentary behavior parameters, in the mild severity group, the number of breaks in sedentary time per day ($r_s = 0.57$), number of sedentary bouts per day ($r_s = 0.55$), and total minutes of sedentary bouts per day ($r_s = 0.51$) had a large, positive association

Table 3

Spearman Correlations between physical activity and sedentary behavior with restless legs syndrome (RLS) severity for persons with multiple sclerosis and RLS as well as across samples differing in severity of RLS.

		IRLS	PSQI	
MS + RLS (n = 66)	PSQI	0.306*	–	
	LPA (min/day)	–0.090	–0.005	
	MVPA (min/day)	–0.013	0.065	
	Active Bouts (#/day)	–0.075	0.029	
	Total time of Active Bouts (min/day)	–0.075	0.011	
	Active Bout Length (min)	–0.064	0.008	
	Sedentary Behavior (min/day)	0.098	–0.197	
	Breaks in Sedentary Time (#/day)	0.076	–0.081	
	Average Sedentary Bout Length (min)	0.151	0.038	
	Sedentary Bouts (#/day)	0.073	–0.083	
	Total time of Sedentary Bouts (min/day)	0.048	–0.020	
	Mild (n = 26)	PSQI	–0.297	–
		LPA (min/day)	–0.393*	–0.202
		MVPA (min/day)	–0.049	–0.050
Active Bouts (#/day)		–0.076	0.161	
Total time of Active Bouts (min/day)		–0.091	0.142	
Active Bout Length (min)		–0.086	0.184	
Sedentary Behavior (min/day)		0.226	–0.105	
Breaks in Sedentary Time (#/day)		0.568**	0.024	
Average Sedentary Bout Length (min)		0.197	0.101	
Sedentary Bouts (#/day)		0.546*	0.069	
Total time of Sedentary Bouts (min/day)		0.510*	0.108	
Moderate-Very Severe (n = 31)		PSQI	0.309	–
		LPA (min/day)	–0.066	0.220
		MVPA (min/day)	–0.035	0.340
	Active Bouts (#/day)	0.113	0.048	
	Total time of Active Bouts (min/day)	0.124	0.047	
	Active Bout Length (min)	0.148	0.033	
	Sedentary Behavior (min/day)	–0.157	–0.432*	
	Breaks in Sedentary Time (#/day)	–0.260	0.220	
	Average Sedentary Bout Length (min)	0.287	–0.171	
	Sedentary Bouts (#/day)	–0.291	–0.285	
	Total time of Sedentary Bouts (min/day)	–0.211	–0.273	

Notes: MS Multiple Sclerosis; IRLS International Restless Legs Syndrome Study Group Scale; PSQI Pittsburgh Sleep Quality Index; LPA Light Physical Activity; MVPA Moderate-to-vigorous Physical Activity. * $p < .05$; ** $p < .01$

with RLS severity. In the moderate-to-very severe RLS group, time spent in sedentary behavior had a moderate, negative association with perceived sleep quality ($r_s = -0.43$). There were no other significant associations among RLS severity and parameters of sedentary behavior in the MS + RLS group or the subgroup of persons with moderate-to-very severe RLS.

4. Discussion

This study examined the relationships among parameters of physical activity and sedentary behavior with the presence and severity of RLS in persons with MS. There were no significant differences in the volume or pattern of physical activity or sedentary behavior between persons with MS and RLS and persons with MS who did not have RLS. There further were no significant differences in parameters of physical activity or sedentary behavior between persons with mild RLS symptoms and persons with moderate-to-very severe symptoms within the sample of persons with MS and RLS. Among those characterized as having mild RLS, time spent in LPA and a large, positive association with RLS severity and the number of breaks in sedentary time per day, number of sedentary bouts per day, and total minutes of sedentary bouts per day had a moderate, negative association with RLS severity.

To date, this is the first study to evaluate the relationship between volume and patterns of physical activity and RLS in adults with MS. Our sample with MS and RLS spent an average of 248.5 min/day (4.1 h) in LPA and 14.9 min/day in MVPA, and this was comparable with the sample of persons with MS who did not have RLS (i.e., 242.3 min (4.0 h) and 14.9 min, respectively) and previous values reported for MS [38]. Additionally, there was no significant difference in the volume of physical activity between severity subgroups in those with MS and RLS;

however, persons with mild RLS severity spent approximately 31 more minutes per day in LPA and 5 more minutes per day in MVPA than those with moderate-to-very severe RLS severity. Additionally, in persons with mild RLS severity, more time spent in LPA was associated with lower RLS severity suggesting that persons who are more active, particularly engaging in more LPA per day, may have lower RLS severity. However, our results suggest no evidence of a relationship among parameters of physical activity and RLS severity in individuals with moderate-to-very severe RLS. This is unexpected, as there is evidence that exercise, one form of physical activity, can effectively reduce symptoms of RLS in the general population and other clinical populations [10,20,21]. Notably, only 11 (17%) persons in the MS + RLS group were meeting guidelines for MVPA (≥ 30 min/day) which may have limited our ability to detect a relationship in this sample. This suggests that persons with MS, including those with MS and RLS, may not be engaging in sufficient levels of physical activity necessary for the benefits associated with this health behavior [39], consistent with the general trend seen in MS. Overall, our results suggest LPA may be a target for behavioral interventions to manage RLS severity in persons with mild RLS and MS.

With regard to the volume of sedentary behavior, our sample engaged in 548.5 min/day (9.1 h) in sedentary behavior, comparable to that previously reported in adults with MS [38,40]. There were no differences in parameters of sedentary behavior between persons with MS and RLS and persons with MS without RLS or between RLS severity subgroups. Although not statistically significant, persons with MS and RLS spent approximately 17 min/day less in sedentary behavior than persons with MS alone and persons with mild RLS spent 16 min/day less in sedentary behavior than persons with moderate-to-very severe RLS. This suggests that persons with RLS, particularly with mild RLS

severity, may spend less time sedentary and more time moving around (i.e., more time in LPA), potentially in an effort to relieve symptoms that are often exacerbated by periods of resting. Further, persons with moderate-to-very severe RLS may engage in more strategies for energy conservation. Importantly, persons with MS often engage in more sedentary behavior as a means for energy conservation and MS-related symptom (e.g., fatigue) management, and RLS reportedly contributes to further impairments in fatigue for persons with MS [41]. Thus, more time spent sedentary as a means of energy conservation may be related to more severe RLS severity. However, more systematic research is necessary to better understand the relationship among the volume of sedentary behavior, RLS, and other consequences of MS, such as fatigue, in persons with MS.

There were significant associations between the number of breaks in sedentary time, number of sedentary bouts per day, and total time of sedentary bouts and RLS severity in persons with mild RLS severity and MS. These results suggest that persons with mild RLS who have more breaks in sedentary time, more sedentary bouts per day, and spend more time in sedentary bouts report worse RLS severity. Thus, persons with mild RLS who report worse RLS severity may be getting up more frequently throughout the day in an effort to self-manage symptoms. Such results are expected as the movement of the affected leg based on discomfort is a hallmark characteristic of RLS, and this may explain the relationship between parameters of sedentary behavior and RLS severity in persons with mild RLS and MS. Importantly, these relationships were only observed in persons with mild RLS severity, suggesting that self-management of symptoms with frequent breaks in resting may only be beneficial for those with more mild RLS severity. Thus, the pattern of sedentary behavior, specifically breaks in sedentary time, number of sedentary bouts, and the duration of sedentary bouts, may be an important target of behavioral interventions for the management of RLS in persons with mild RLS severity and MS.

There were no consistent correlations between sleep quality and physical activity or sedentary behavior. Although not significant, our sample of persons with MS and RLS reported worse perceived sleep quality compared with the sample of persons with MS alone and this is comparable with previous research [7,8]. Within the sample of persons with MS and RLS, greater RLS severity was significantly associated with worse perceived sleep quality and persons with moderate-to-very severe RLS reported significantly worse perceived sleep quality than persons with mild RLS severity. These results are not surprising as RLS can significantly influence factors of sleep in persons with RLS and MS including longer sleep latency, shorter total sleep time, and a higher prevalence of insomnia symptoms than persons with MS without RLS [7,8]. Additionally, worse sleep quality was significantly associated with less time spent in sedentary behavior for persons with moderate-to-very severe RLS. This is surprising as research outside of MS has demonstrated improvements in sleep quality with reduced sedentary behavior; however, these studies were conducted in older Japanese adults [42] and post-menopausal women [43]. Perhaps this relationship may differ in adults with MS compared with other populations. More research is necessary regarding the relationships among physical activity, sedentary behavior, and sleep quality in persons with RLS and MS.

There are important limitations to consider when interpreting our results. The cross-sectional design of this study precludes any inferences of causality or temporality in the relationships among RLS, physical activity, and sedentary behavior. As this was a mail-based protocol, demographic and clinical characteristics and measures of RLS are self-report in nature. We did not screen for mobility limitations; thus, the sample included participants who used unilateral assistance (e.g., cane), bilateral assistance (e.g., walker), and wheelchairs that could have influenced the volume and pattern of activity. We did not collect data regarding MS-related fatigue in the context of physical activity and RLS which may influence activity levels in this such a sample. Although individuals were screened for a differential diagnosis of RLS,

participants without RLS may present with mimics of RLS that would allow for an IRLS score associated with symptoms of RLS in the MS group. An interview with the ability to clarify items on the diagnostic questionnaire should be utilized in future studies to be more sensitive with diagnostic criteria. Some prescription medications for MS or RLS itself present another limitation to assessing RLS symptom severity in this population, as a number of prescriptions may ameliorate symptoms of RLS (e.g., pramipexole, gabapentin, and rotigotine [44]) or exacerbate symptoms of RLS (e.g., antidepressants, first-generation antihistamines [45]); however, only 27% ($n = 18$) of our sample with MS and RLS were taking a medication that could reduce RLS severity, and 20% ($n = 13$) were taking medications that could exacerbate RLS severity. Although we included a relatively large, random sample of individuals with MS that included all phenotypes of MS (i.e., RRMS, SPMS, and PPMS), our sample consisted primarily of individuals with RRMS (67%) suggesting that our sample may not be fully representative of the MS and RLS population, as prior literature suggest that RLS may be more prevalent in those with PPMS and those with greater disability levels [7,46] and the sample sizes for subgroups of RLS severity were relatively small which may have contributed to less power for detecting more subtle differences between groups. Lastly, we did not collect data regarding RLS symptoms over the course of the day and how this might be associated with changes in physical activity over the course of the day. This should be considered in future research for examining the relationship between the volume and pattern of physical activity measured by an accelerometer throughout the day and appearance of RLS symptoms using experiential sample methodology over the day.

5. Conclusions

This is the first study to evaluate physical activity, sedentary behavior, and RLS specifically. These results suggest that more time spent in light physical activity as well as the pattern of sedentary behavior, specifically the number of breaks in sedentary time, number of sedentary bouts, and total time of sedentary bouts, are important correlates of RLS severity in those with MS who have mild RLS. This study represents the first step toward recognizing a relationship between physical activity, the patterns of sedentary behavior, and RLS in MS and these results suggest that the pattern of sedentary behavior may be an important target for prospective behavioral interventions that target the management of RLS in persons with MS who have mild RLS severity. Future research should also consider whether RLS severity is driving the levels of light physical activity and the pattern of sedentary behavior or if physical activity and sedentary behavior is driving RLS severity in persons with mild RLS severity and MS.

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