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Restless legs syndrome and health-related quality of life in adults with multiple sclerosis

Suggested Running Head: RLS and HRQOL in MS

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Abstract

Restless legs syndrome (RLS) is a sleep disorder that may exacerbate many of the symptoms and consequences of multiple sclerosis(MS), and may have further implications for health-related quality of life(HRQOL). The present study examined the relationship among RLS, symptoms, and HRQOL in people with MS. Participants with MS(N=275) completed the Cambridge-Hopkins Restless Legs Syndrome Questionnaire, the International Restless Legs Syndrome Study Group Scale, the Multiple Sclerosis Impact Scale, the Pittsburgh Sleep Quality Index, the Fatigue Severity Scale, the Hospital Anxiety and Depression Scale, and the Patient Determined Disease Steps. There were 74(26.9%) persons with MS who had RLS (MS+RLS). The MS+RLS group reported worse physical and psychological HRQOL(p=0.020 and p=0.017, respectively) and greater perceived fatigue(p=0.006) and anxiety symptoms(p=0.042) than the MS only group. Within the MS+RLS group, RLS severity was associated with physical (r=0.43) and psychological(r=0.46) HRQOL, sleep quality(r=0.38), perceived fatigue(r=0.28), depression(r=0.38), and anxiety(r=0.28). The relationships between RLS severity and the domains of HRQOL were attenuated when accounting for fatigue, depression, and/or anxiety. Worse RLS severity was associated with reduced HRQOL that was accounted for by fatigue, depression, and anxiety.

Keywords: restless legs syndrome, multiple sclerosis, health-related quality of life, anxiety, depression, fatigue

1. Introduction

Restless legs syndrome (RLS) is a sleep disorder characterized by uncomfortable sensations and an intense, often uncontrollable urge to move the legs(Restless Legs Syndrome

Foundation,2018). The defining features of RLS include:(a) an urge to move the extremities that is accompanied by uncomfortable or unpleasant sensations;(b) the sensations are partially or totally relieved by movement;(c) the sensations begin or worsen during periods of rest or inactivity;(d) the sensations worsen in the evening(Walters et al.,2003). RLS occurs in upwards of 15% of the general population(Ohayon et al.,2012), and the prevalence is substantially higher among persons with multiple sclerosis (MS), with estimates as high as 65%(Sieminski et al.,2015). This presents RLS as one of the most common, and potentially burdensome, sleep disorders among persons with MS(Braley and Chervin,2015) .

RLS may exacerbate many of the symptoms and consequences of MS and could have implications for health-related quality of life(HRQOL). Persons with MS who have RLS report greater daytime sleepiness, lower sleep quality, worse clinical disability(Manconi et al., 2008, Moreira et al., 2008), and greater symptoms of depression and fatigue(Aydar et al., 2011, Moreira et al., 2008) than with those with MS who do not have RLS. Such co-occurring consequences of RLS are common influences of HRQOL in MS (Benito-Leon et al.,2003), yet there is limited evidence regarding the nature of the relationship between RLS and HRQOL in MS.

The present study examined the relationship between RLS and HRQOL in people with MS. We compared common symptoms and consequences associated with MS between groups with and without RLS (i.e.,MS+RLS and MS groups, respectively) and further examined the association between RLS severity, MS-related outcomes, and HRQOL in people with both MS and RLS. This was followed by a search for possible intermediary factors in the relationship, including disability status, sleep quality, fatigue, depression, and anxiety in adults with both MS and RLS. We hypothesized that those with MS and RLS (i.e.,MS+RLS group) would report worse HRQOL, clinical disability, sleep quality, fatigue, depression, and anxiety than those with MS alone (i.e.,MS group). We further hypothesized that the relationship between RLS severity and HRQOL in those with MS and RLS might be accounted for by the aforementioned co-occurring consequences of RLS (i.e.,sleep quality, clinical disability status, fatigue, and depression).

2. Materials and Methods

2.1 Participants

We recruited a sample of persons with MS through the North American Research Committee on Multiple Sclerosis(NARCOMS) patient registry. The random sample of 1,000 persons with MS received printed letters by NARCOMS staff, and the sample size was selected based on an expectation of 25% participation in the actual study that was estimated by NARCOMS. Those who were interested in participating contacted the research team through e-mail or telephone, and members of the research team conducted a brief screening interview for inclusion. The inclusion criteria were:(a) age 18 years or older;(b) self-reported diagnosis of MS;(c) member of the NARCOMS registry; and (d) willingness to complete the questionnaires and return the materials via the United States Postal Service (USPS). Of the 1,000 persons with MS recruited through NARCOMS, 316 made contact with the research team, and 296 were screened for eligibility(Figure 1); one person declined participation after the description of the study. The research team distributed study materials to 295 persons, and 284 individuals returned study materials to the research team. Of those who returned materials, nine declined participation and 11 persons did not return packets for unknown reasons. The final sample consisted of 275 persons with MS.

2.2 Restless Legs Syndrome

Diagnosis. The diagnosis of RLS was based on the Cambridge-Hopkins Restless Legs Syndrome Questionnaire(CH-RLSq) which has demonstrated validity and sensitivity for diagnosing RLS via survey form(Allen et al.,2009). The CH-RLSq requires that participants fulfill the five criteria for a positive diagnosis of RLS and further includes items to help exclude common mimics of RLS(i.e.,leg cramps and positional discomfort). These items consisted of five yes or no questions, two questions assessing when symptoms occur(i.e.,at rest or when active as well as time of day), and one question for assessing if a single occurrence of movement relieves the symptoms(i.e.,usually relieves, does not usually relieve, or don't know). Items were reviewed by a researcher and scored as positive for RLS(i.e.,MS+RLS group) if responses were consistent with the aforementioned RLS diagnostic criteria or as negative for RLS(i.e.,MS group) if any item was inconsistent with RLS diagnostic criteria.

Symptom Severity. RLS symptom severity was measured 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 over the previous seven days(Walters et al.,2003). Items were rated on a scale ranging from 0 to 4 and

individual item scores were summed for a measure of overall symptom severity ranging from 0 to 40. IRLS scores were further categorized into no symptoms(score of 0), mild(scores 1 – 10), moderate(scores 11 – 20), severe(scores 21 – 30), and very severe(scores 31 – 40)(Walters et al.,2003). The IRLS has demonstrated validity, reliability, and responsiveness in clinical trial settings(Abetz et al.,2006).

2.3 Health-related Quality of Life

The Multiple Sclerosis Impact Scale(MSIS-29) provides a disease-specific measure of HRQOL(Hobart et al.,2001). The MSIS-29 measures physical and psychological aspects of HRQOL using 29 separate items rated on a five-point Likert scale from 1(not at all) to 5(extremely) with regard to the past four weeks. Respective items were utilized to generate subscale scores for the physical and psychological domains of HRQOL. The physical domain was scored by summing the scores for items 1 to 20, subtracting 20, dividing the difference by 80, and then multiplying the result by 100. The psychological domain was scored by summing the scores for items 21 through 29, subtracting nine, dividing the difference by 36, and then multiplying by 100. Higher scores on both subscales represent a greater impact of MS on HRQOL during the previous two weeks. Reliability and validity of the MSIS-29 has been demonstrated in samples with MS(Learmonth et al.,2014).

2.4 Demographics and Clinical Characteristics

Participants completed a demographic and clinical characteristics questionnaire for information regarding age, sex, race, MS subtype, and disease duration. Participants further completed the Patient Determined Disease Steps(PDDS), a single item measure of self-reported disability status(Hohol et al., 1995, Hohol et al., 1999). PDDS scores ranged between 0(normal) and 8(bedridden), and the scores have demonstrated evidence for validity and strong correlations with the Expanded Disability Status Scale(EDSS), pyramidal and cerebellar functional scores, and walking ability in persons with MS(Learmonth et al., 2013).

2.5 Sleep Quality

Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index(PSQI)(Buysse et al.,1989). The PSQI consists of 19 items that measure the quality of one's sleep and sleep disturbances over the past month. The items include a number of factors associated with sleep quality, including subjective sleep quality, duration of sleep, sleep latency, habitual sleep efficiency(i.e.,frequency and severity of sleep-related problems including

breathing difficulty, pain, urinary frequency), use of sleeping medications, and the impact of poor sleep on daily functioning. Components were scored from 0(fairly good) to 3(very bad) and component scores are summed for a global score ranging from 0 to 21; higher scores reflect worse sleep quality. Of note, scores greater than 5 are indicative of severe difficulties in at least two domains or moderate difficulties in more than three areas and the PSQI has demonstrated evidence for validity and reliability in assessing sleep quality in the general population(Buysse et al.,1989).

2.6 Fatigue Symptoms

Perceived fatigue was measured using the Fatigue Severity Scale(FSS)(Krupp et al.,1989). The FSS contains nine Likert-scale items that assess fatigue symptoms during the past week, rated on a seven-point scale ranging between 1(strongly disagree) and 7(strongly agree). Items were averaged for an overall measure of a person's severity of fatigue that ranges between 1 and 7. Of note, FSS scores of 4(or total scores of 36) or above indicate severe MS-related fatigue(Andreasen et al.,2011). There is evidence for the internal consistency, test-retest reliability, validity, and precision of FSS scores as a measure of fatigue(Krupp et al.,1989).

2.7 Anxiety and Depression Symptoms

The Hospital Anxiety and Depression Scale(HADS) contains 14 items that measure perceived symptoms of depression and anxiety over the past 4 weeks(Zigmond and Snaith,1983). Items were individually rated on a 4-point scale ranging from 0(most of the time) to 3(not at all). A subset of seven items were reverse-scored per subscale and summed into a subscale score for symptoms of depression(HADS-D) or symptoms of anxiety(HADS-A) that ranged from 0 to 21; higher scores reflected a greater frequency of depressive and anxiety symptoms. Of note, a cut-point score of 7 has been identified for depression and anxiety screening and a score of 11 suggests major depression and generalized anxiety disorder in individuals with MS(Marrie et al.,2018). Additionally, the HADS has demonstrated evidence for the reliability and validity of these scores in people with MS(Marrie et al.,2018).

2.8 Procedures

This study was approved by the University's Institutional Review Board and all participants provided written informed consent. After initial telephone contact and screening, all participants who verbally volunteered were mailed a packet containing the informed consent document, questionnaire battery, and a pre-stamped and pre-addressed envelope for return

service through the USPS. The participants were instructed to complete the battery of questionnaires over a 7 day period of time. After completing the questionnaires, participants returned a signed copy of the informed consent along with the study materials through the USPS. All participants received $10 for voluntary participation.

2.9 Statistical Analysis

All statistical analyses were conducted using SPSS version 24 and descriptive data are presented as mean scores along with the standard deviations(SD), unless otherwise specified. We examined skewness and kurtosis estimates and frequency distributions for establishing normality of the variables; the skewness and kurtosis estimates along with inspection of frequency distributions did not identify problems with normality for any of the main study variables (i.e.,age, sex, race, MS type, disease duration, PDDS, IRLS, MSIS, PSQI, FSS, HADS). The differences in outcome measures between groups(MS+RLS vs. MS) were therefore determined using an independent samples *t*-test for continuous variables, Mann-Whitney U test for categorical variables, and Chi Squared test for nominal variables. Cohen's *d* was utilized to estimate the magnitude of difference between groups and effect sizes of 0.2, 0.5, and 0.8 were interpreted as small, moderate, and large, respectively(Cohen,1988). Within the MS+RLS group, the associations among RLS severity, physical and mental components of HRQOL, and MS-related consequences (i.e.,disability status, sleep quality, fatigue, depression, and anxiety) were examined by means of Pearson Product (*r*) correlation coefficients; values of 0.1, 0.3, and 0.5 were interpreted as small, moderate, and large, respectively(Cohen,1988).

We evaluated the relationship between RLS diagnosis and physical and psychological HRQOL scores using multivariate linear regressions with forward stepwise selection(α=0.05). We regressed CH-RLSq on each domain of HRQOL (i.e.,physical and psychological) in Step 1, and CH-RLSq plus variables that were significantly different between groups (i.e.,MS+RLS vs. MS) with the HRQOL domains in Step 2. We examined the change in the standardized beta-coefficient for CH-RLSq and the domain of HRQOL between Steps 1 and 2 for judging the variables that may be intermediary factors in the associations within the total sample of participants. Within the MS+RLS group, we examined potential intermediary variables in the relationship between RLS severity and physical and psychological HRQOL scores using multivariate linear regressions with forward stepwise selection(α=0.05). We regressed the total IRLS score on each domain of HRQOL in Step 1, and RLS severity plus variables that were

significantly associated with the HRQOL domain in Step 2. We examined the change in the standardized beta-coefficient for IRLS and the domain of HRQOL between Steps 1 and 2 for judging the variables that may be intermediary factors in the associations within those with MS+RLS. A *p*-value of less than 0.05 was adopted for determining statistical significance with all inferential analyses.

3. Results

3.1 Overall Sample Characteristics

Demographic and clinical characteristics for the overall sample of participants(N=275) are presented in Table 1. The sample was largely female(81%) and Caucasian(94.9%) with a mean age of 60±10 years. Participants had mostly RRMS(65.6%) with moderate disability (median [interquartile range] PDDS score: 3.0 [5.0]), an average disease duration of 20±9.7 years and most participants were using an MS-specific disease modifying therapy(DMT; 84.3%). The sample reported scores consistent with moderate-to-severe sleep disturbances(PSQI global score: 7.2±3.6) and severe MS-related fatigue(FSS: 4.7±1.8), based on cut-off scores of greater than 5(Buysse et al.,1989) and greater than 4(Andreasen et al.,2011), respectively.

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Demographic and clinical characteristics of subsamples of MS+RLS(n=74) and MS only(n=201) are presented in Table 1. Approximately 27% of our sample fit the criteria for a positive diagnosis of RLS based on the CH-RLSq diagnostic questionnaire. Within the MS+RLS group, 9(12.2%) individuals reported no symptoms, 26(35.1%) mild symptoms, 28(37.8%) moderate symptoms, 10(13.5%) severe symptoms, and 1(1.4%) reported very severe symptoms of RLS. Of note, 20(27%) participants with MS+RLS were taking medications that can reduce symptoms of RLS and 14(18.9%) were taking medications that can exacerbate symptoms of RLS(Buchfuhrer,2012, Restless Legs Syndrome Foundation, 2018). The two groups (i.e.,MS+RLS and MS) were not significantly different in age, sex, race, MS type, disease duration, self-reported clinical disability status, number of participants on DMTs, sleep quality, or depression symptoms.

The MS+RLS group reported significantly worse HRQOL in both domains(MSIS-physical:p=0.020; and MSIS-psychological:p=0.007). The MS+RLS group reported significantly greater perceived fatigue(FSS:p=0.007) and anxiety symptoms(HADS-A:p=0.042) than the MS only group. Additionally, the MS+RLS group had a positive screening for anxiety and

depression based on a cut-off score of 7(Marrie et al.,2018). The difference between groups was small for the physical(d=0.32) and psychological(d=0.35) domains of HRQOL, perceived fatigue(d=0.40), depression symptoms(d=0.21), and anxiety symptoms(d=0.25).

3.2 Correlation Analysis

The bivariate correlations among RLS severity, HRQOL, clinical disability status, sleep quality, fatigue, depression, and anxiety in the MS+RLS group are presented in Table 2. RLS severity was significantly associated with physical(r=0.43) and psychological(r=0.46) HRQOL, sleep quality(r=0.38), perceived fatigue(r=0.28), and symptoms of depression(r=0.38) and anxiety(r=0.28). The physical domain of HRQOL was significantly associated with clinical disability status(r=0.74), sleep quality(r=0.33), fatigue(r=0.68), and depression(r=0.60); the psychological domain of HRQOL was significantly associated with sleep quality(r=0.56), fatigue(r=0.47), depression(r=0.78), and anxiety(r=0.74).

3.3 Linear Regression Analysis

The summary of linear regression analyses for evaluating the relationship between RLS diagnosis and HRQOL in the total sample(N=275) are presented in Table 3. RLS diagnosis significantly predicted the physical domain of HRQOL in Step 1(F=5.310, p=0.022; R^2=0.019), and this relationship was accounted for by FSS and HADS-A in Step 2(F=29.564, p=0.000; R change=0.228). RLS diagnosis significantly predicted the psychological domain of HRQOL in Step 1(F=7.362, p=0.007; R^2=0.026), and this relationship was accounted for by FSS and HADS-A in Step 2(F=109.293, p=0.000; R^2 change=0.522).

The summary of linear regression analyses for evaluating variables that may be intermediary in the relationship between RLS severity and HRQOL in those with MS+RLS(n=74) are presented in Table 4. RLS severity significantly predicted the physical domain of HRQOL in Step 1(F=16.259, p=0.000; R^2=0.184), and this relationship was partially accounted for by FSS and HADS-D in Step 2(F=26.626; p=0.000; R^2 change=0.423). RLS severity significantly predicted the psychological domain of HRQOL in Step 1(F=19.646, p=0.000; R^2=0.214), and this relationship was partially accounted for by FSS, HADS-D, and HADS-A in Step 2(F=37.113; p=0.000; R^2 change=0.596).

4. Discussion

This study provided a novel evaluation of the relationship between RLS severity and HRQOL as well as identified potential intermediary variables in this relationship for persons

with MS and RLS. Persons with MS and RLS had reduced HRQOL in both the physical and psychological domains. Consistent with previous research, persons with MS and RLS experienced more severe fatigue and a greater frequency of anxiety symptoms than those without RLS(Giannaki et al.,2018, Cederberg and Motl,2016). Among those with MS and RLS, RLS severity was moderately correlated with HRQOL, whereby greater RLS severity was associated with a greater impact of MS on both physical and psychological domains of HRQOL. The relationships between RLS severity and the domains of HRQOL were attenuated when accounting for fatigue, depression, and/or anxiety, suggesting that these symptoms may be intermediary factors of the association between RLS severity and HRQOL.

Within this study of adults with MS, meeting the diagnostic criteria for RLS was associated with significantly worse physical and psychological HRQOL, fatigue, anxiety, and depression, thereby suggesting that the presence of RLS in adults with MS may negatively impact HRQOL and associated outcomes. The presence of RLS significantly predicted the physical and psychological domains of HRQOL, yet our results suggest that the severity of fatigue and frequency of anxiety symptoms partially account for such relationships. This further suggests that fatigue and symptoms of anxiety may be important intermediaries in the relationship between RLS diagnosis and HRQOL in adults with MS.

Our results indicated that anxiety was significantly worse in adults with MS and RLS and that anxiety was positively associated with RLS severity and the psychological domain of HRQOL. To date, this is the first study to evaluate symptoms of anxiety in adults with MS and RLS. Anxiety is characterized by the excessive worry which an individual finds difficult to control that can cause significant problems in other areas of life (National Institute of Mental Health,2018). Results from the current study suggest that anxiety may be an important factor in the relationship among RLS, RLS severity, and HRQOL; however, the pathological connection between RLS and anxiety is unclear. One potential explanation is that RLS shares similar characteristics with anxiety disorders wherein the diagnostic criteria for generalized anxiety disorder include symptoms of restlessness, fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbance(Patriquin and Mathew,2017). Thus, the unpredictable and uncontrollable nature of RLS symptoms may contribute to or exacerbate anxiety symptoms which in turn impact HRQOL in adults with MS. More research is necessary to further evaluate

the temporal relationship between RLS severity and anxiety, as well as the impact of anxiety in persons with MS and RLS.

Results from the current study indicate that a reduced HRQOL in the physical domain was associated with worse RLS severity, greater self-reported clinical disability, poorer sleep quality, greater fatigue severity, and a higher frequency of depression. Similarly, reduced HRQOL in the psychological domain was associated with worse RLS severity, poorer sleep quality, greater fatigue severity, and a greater frequency of depression and anxiety symptoms. These results are similar to previous literature that has demonstrated significant correlations between HRQOL and fatigue, poor sleep(Lobentanz et al.,2004, Amato et al.,2001, Boe Lunde et al.,2012, Tabrizi and Radfar,2015, Kotterba et al.,2018), depression(Lobentanz et al.,2004, Amato et al.,2001), and anxiety(Fruehwald et al.,2001) in persons with MS. Importantly, this is the first study to identify RLS severity as an important correlate of HRQOL and this association may be accounted for by fatigue, depression, and anxiety. These results build upon current literature that identifies depression and fatigue as strong predictors of HRQOL in persons with MS(Lobentanz et al.,2004, Amato et al.,2001, Fruehwald et al.,2001, Nourbakhsh et al.,2016). Future research should consider other possible factors that may mediate the relationship between the severity of RLS symptoms experienced and HRQOL in persons with MS.

5. Limitations

There are important limitations to consider when interpreting our results. The cross-sectional design of this study precludes any inferences of causality or temporality. The response rate from the NARCOMS registry was low (i.e., 31%) and further reduced (27%) based on valid questionnaires. Thus, selection bias may have played a role in our results. As this was a mail-based protocol, all measures are self-report in nature. The lack of an interview for RLS diagnosis may have led to false negative or false positive diagnoses as the CH-RLSq. However, the RLS diagnostic questionnaire (i.e.,CH-RLSq) that has been validated for diagnosing RLS with consideration of certain RLS mimics via survey form for the general population(Allen et al.,2009). We did not include criteria for a minimum time since diagnosis. Some prescription medications for MS present another limitation to assessing RLS symptom severity in this population as a number of prescriptions for symptoms and consequences of MS can be used to treat symptoms of RLS (e.g., pramipexole, gabapentin, and rotigotine(Restless Legs Syndrome Foundation,2018)) or may exacerbate symptoms of RLS (e.g., antidepressants, first-generation

antihistamines(Buchfuhrer,2012)) wherein 25.1% (n=69) of our sample with MS and RLS were taking a medication that could reduce RLS severity and 14.2% (n=39) were taking medications that could exacerbate RLS severity. This paper included only a single measure for the evaluation of sleep, but it did not include a measure for assessing daytime sleepiness(e.g.,Epworth Sleepiness Scale). This is a limitation as daytime sleepiness is a common correlate of RLS that may impact HRQOL. Our sample consisted primarily of persons with RRMS(65.8%) suggesting that our sample may not be fully representative of the MS population, and we further note that some subjects may be unaware of a transition from RRMS to SPMS. Additionally, this high prevalence of individuals with RRMS may not be representative of the MS+RLS population as prior literature suggest that RLS may be more prevalent in those with PPMS and those with greater disability levels(Manconi et al.,2007, Manconi et al.,2008). However, we included a large, random sample of individuals with MS that included all phenotypes of MS and our sample was representative of U.S. peak prevalence (i.e., 55-64 years) for age and sex(Wallin et al.,2019), disease duration, and MS type(Multiple Sclerosis International Foundation,2013).

6. Conclusions

This study sheds new light on the relationships among RLS severity, MS symptomology, and physical and psychological domains of HRQOL. Persons with MS and RLS experience reduced HRQOL in both physical and psychological domains, worse fatigue, and more frequent symptoms of depression and anxiety. Worse RLS severity was associated with both physical and psychological domains of HRQOL that was seemingly accounted for by fatigue, depression, and anxiety. These results identify a possible pathway for mitigating reductions in HRQOL through the reduction of RLS and other MS symptoms(e.g.,fatigue and anxiety). The identification of intermediary factors in the relationship between RLS and QOL in MS provides valuable information that could be utilized to improve symptomatic treatment and modulate treatment over time, consequently improving HRQOL, in persons with MS and RLS. Future research should further examine the role of anxiety in persons with MS and RLS as well as identify correlates and factors that may mediate the relationship between RLS and HRQOL as early identification and treatment of modifiable factors, such as fatigue, depression, and anxiety, may improve quality of life in people with MS and RLS.

Acknowledgements: none.

References

Table 1: Participant characteristics for all participants (N = 275) and the subsamples of participants with and without restless legs syndrome.

	All Participants (N = 275)	MS+RLS (n = 74)	MS (n = 201)	*p*-value	*d*
Age (years)	59.7 ± 10.1	59.4 ± 9.9	59.9 ± 10.2	0.748	--
Sex (n (%))	223 (81.1%) F / 52 (18.9%) M	60 (81.1%) F / 14 (18.9%) M	163 (81.1%) F / 38 (18.9%) M	0.998[a]	--
Race (n (%))				0.422[a]	--
American Indian	1 (0.4%)	0 (0.0%)	1 (0.5%)	--	--
Black/African American	4 (1.5%)	0 (0.0%)	4 (2.0%)	--	--
Caucasian	261 (94.9%)	73 (98.6%)	188 (93.4%)	--	--
Latino/Latina	5 (1.8%)	0 (0.0%)	5 (0.3%)	--	--
Other	3 (1.1%)	1 (1.4%)	2 (1.0%)	--	--
MS Type (n (%))				0.731[a]	--
RRMS	181 (65.8%)	48 (64.9%)	133 (66.2%)	--	--
SPMS	58 (21.1%)	17 (23.0%)	41 (20.4%)	--	--
PPMS	33 (12.0%)	9 (12.2%)	24 (11.9%)	--	--
Benign	3 (1.1%)	0 (0.0%)	3 (1.5%)	--	--
Disease Duration (years)	20.4 ± 9.7	20.0 ± 9.7	20.5 ± 9.7	0.686	--
MS DMT (n (%))	231 (84.3%)	53 (71.6%)	149 (74.1%)	0.676[a]	--
PDDS (median (IQR))	3.0 (5)	3.5 (3)	3.0 (5)	0.291[b]	--
IRLS	7.6 ± 8.0	11.4 ± 7.6	6.2 ± 7.7	**0.000**	0.680
RLS Modifying Rx	69 (25.1%)	20 (27.0%)	49 (24.4%)	0.653[a]	--
RLS Exacerbating Rx	39 (14.2%)	14 (18.9%)	25 (12.4%)	0.172[a]	--

MSIS-Physical	35.0 ± 25.0	40.7 ± 24.6	32.8 ± 24.8	**0.020**	0.319
MSIS-Psychological	25.3 ± 19.1	30.4 ± 22.7	23.4 ± 17.3	**0.007**	0.347
PSQI	6.9 ± 3.4	7.3 ± 3.8	6.7 ± 3.2	0.172	0.171
FSS	4.7 ± 1.8	5.2 ± 1.7	4.5 ± 1.8	**0.007**	0.400
HADS-D	6.9 ± 2.8	7.3 ± 3.1	6.7 ± 2.7	0.115	0.206
HADS-A	6.7 ± 2.7	7.2 ± 3.1	6.5 ± 2.5	**0.042**	0.249

Note: Data are presented in mean ± standard deviation unless otherwise specified. *MS* multiple sclerosis; *RLS* restless legs syndrome; *RRMS* relapsing-remitting MS; *SPMS* secondary progressive MS; *PPMS* primary progressive MS; *PDDS* Patient Determined Disease Status; *IQR* interquartile range; *IRLS* International Restless Legs Syndrome Study Group Scale; *MSIS* Multiple Sclerosis Impact Scale; *PSQI* Pittsburgh Sleep Quality Index; *FSS* Fatigue Severity Scale; *HADS-D* Hospital Anxiety and Depression Scale-Depression domain *HADS-A* Hospital Anxiety and Depression Scale-Anxiety domain. [a] Chi Square Analysis; [b] Wilcoxon-Mann-Whitney Test

Table 2: Summary of Pearson-product bivariate correlations in adults with restless legs syndrome and multiple sclerosis (n = 74)

	IRLS	MSIS-Physical	MSIS-Psychological	PDDS	PSQI	FSS	HADS-D
MSIS-Physical	0.429**	-					
MSIS- Psychological	0.463**	0.563**	-				
PDDS	0.194	0.737**	0.075	-			
PSQI	0.382**	0.334**	0.561**	0.096	-		
FSS	0.277*	0.678**	0.474**	0.363**	0.409**	-	
HADS-D	0.375**	0.599**	0.776**	0.284*	0.443**	0.437**	--
HADS-A	0.278*	0.202	0.740**	-0.168	0.383**	0.102	0.562**

Notes: *IRLS* International Restless Legs Syndrome Study Group Scale; *MSIS* Multiple Sclerosis Impact Scale; *PDDS* Patient Determined Disease Status; *PSQI* Pittsburgh Sleep Quality Index; *FSS* Fatigue Severity Scale; *HADS-D* Hospital Anxiety and Depression Scale-Depression domain; *HADS-A* Hospital Anxiety and Depression Scale-Anxiety domain. *$p < 0.05$; **$p < 0.01$

Table 3: Summary of linear regression analysis for restless legs syndrome diagnosis and other variables predicting the physical and psychological domains of health-related quality of life in adults with multiple sclerosis (N = 275).

	MSIS-Physical		
	B	**SE B**	**β**
Step 1			
CH-RLSq	7.764	3.369	0.138*
Step 2			
CH-RLSq	3.036	3.019	0.054
FSS	6.684	0.756	0.476*
HADS-A	0.482	0.494	0.052
R^2 = .019 for step 1; ΔR^2 = .228 for step 2. *p < 0.05			

	MSIS-Psychological		
	B	**SE B**	**β**
Step 1			
CH-RLSq	6.975	2.571	0.162*
Step 2			
CH-RLSq	1.393	1.791	0.032
FSS	3.695	0.449	0.343*
HADS-A	4.297	0.293	0.607*
R^2 = .026 for step 1; ΔR^2 = .522 for step 2. *p < 0.05			

Notes: *MSIS* Multiple Sclerosis Impact Scale; *CH-RLSq* Cambridge-Hopkins Restless Legs Syndrome Questionnaire; *FSS* Fatigue Severity Scale; *HADS-A* Hospital Anxiety and Depression Scale-Anxiety domain. *p < 0.05

Table 4: Summary of linear regression analysis for restless legs syndrome severity and other variables predicting the physical and psychological domains of health-related quality of life in adults with restless legs syndrome and multiple sclerosis (n = 74).

	MSIS-Physical		
	B	**SE B**	**β**
Step 1			
IRLS	1.393	0.345	0.429*
Step 2			
IRLS	0.641	0.275	0.198*
PSQI	-0.647	0.548	-0.105
FSS	7.508	1.271	0.515*
HADS-D	2.686	0.704	0.343*
R^2 = .184 for step 1; ΔR^2 = .423 for step 2. *p < 0.05			

	MSIS-Psychological		
	B	**SE B**	**β**
Step 1			
IRLS	1.383	0.312	0.463*
Step 2			
IRLS	0.338	0.178	0.113
PSQI	0.512	0.363	0.090
FSS	2.809	0.852	0.209*
HADS-D	2.488	0.532	0.345*
HADS-A	3.410	0.499	0.461*
R^2 = .214 for step 1; ΔR^2 = .594 for step 2. *p < 0.05			

Notes: *MSIS* Multiple Sclerosis Impact Scale; *IRLS* International Restless Legs Syndrome Study Group Scale; *PSQI* Pittsburgh Sleep Quality Index; *FSS* Fatigue Severity Scale; *HADS-D* Hospital Anxiety and Depression Scale-Depression domain; *HADS-A* Hospital Anxiety and Depression Scale-Anxiety domain. *p < 0.05

Figure 1: CONSORT Diagram.