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SCIENTIFIC INVESTIGATIONS

Effects of a 12-week yoga versus a 12-week educational film intervention on symptoms of restless legs syndrome and related outcomes: an exploratory randomized controlled trial

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Study Objectives: To assess the effects of a yoga versus educational film (EF) program on restless legs syndrome (RLS) symptoms and related outcomes in adults with RLS.

Methods: Forty-one community-dwelling, ambulatory nonpregnant adults with moderate to severe RLS were randomized to a 12-week yoga (n = 19) or EF program (n = 22). In addition to attending classes, all participants completed practice/treatment logs. Yoga group participants were asked to practice at home 30 minutes per day on nonclass days; EF participants were instructed to record any RLS treatments used on their daily logs. Core outcomes assessed pretreatment and posttreatment were RLS symptoms and symptom severity (International RLS Study Group Scale (IRLS) and RLS ordinal scale), sleep quality, mood, perceived stress, and quality of life (QOL).

Results: Thirty adults (13 yoga, 17 EF), aged 24 to 73 (mean = 50.4 ± 2.4 years), completed the 12-week study (78% female, 80.5% white). Post-intervention, both groups showed significant improvement in RLS symptoms and severity, perceived stress, mood, and QOL-mental health ($P \leq .04$). Relative to the EF group, yoga participants demonstrated significantly greater reductions in RLS symptoms and symptom severity ($P \leq .01$), and greater improvements in perceived stress and mood ($P \leq .04$), as well as sleep quality ($P = .09$); RLS symptoms decreased to minimal/mild in 77% of yoga group participants, with none scoring in the severe range by week 12, versus 24% and 12%, respectively, in EF participants. In the yoga group, IRLS and RLS severity scores declined with increasing minutes of homework practice ($r = .7$, $P = .009$ and $r = .6$, $P = .03$, respectively), suggesting a possible dose-response relationship.

Conclusions: Findings of this exploratory RCT suggest that yoga may be effective in reducing RLS symptoms and symptom severity, decreasing perceived stress, and improving mood and sleep in adults with RLS.

Clinical Trial Registration: Registry: Clinicaltrials.gov; Title: Yoga vs. Education for Restless Legs: a Feasibility Study; Identifier: NCT03570515; URL: https://clinicaltrials.gov/ct2/show/NCT03570515

Keywords: education, exercise therapy, mental health, mind-body, quality of life, restless legs syndrome, sleep disorders, yoga

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Relaxation and other nonpharmacologic therapies are often recommended for management of restless legs syndrome (RLS), a common and burdensome sleep and sensorimotor disorder. However, rigorous supporting research remains sparse. This exploratory randomized controlled trial assessed the effects of a yoga versus educational film program on RLS symptoms and related outcomes in adults with moderate to severe RLS.

Study Impact: Findings of this study suggest that yoga may offer a safe, viable, and effective therapy for reducing RLS symptoms and symptom severity, decreasing perceived stress, and improving sleep and mood in adults with RLS, with effects that were comparable to those of RLS medications.

INTRODUCTION

Restless legs syndrome (RLS) is a burdensome sleep and sensorimotor disorder affecting up to 29% of US and European adults, with estimated prevalence rates averaging 12% in the general population and 19.5% in primary care patients.[1] RLS is characterized by a compelling urge to move the legs that is usually accompanied by unpleasant, often painful sensations in the legs, begins or worsens during periods of inactivity, is worse at night, and is at least partially alleviated by movement.[2] Up to 65% of those affected by RLS experience moderate to severe symptoms.[1] Associated with significant economic and societal burden,[3,4] RLS can lead to reductions in quality of life (QOL) and declines in productivity that are comparable to or greater than those reported in other serious chronic disorders, including diabetes, depression, Parkinson disease, and stroke.[1,4] A major

cause of chronic sleep loss,[5] RLS is also associated with significant deterioration in mood,[6,7] which can further exacerbate sleep deficits.[8,9]

Although RLS is increasingly recognized as a disorder of significant clinical and economic importance,[1,3,4,10] RLS etiology remains incompletely understood.[4,11] Currently, the primary underlying causes of RLS are thought to be dopaminergic dysfunction, genetic predisposition, and deficiencies in iron metabolism,[11–13] although these factors have to date offered only a partial explanation.[9] A growing body of evidence also suggests that autonomic and hypothalamic–pituitary-adrenal axis dysregulation may also play an important role in RLS pathogenesis and progression.[1,9,14] Recent studies suggest that RLS may also be linked, in a bidirectional manner, to cardiovascular disease, stroke, and key components of the metabolic syndrome,[9] associations that may be in part mediated by RLS's adverse effects on sleep and mood.[15,16]

Unfortunately, there is no cure for RLS, with current treatments aimed at symptom management. Pharmaceutical agents, specifically dopaminergic agents and antiseizure medications (α2δ ligands), remain first-line treatments for RLS, with opioids and less commonly, benzodiazepines, employed as second-line therapies.[17,18] Regrettably, all medications used in the management of RLS carry risk of serious side effects (affecting 6% to 80% of patients, depending on the medication and treatment duration).[15,17] Among the most problematic is augmentation of symptoms, a serious clinical sequelae reported for all dopaminergic drugs and certain opioids, with risk increasing with longer treatment duration.[15,17] Other common side effects include somnolence and general toxicity (all RLS medications); impulse control disorders (dopamine receptor agonists); nausea and vomiting (dopaminergic agents, opioids); mood disturbances (α2δ ligands, opioids, benzodiazepines); weight gain (α2δ ligands); addiction (opioids, benzodiazepines); dizziness; unsteadiness; increased risk for falls (α2δ ligands, opioids, benzodiazepines); and other adverse side effects.[15,17,19–21] In addition, these sequelae can be a particularly serious for older adults,[22,23] who are also disproportionately affected by RLS.[20,24] In addition, the efficacy of all RLS medications often diminishes with time,[17,25] leaving patients with few treatment options.

Given the drawbacks of medications currently prescribed for RLS, investigation of safe, sustainable nonpharmacologic therapies that are suitable for long-term use and that may not only alleviate RLS symptoms but address associated declines in psychosocial status and QOL is clearly warranted. Although clinical guidelines often recommend lifestyle and other nonpharmacologic approaches for patients with RLS,[17,26,27] recommendations are generally nonspecific and rigorous supportive research remains sparse.[8,28] One nonpharmacological approach that may hold particular promise for adults with RLS is yoga, an ancient mind-body practice that is increasingly used as a therapeutic modality.[29,30] Numerous studies have shown yoga to improve QOL, enhance well-being, and decrease pain,[31–37] outcomes of clear relevance to those with RLS. In addition, our recent proof-of-concept studies suggest that yoga may attenuate RLS symptoms, improve sleep, enhance mood, and decrease stress in adults with RLS.[14,38] However, although findings of these trials suggest that yoga may be beneficial for those with RLS, interpretation is hindered by design and other methodological limitations, including lack of a control group,[38] restriction to women,[14,38] and lack of RLS-specific measures.[14] Designed to help address these limitations, this pilot randomized controlled trial (RCT) investigated the effects of a gentle yoga versus an educational film (EF) program on RLS symptoms and symptom severity, and on the associated outcomes of sleep, mood, perceived stress, and QOL in adults with moderate to severe RLS.

METHODS

Study participants and methods for this exploratory RCT are described in the next paragraphs and in the literature.[8] The study was approved by the West Virginia University (WVU) Institutional Review Board (IRB), The Ohio State University (OSU) IRB, and the National Center for Complementary and Integrative Health/National Institutes of Health Office of Clinical and Regulatory Affairs.

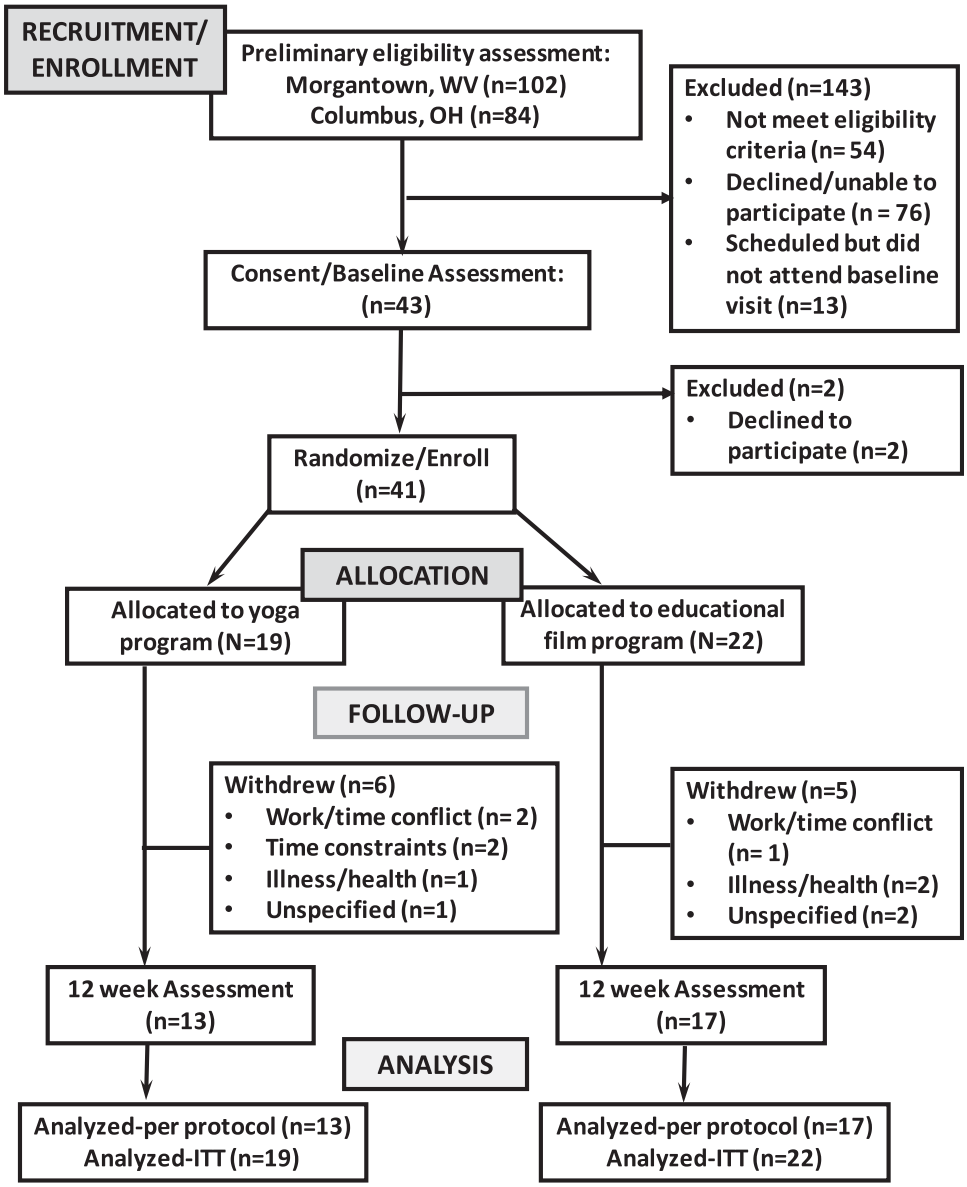
Study participants

Eligible participants were community-dwelling, ambulatory adults aged 18 years or older with moderate to severe RLS defined as follows: (1) symptoms that meet all five of the International Restless Legs Syndrome Study Group Rating Scale (IRLS) essential diagnostic criteria for RLS[2,39] (an urge to move the legs, often associated with discomfort or disagreeable sensations in the legs, that begins or worsens during periods of rest or inactivity, is partially or totally relieved by movement, is worse or only occurs in the evening or night, and is not solely accounted for by another condition [eg, positional discomfort, leg cramps, habitual foot tapping]); (2) RLS symptoms at least once a week in the past 3 months; (3) a score of at least 2 points (moderate) on IRLS question 6: "How severe was your RLS as a whole?"[40,41]; and (4) confirmation of RLS diagnosis and study eligibility by a physician trained in sleep medicine. These criteria helped to ensure exclusion of mimics (such as positional discomfort, leg cramps, arthritis pain.).[5,42] We excluded those who screened positive for anemia (hemoglobin [Hb] levels < 12 g/dL for women,<13 g/dL for men); had practiced yoga within the past year; were currently on antipsychotic medication or had changed dosage of dopaminergic or any other central nervous system agents (eg, opiates, sedative hypnotics, anticonvulsants, adrenolytic agents, benzodiazepines) within the past 3 months; had any orthopedic, neurologic or other concomitant condition that could prevent safe completion of a 12-week yoga program or confound assessments (eg, neuropathy; Parkinson disease; stroke; rheumatoid arthritis; renal or heart failure; sleep apnea; myocardial infarction within the past 6 months; cancer (except nonmelanoma skin cancer); had evidence of anemia; or were pregnant or within 6 months postpartum. These exclusion criteria are consistent with those commonly used in trials of RLS drugs and other RLS interventions.[43–48]

Recruitment and screening

Participants were recruited from the Morgantown, West Virginia metropolitan area (WVU site) and Columbus, Ohio (OSU

Figure 1—Study flow diagram.



site) via a combination of print and electronic advertisements, flyers, and brochures posted in public places such as community bulletin boards (physical and electronic); health center waiting areas, work place settings, churches, the Intranet, and other venues. In the WVU site, recruitment letters were sent to all adults visiting a local WVU Medicine clinic who had received a diagnosis of RLS (ICD-9 code: 333.94, 333.99) within the past 5 years. Eligibility criteria were reviewed with all potential participants via telephone, along with the study protocol, timing, and class schedules.

At visit 1, following informed consent each consented adult still interested in participating was formally screened for trial eligibility using a standard screening checklist,[8] with RLS confirmed via consultation with the study physician. Hb levels were also measured using a simple, hand-held pulse oximetry Hb monitor (Masimo Pronto); any individuals with evidence of anemia (Hb levels < 12 g/dL for women, < 13 g/dL for men) were excluded (n = 1). Participants meeting all eligibility criteria then underwent a comprehensive baseline assessment and treatment randomization. Of a total of 186 potential participants who made initial inquiries, (102 WVU, 84 OSU), 56 indicated that they were eligible, willing, and available to participate and were scheduled for a consent visit, full eligibility screen, and baseline assessment. Of these, 41 were ultimately enrolled in the study (**Figure 1**).

Treatment allocation and randomization

Following confirmation of eligibility and baseline assessment, randomization was performed by a team member who had no advance knowledge of treatment allocation; uniquely numbered, sealed, opaque envelopes containing information regarding the participant's assigned intervention were given to

each participant in sequence; as in previous studies, participants were instructed to open their envelopes upon exiting the building. Enrolled participants were randomized to one of the two treatment groups described in the next paragraphs, in a 1:1 ratio, based on the allocation sequence generated by the study statistician using a permuted block design.[8] The statistician, who had no contact with participants, generated the randomized assignment master list and provided the sequentially numbered opaque envelopes containing the group assignment and corresponding study forms. The list linking participant numbers with personally identifiable information was maintained by the study coordinator.

Baseline and outcome assessments

Participants underwent an assessment at baseline and following the 12-week intervention period. All assessments and data entry were performed by trained study personnel blinded to participant treatment assignment. Detailed baseline information was gathered on medical and reproductive history, demographic characteristics, body mass index (BMI, kg/m^2), and lifestyle factors. The primary outcome for this study was RLS symptomatology, measured using the IRLS, a 10-item scale that includes questions related to frequency, intensity, and impact.[40] The IRLS is considered the gold standard for measuring RLS symptoms,[49] and is recommended for use in RLS clinical trials by the European RLS Study Group[50] and other RLS experts[51]; this instrument is widely used both in the United States and internationally.[1,9] We also evaluated the effects of yoga on RLS symptom severity using the IRLS severity subscale[52] (considered relatively robust to placebo effects[50]), and the single-item RLS ordinal scale.[48,53]

Secondary outcomes included sleep quality, mood, perceived stress, and health-related QOL, endpoints recommended for inclusion in all clinical trials of RLS.[15,50] These outcomes were assessed via a short battery of self-report instruments commonly used in pharmaceutical trials of patients with RLS.[54–57] Sleep quality was assessed using the 9-item Pittsburgh Sleep Quality Index[58]; mood was evaluated using the 65-item Profile of Mood States[59] and 10-item Perceived Stress Scale[60]; and health-related QOL) was measured using the 36-item Medical Outcomes Study Short Form-36 (SF-36).[61] These self-report instruments are well-established scales that have been shown to be sensitive to short-term behavioral interventions, and have been validated in a wide range of populations, including patients with RLS.[14,59,62–69] Blood pressure and heart rate were also measured in a seated position following a 5-minute rest period, with measurements taken three times using an automatic blood pressure monitor (OMRON HEM-780) and averaged for a final score.

To assess possible change in social support and physical activity (other than yoga) potential confounding factors, participants also completed the 11-item Duke Social Support Index[70] and 10-item Physical Activity Scale for Elderly[71] at each visit. In addition, information on BMI,[2] caffeine and alcohol consumption, smoking, and use of non-RLS medications was gathered at each assessment. To assess expectation of benefit, the Credibility/ Expectancy Questionnaire[72] was collected from participants after their first class. Participants were also asked to record use of other RLS treatments on their weekly logs (see next paragraphs). In addition, all participants were asked to complete a short, anonymous exit questionnaire, modeled after that used in our previous trials.[73]

Interventions

Yoga program (active intervention)

Participants randomized to the yoga group completed a 12-week gentle Iyengar yoga program based on that developed and successfully implemented in our two pilot studies[14,38] and finalized following detailed review and input from an Iyengar Master Trainer. Participants attended two 75-minute classes per week for the first 4 weeks, then one 75-minute class for the remaining 8 weeks and were asked to complete a 30-minute homework routine 5 days a week on nonclass days. Yoga classes were held at two yoga studios in close proximity to the WVU Health Sciences Center campus (WVU site) and OSU Center for Integrative Health and Wellness (OSU site), respectively. As in our prior trials,[14,38] each yoga class began with simple yogic centering and breathing exercises, followed by a sequence of active and restorative poses (asanas), and ending with a 10-minute guided supine relaxation practice. The yoga routines, including a collective total of 25 commonly used asanas, were tailored for sedentary adults naïve to yoga, designed to increase gradually in difficulty as participants progress. Pose modifications and props (eg, chairs, blankets, and straps) were used as needed to allow all participants to perform the poses safely and easily. In addition, each class was restricted to a maximum of 12 participants to allow for personalized attention if needed. All study yoga instructors were certified in Iyengar yoga ($\geq$ 500 hours), with a minimum of 5 years' experience teaching adults with a range of chronic health conditions; all were specifically trained in the final RLS yoga protocol by lead study yoga teacher, Dr. Kimberly Williams. To facilitate home practice, all participants received yoga mats and straps, along with a yoga DVD and a comprehensive, indexed training manual illustrating the homework routines.[8]

Educational film program (comparator)

Participants assigned to the film group attended one 75-minute class per week for 12 weeks, and were asked to complete, as their study homework assignments, a daily log at home recording any RLS or sleep treatments they tried. Class sizes were equivalent to those in the yoga group to facilitate personal interaction with the instructor. At the first class, film group participants received a comprehensive set of lay educational materials regarding RLS symptoms, causes, and epidemiology and detailing recommended nonpharmacologic approaches to RLS management based on current national guidelines. Classes were held in an easily accessible private seminar room on the WVU or OSU campus, and were administered by health educators familiar with sleep disorders and common nonpharmacologic treatments and specifically trained for this purpose. Each class began with a brief meet-and-greet period, followed by a 60-minute instructional film segment, and a 10- to 15-minute group discussion.

As described in detail elsewhere,[8] course content for this standardized film education program included a total of 11 films providing information on: RLS symptoms, epidemiology, and management, including sleep hygiene practices; other sleep disorders and associated comorbidities; and on mind-body and other complementary therapies likely to be of interest to those participating in a yoga and sleep education study. The film selection procedure was similar to that used in our earlier studies.[8,14,73]

Upon study completion, yoga group participants were given access to all EF group materials and films; the film group participants received all yoga homework materials, as well as a half- day workshop in yoga for RLS. All participants were given modest compensation for their time and travel expenses.

Adherence and adverse events

Yoga and film class attendance was recorded by the instructor on standardized check sheets. Yoga participants also completed a daily log after each home practice session, indicating the number of minutes practiced, as well as any comments regarding the session; as noted previously, film group participants documented any RLS treatments used on their daily log, along with any comments or perceptions. Daily logs were turned in to the participant's respective instructor at the first group class each week. Logs and attendance records were collected weekly.

Adverse events were tracked via weekly review of participant logs. At the beginning of each class, the instructor also queried participants discretely regarding any potential problems; these were likewise recorded. A trained study team member also followed up with all participants within the first 10 days following the onset of the intervention, and periodically thereafter to address any potential issues or questions. In addition, participants were encouraged to contact study investigators and/or staff if they had any questions or concerns.

Fidelity

Program fidelity was assessed at least twice for each cohort and intervention. A trained study team member recorded adherence to the intervention protocol using a standardized check list tailored for this study. The study coordinator and principal investigator were notified of any protocol deviations, and these were immediately discussed with the instructor(s) and corrective action, if necessary, taken.

Statistical analysis

Data analysis was performed using SPSS, Version 25 (IBM Corp, Armonk, New York, United States). Baseline differences between the intervention groups, between participants at the two sites, and between dropouts and nondropouts were assessed using chi-square (for categorical variables), independent samples *t* tests (for normally distributed continuous variables), or Mann-Whitney *U* tests (for ordinal or continuous variables with evidence of skewing). Potential differences between treatment groups were analyzed using chi-square for retention, and one-way analysis of variance for treatment expectancies and adherence. In preliminary assessments, within-group changes over time at 3 months were assessed using analysis of covariance with baseline scores and site as covariates; site-adjusted between-group differences in treatment outcomes were assessed using repeated-measures analysis of variance. Distributions of dependent variables were examined to ensure the assumptions of normality and sphericity were met and variables transformed as necessary. In our intention-to-treat analyses, we used the SPSS multiple imputation function (10 iterations) to handle missing data.[74] As this was a pilot feasibility study, alpha was set at 0.05. Effect sizes were calculated using Cohen *d*. Bivariate correlations were performed using Pearson r. To assess the potential influence of RLS medication use and medication change, we conducted additional analyses, both adjusting for these factors statistically and excluding those reporting use or change in RLS medication.

RESULTS

Baseline characteristics

A total of 41 eligible adults with moderate to severe RLS were enrolled in the final study (15 from the WVU site, 26 from the OSU site). Participant characteristics, stratified by treatment group, are given in **Table 1**. Participant age ranged from 24 to 73 years (mean ± standard error [SE] = 50.9 ± 2.4 years). Most participants were female (78%) and non-Hispanic white (80.5%), college educated (75.6%), married or cohabiting (63.4%), and employed full time (65.9%) or part time (24.4%). Most consumed caffeinated beverages (58.5%), had never smoked (58.5%), and had received a diagnosis of at least one chronic comorbid condition (56.1%), with 43.9% reporting a history of depression or anxiety disorder (**Table 1**). Over 40% of participants were obese (mean BMI = 29.6 ± 1.0 kg/m^2); 41.5% were taking at least three medications. Most (80.5%) reported RLS symptoms at least 3 days a week, with 56.1% scoring in the severe to very severe range, and 17.1% indicating they currently were on RLS medications.

Between-group differences at baseline

The yoga and EF group did not differ significantly in baseline demographics, in lifestyle characteristics, or in reproductive or medical history ($P > .1$, **Table 1**) Although 7 participants (17%) indicated a prior history of anemia, no participants had evidence of anemia or were undergoing treatment for this condition. However, yoga group participants were more likely to have a previous diagnosis of RLS and to have more frequent RLS symptoms ($P \leq .05$, **Table 1**). As detailed in **Table 2**, yoga group participants also scored significantly higher on the IRLS severity subscale, but did not differ significantly in other measures of RLS symptom frequency, severity, or impact ($P > .1$), or in measures of stress, sleep quality, mood, QOL, social support or physical activity ($P \geq .3$). Likewise, the two groups indicated similar expectations regarding treatment benefit ($P \geq .45$).

OSU participants reported significantly lower frequency and severity of RLS symptoms than did those from the WVU site ($P < .05$) and were more likely to indicate full-time or part-time employment ($P = .04$), but did not differ significantly in other baseline characteristics or scores or in treatment expectations.

Table 1—Participant baseline characteristics: pilot randomized controlled trial of a 12-week beginner Iyengar yoga program versus a 12-week educational film program in adults with moderate to severe RLS.

	Overall (n = 41)	Yoga (n = 19)	EF (n = 22)	*P*
Demographic Characteristics				
Age (years); range 24–73				.33
< 35	8 (19.51)	4 (21.05)	4 (18.18)	
35–50	11 (26.83)	3 (15.79)	8 (36.36)	
> 50	22 (53.66)	12 (63.16)	10 (45.45)	
Mean ± SE	50.90 ± 2.40	52.29 ± 3.86	47.41 ± 2.99	.32
Sex				.38
Female	32 (78.05)	16 (84.21)	16 (72.73)	
Male	9 (21.95)	3 (15.79)	6 (27.27)	
Race/ethnicity				.82
Non-Hispanic white	33 (80.49)	15 (78.95)	18 (81.82)	
Minority	8 (19.51)	4 (21.05)	4 (18.18)	
Education				.22
12 years or less	2 (4.88)	1 (5.26)	1 (4.55)	
Some after high school	8 (19.51)	2 (10.53)	6 (27.27)	
4 years of college or more	31 (75.61)	16 (84.21)	15 (68.18)	
Mean ± SE in years	16.27 ± 0.30	16.21 ± 0.39	16.32 ± 0.46	.83
Employment status				.13
Full time or part time	27 (65.85)	10 (52.63)	17 (77.27)	
Retired	10 (24.39)	5 (26.32)	5 (22.73)	
Other	4 (9.76)	4 (21.05)	0 (0.00)	
Marital status				.58
Married/cohabiting	26 (63.41)	12 (63.16)	14 (63.64)	
Single	9 (21.95)	3 (15.79)	6 (27.27)	
Divorced/Widowed	6 (14.63)	4 (21.05)	2 (9.09)	
Lifestyle and Health-Related Factors				
Smoking status				.99
Never smoked	24 (58.54)	11 (57.89)	13 (59.09)	
Ever smoker	17 (41.46)	8 (42.11)	9 (40.91)	
Caffeinated beverages (oz/day)				.30
None	17 (41.46)	9 (47.37)	8 (36.36)	
4 to 16	14 (34.15)	6 (31.58)	8 (36.36)	
Mean ± SE	11.23 ± 2.09	8.88 ± 2.49	13.05 ± 3.16	.61
Physical activity				
PASE score total Mean ± SE	154.35 ± 12.64	149.32 ± 14.12	160.11 ± 19.10	.66
Body mass index Mean ± SE	29.59 ± 0.97	29.30 ± 1.65	29.30 ± 1.65	.79
Obese	17 (41.46)	7 (36.84)	10 (45.45)	.58
RLS history				
Previous diagnosis	14 (34.15)	11 (57.89)	3 (15.79)	.003
Prior drug treatment	14 (34.15)	11 (57.89)	3 (15.79)	.003
Duration of symptoms (years)	11.52 ± 1.32	14.29 ± 2.11	9.13 ± 1.52	.05
Family history	4 (9.76)	2 (10.53)	2 (10.53)	.88
RLS symptom frequency				.05
1–2 days/week	8 (19.51)	2 (10.53)	6 (27.27)	
3–5 days/week	22 (53.66)	8 (42.11)	14 (63.64)	
6–7 days/week	11 (26.83)	9 (47.37)	2 (9.09)	
Mean ± SE	3.98 ± 0.31	4.71 ± 0.52	3.17 ± 0.30	.02
History of diagnosed				
Anemia	7 (17.07)	4 (21.05)	3 (13.64)	.53
Diabetes	4 (9.76)	1 (5.26)	3 (13.64)	.37
Hypertension	7 (17.07)	3 (15.79)	4 (18.18)	.84
Hyperlipidemia	5 (12.20)	3 (15.79)	2 (9.09)	.51
Asthma	7 (17.07)	5 (26.32)	2 (9.09)	.14
Osteoarthritis/chronic pain	11 (26.83)	6 (31.58)	5 (22.73)	.53

(continued on following page)

Table 1—Participant baseline characteristics: pilot randomized controlled trial of a 12-week beginner Iyengar yoga program versus a 12-week educational film program in adults with moderate to severe RLS. (continued)

	Overall (n = 41)	Yoga (n = 19)	EF (n = 22)	*P*
Cancer	4 (9.76)	2 (10.53)	2 (9.09)	.98
Depression/anxiety	18 (43.90)	11 (57.89)	7 (31.82)	.17
Number of comorbid conditions[a]				.40
None	18 (43.90)	7 (36.84)	11 (50.00)	
One	10 (24.39)	4 (21.05)	6 (27.27)	
Two or more	13 (31.71)	8 (42.11)	5 (22.73)	
Mean ± SE	1.14 ± 0.23	1.29 ± 0.31	1.00 ± 0.34	.50
Including mental health conditions	1.58 ± 0.26	1.86 ± 0.35	1.32 ± 0.39	.31
Reproductive history				
Live births	1.47 ± 0.22	1.44 ± 0.30	1.50 ± 0.33	.89
0	8 (36.36)	4 (21.05)	4 (18.18)	
1	10 (45.45)	5 (26.32)	5 (22.73)	
≥ 2	14 (63.64)	7 (36.84)	7 (31.82)	
Pregnancies	1.66 ± 0.25	1.56 ± 0.34	1.75 ± 0.38	.72
0	8 (36.36)	4 (21.05)	4 (18.18)	
1	8 (36.36)	4 (21.05)	4 (18.18)	
≥ 2	16 (72.73)	8 (42.11)	8 (36.36)	
RLS in pregnancy	6 (18.75)	3 (15.79)	3 (13.64)	1.00
Medications				
RLS[b]	7 (17.07)	5 (26.32)	2 (9.09)	.15
Analgesic	15 (36.59)	5 (26.32)	10 (45.45)	.21
Antidepressant/antianxiety	17 (41.46)	9 (47.37)	8 (36.36)	.48
Steroids	13 (31.71)	8 (42.11)	5 (22.73)	.32
Antihypertensive	9 (21.95)	3 (15.79)	6 (27.27)	.38
Antihistamines	8 (19.51)	4 (21.05)	4 (18.18)	.82
Total	2.77 ± 0.41	3.14 ± 0.53	2.41 ± 0.63	.38

Data presented as n (%) or mean ± SE. [a]Including other serious chronic physical conditions. [b]Including dopaminergic agents, gabapentin. EF = educational film, PASE = Physical Activity Scale for the Elderly, RLS = restless legs syndrome, SE = standard error.

Retention and adherence

Of the original 41 participants, 30 (73%) completed the 12-week study and follow-up assessment (13 yoga, 17 EF). Reasons for dropout included: change in work schedule (n = 3), unexpected health issues unrelated to the study (n = 3), time constraints (n = 2), and unspecified (n = 3). Attrition rates did not differ between groups or sites ($P > .4$). Dropouts reported significantly shorter duration of RLS than did those completing the study (7.3 ± 1.5 versus 13.3 ± 1.6 years, $P < .01$) but did not otherwise differ in any demographic or lifestyle factors, medical history, BMI, or other health-related factors, treatment expectations, or baseline scores on any measure ($P \geq .4$).

Among those who completed the study, adherence exceeded our target goals for the study,[8] with participants in the yoga and EF group attending an average of 13.0 ± 0.84 (81%) and 10.3 ± 0.3 classes (85%), respectively. Yoga group participants completed an average of 45.5 ± 3.8 (81%) homework sessions and 1.9 ± 0.6 breathing exercises/nonclass day. Adherence did not differ significantly by site or by treatment assignment (class attendance).

Change over time

As detailed in **Table 3**, both the yoga and EF groups improved significantly over time in their IRLS symptom scores, overall and in both subscales ($P \leq .03$), although only yoga group participants showed significant reductions in the RLS Severity Scale ($P = .0004$). Likewise, both groups showed significant improvements in perceived stress, mood (overall and several subscales, ie, tension-anxiety, anger-hostility, depression), and QOL-mental health ($P < .05$). Yoga group participants also showed significant improvements in other mood domains (vigor, fatigue, confusion, Ps $\leq .003$) and in sleep quality ($P = .04$), whereas the EF group participants indicated significant gains in QOL-physical health ($P = .04$).

Relative to the EF group, the yoga group demonstrated significantly greater improvement in RLS symptom burden as measured by the IRLS total and severity subscale ($P \leq .015$) and the RLS Severity Scale ($P = .003$) (**Table 3**). Although a higher percentage of yoga than EF group participants tested in the severe to very severe range at baseline (61.5 versus 47.1%), 77% of yoga group participants tested in the minimal range at 12 weeks, with no participants scoring in the severe range, versus 23.4% and 12%, respectively in the education group ($P < .05$). Yoga group participants also showed significantly greater improvements in perceived stress ($P = .0009$), marginally significant reductions in sleep impairment ($P < .09$), as well as greater improvements in mood, both overall ($P = .04$) and in certain individual domains, including vigor ($P = .015$), fatigue ($P = .04$), and tension-anxiety ($P = .057$). Improvements in QOL

Table 2—Mean baseline scores on RLS symptoms and related outcomes; and on sleep, stress, mood, well-being, quality of life, and other factors in adults with moderate to severe RLS, stratified by treatment group.

Outcomes	Yoga (n = 19)	EF (n = 21)	*P*
Primary outcomes			
IRLS score total	23.42 ± 1.03	20.68 ± 0.91	.11
IRLS impact scale	5.42 ± 0.48	4.86 ± 0.47	.41
IRLS severity scale	15.58 ± 0.68	13.82 ± 0.55	.05
RLS severity	5.00 ± 0.34	4.23 ± 0.29	.11
Secondary outcomes			
Stress, sleep quality, mood, and well-being			
Perceived stress scale	14.21 ± 1.00	13.50 ± 1.28	.67
Pittsburgh Sleep Quality Index	11.65 ± 0.84	10.67 ± 0.78	.40
Profile of mood states (total score)	22.14 ± 5.08	22.73 ± 7.48	.70
Health-related quality of life (SF-36)			
Mental health component score	68.39 ± 3.71	70.58 ± 4.01	.69
Physical health component score	70.10 ± 4.16	73.10 ± 4.34	.62
Potential mediators			
Duke Social Support Index			
Social interaction	9.00 ± 1.03	8.27 ± 0.74	.56
Social support	19.10 ± 0.40	18.95 ± 0.49	.82
Physical activity (PASE)	147.20 ± 14.76	160.11 ± 19.10	.61
Treatment expectancy (CEQ)			
Confidence that treatment will be beneficial (1–10)	7.00 ± 0.55	7.27 ± 0.58	.75
Degree improvement expected (1–10)	5.86 ± 0.63	6.60 ± 0.68	.45

Data presented as mean ± standard error. CEQ = Credibility Expectancy Questionnaire (higher numbers indicate higher expectancy), IRLS = International RLS Study Group Scale, PASE = Physical Activity Scale for the Elderly, RLS = restless legs syndrome, SF-36 = Short Form-36.

did not differ by treatment group, nor did changes in either social support or physical activity. Repeated intention-to-treat analyses yielded similar results. Additional adjustment for medication change, prior history of anemia, report of previous RLS diagnosis or drug treatment, RLS duration, or treatment expectations did not appreciably alter the findings. Exclusion of those on dopaminergic medications (n = 3 yoga, 2 EF group participants) in the analyses slightly strengthened the between-group differences in sleep quality (mean differences in the yoga versus film (P = .056) but did not substantively alter other findings.

In the yoga group, class attendance was significantly and positively associated with improvement in RLS symptom burden in the yoga group (r for IRLS and RLS severity scale = .4 and .5, respectively, $P \leq .05$), as were the number of home practice sessions (r for IRLS and RLS severity scale = .6 and .7, respectively, $P \leq .03$). Likewise, home practice sessions were significantly correlated with improvements in perceived stress (r = .5), several domains of mood (overall, depression, fatigue, and vigor, r = .45–.6), and QOL-mental health (r = .6) ($P \leq .05$).

In contrast, EF participants showed no significant relationships between adherence (class attendance) and reduction in RLS symptom burden (r's = .1–.2, P's > .2) or improvement in any measure of stress, mood, or QOL. Sixteen EF group participants (94%) reported regular use of nonpharmacologic RLS management strategies recommended in the films and readings, often in combination. For example, 82% used relaxation practices, including hot showers/baths (60%), stretching and progressive muscle relaxation (59%), and breathing exercises, visualization, and/or yoga/meditation (59%). Eight EF participants (41%) used exercise to help reduce their symptoms, and several employed sleep hygiene practices (n = 4), sought care from an alternative/allied health care provider (n = 4), and/or used other measures (n = 13).

Treatment expectations were unrelated to change in any outcome in either group. No adverse events were observed or reported.

DISCUSSION

To our knowledge, this preliminary investigation is the first RCT to assess the potential efficacy of yoga for reducing RLS symptoms and symptom severity, and the first RCT specifically designed to examine the potential benefits of this popular mind-body therapy for adults with RLS. Consistent with findings from our two pilot studies in women with RLS,[38,75] findings of this preliminary RCT suggest that a gentle 12-week yoga program can significantly alleviate RLS symptoms and symptom severity, improve mood, and reduce perceived stress in adults with moderate to severe RLS. In this

Table 3—Change at 3 months in RLS symptoms, perceived stress, sleep, mood, and related outcomes in adults with RLS randomized to a 12-week Iyengar yoga or educational film program.

	Yoga			EF			*P*[b]
	Mean ± SE	*P*[a]	ES	Mean ± SE	*P*[a]	ES	
RLS symptoms, severity, impact							
IRLS symptom total	−9.35 ± 1.70	.0001	1.8	−4.11 ± 1.36	.004	0.8	.015
Symptom severity subscale	−6.19 ± 0.98	.00004	1.9	−2.41 ± 0.98	.03	0.7	.01
Symptom impact subscale	−2.54 ± 0.80	.008	1.1	−1.53 ± 0.45	.004	0.7	.16
RLS severity scale	−2.54 ± 0.53	.0004	2.3	−0.58 ± 0.45	.21	0.4	.003
Secondary outcomes							
Stress, mood, well-being, and sleep quality							
Perceived stress scale	−8.00 ± 1.79	.0008	1.5	−2.41 ± 0.96	.02	0.4	.0009
Profile of mood states (total score)	−32.00 ± 6.60	.0004	2.3	−19.31 ± 9.00	.05	0.8	.04
Tension-Anxiety	−5.62 ± 1.14	.00035	1.8	−2.94 ± 1.18	.02	0.7	.057
Anger-Hostility	−6.70 ± 2.00	.006	1.8	−4.76 ± 2.13	.04	1.3	.365
Vigor	4.00 ± 1.08	.00035	0.7	0.23 ± 0.88	.79	0.0	.015
Fatigue	−5.92 ± 1.61	.003	1.8	−2.71 ± 1.58	.10	0.4	.04
Confusion	−4.92 ± 1.26	.002	2.1	−3.25 ± 1.67	.07	0.7	.25
Depression	−4.85 ± 1.95	.03	1.4	−5.00 ± 2.14	.03	0.8	.79
Pittsburgh Sleep Quality Index (total score)	−2.11 ± 0.84	.04	0.8	−0.94 ± 0.57	.12	0.3	.09
Health-related quality of life (SF-36)							
Mental health component	11.40 ± 5.01	.04	0.6	7.52 ± 2.72	.01	0.4	.44
Physical health component	2.40 ± 3.33	.48	0.2	6.43 ± 2.75	.03	0.3	.46
Potential mediators							
Duke Social Support Index							
Social interaction	1.46 ± 0.62	.04	0.3	1.94 ± 0.93	.05	0.6	.38
Social support	0.38 ± 0.49	.45	0.2	0.59 ± 0.40	.16	0.3	.49
Physical activity (PASE)	6.07 ± 22.2	.79	0.2	8.90 ± 17.67	.63	0.2	.78

[a]Repeated-measures analysis of variance. [b]Between-group difference at 3 months, adjusted for site. EF = educational film, ES = effect size, IRLS = International Restless Legs Syndrome Study Group Scale, PASE = Physical Activity Scale for the Elderly, SE = standard error, SF-36 = Short Form-36.

preliminary study, participants completing a 12-week yoga program showed significant improvements relative to those in the EF group in RLS symptoms and burden overall as measured by both the IRLS and the RLS Severity Scale. Effect sizes were moderate to large, and, in the yoga group, all but 3 adults (all in the severe to very severe range at baseline) tested in the minimal to mild RLS symptom range following the 12-week yoga program, indicating a robust response rate to this nonpharmacologic therapy.

Studies of yoga for RLS are limited to our two previous pilot trials in women, including a nested RCT of 20 sedentary older women at risk for cardiovascular disease that did not include RLS-specific measures,[14] and a single arm study of 13 community-dwelling women with moderate to severe RLS.[38] In agreement with findings from our prior research, participants assigned to the yoga program showed significant attenuation of RLS symptoms and symptom severity, with pre-post effect sizes ranging from 1.8 for IRLS total to 2.3 for RLS severity. The reductions in RLS symptoms and symptom severity observed in the current study are comparable to or greater than those documented in several previous controlled trials of exercise interventions in adults with RLS.[48,76–81] In four RCTs of adults with RLS who were on hemodialysis (total n = 178), participants assigned to a 4-week[76] to 6-month[77] exercise program showed significant declines in RLS symptoms and symptom severity compared to those receiving a placebo medication[77] or no intervention/usual care[76,78,79]; pre-post effect sizes for RLS symptoms overall ranged from an estimated 1.1[79] to 2.55[76] (estimated weighted mean effect size = 1.85), with only one study, a 3-arm, 4-week study of 90 Iranian adults with severe RLS demonstrating an effect size greater than 1.6.

Similarly, an RCT of 23 community-dwelling adults reported significant declines in RLS symptoms and symptom severity in those assigned to a 12-week exercise program relative to those receiving usual care,[48] with pre-post effect sizes of 1.4 and 0.9 for IRLS total and RLS severity, respectively. In contrast, a recent 6-week, 3-arm RCT of exercise versus discussion/waitlist in 18 Australian adults[81] showed no differences between groups in RLS symptoms or symptom severity; as in our study, both the active and control groups in

this study showed significant improvements, although estimated effect sizes for the active (exercise) intervention were more modest (1.1 IRLS total, 0.55 for RLS severity) than those observed in our trial. By contrast, in all other studies of exercise and RLS, participants assigned to the control group demonstrated either no change or nonsignificant deterioration in symptoms.[48,76–79] This discrepancy may be due in part to the choice of control group. Whereas the latter studies used a usual care/no intervention control, we, like Harrison et al,[81] used a more active comparator designed, at minimum, to control for time, attention, and setting. Moreover, almost all participants in the EF group engaged in RLS management strategies recommended in the films and readings, perhaps helping to explain the improvements observed in this group.

Likewise, the improvements in sleep, mood and perceived stress observed in this exploratory RCT are consistent with those demonstrated in our recent pilot trials regarding the effects of yoga in women with RLS.[14,38] However, the three studies assessing the effects of exercise on psychosocial outcomes in adults with RLS (two RCTs[77,81] and one non-RCT[80] in adults with[77,80] and without end-stage renal disease[14,81]) have yielded mixed findings. One study, a small community-based RCT, reported significant reductions in sleep impairment, global stress, and depressive symptoms in both the exercise and control groups, but no between-group differences in any outcome.[81] In a small three-arm RCT of patients on hemodialysis, participants completing the 6-month exercise program showed no change in measures of sleep quality (effect sizes 0.0–0.1), but a significant improvement in depressive symptoms relative to those in the placebo group (with the latter demonstrating significant deterioration).[77] In contrast, a non-RCT in 14 hemodialysis patients indicated significant improvement in sleep quality (one measure) but not depression following a 16 week exercise program, although between-group differences were not reported.[80] In agreement with the two RCTs in patients with RLS on hemodialysis,[77,79] we found no evidence for between-group differences in QOL, although both the yoga and the EF groups showed significant within group improvements in QOL-mental health.

Although the mechanisms underlying the improvements observed following completion of the yoga program in this study remain unknown, yoga may benefit those experiencing RLS via several possible interrelated pathways.[8,14,38] For example, yoga may reduce RLS symptoms and symptom burden by decreasing sympathoadrenal and hypothalamic–pituitary-adrenal axis activation, restoring parasympathetic/sympathetic balance, and improving cardiometabolic function, factors linked to RLS etiology and progression, and bidirectionally associated with sleep impairment, mood disturbance, stress, and poor QOL.[9,82] In addition, findings from neurophysiological and neuroimaging studies[83–86] suggest that yogic practices may, by selectively activating specific neurochemical systems implicated in RLS, also promote beneficial changes in autonomic, neuroendocrine, and metabolic function, and in sleep, mood, and pain processing, changes which may, in turn, lead to reduced RLS symptoms and symptom burden.[8,14,38] Yoga may also lower motor cortex excitability and promote muscle relaxation, factors implicated in RLS pathophysiology.[14,87]

Notably, improvements in RLS symptoms, sleep, and mood observed following our 12-week yoga program were comparable or superior to those reported in recent meta-analytic reviews of RLS medication trials.[21,88] In addition, no adverse events were reported, retention was acceptable, and compliance very good overall. Together, these findings suggest that yoga may offer a safe and viable complement or alternative to pharmacologic treatment for patients with this burdensome disorder. Given the promising findings of this exploratory RCT, larger, longer term RCTs are warranted to further evaluate the efficacy of yoga for the management of RLS.

Strengths and limitations

Strengths of this study are several, including the community-based design, recruitment of participants from two sites, randomization of participants and between-group similarity in most baseline characteristics, acceptable participant retention, overall excellent adherence, and a comparison condition designed to help control for time, attention, and social interaction. The study population comprised a diverse sample of adults characterized by broad variation in demographic, lifestyle, and health-related characteristics. All participants tested in the moderate to severe range, with symptom scores comparable to those of participants in other RLS intervention trials.[48,77–79,81,88] In addition to change in RLS symptoms and symptom severity, we also assessed change in sleep quality, mood, and QOL, recommended endpoints for clinical trials of RLS.[15] To account for the potential placebo effects, we also measured treatment expectations after the first class, as well as change in social support/interaction to account for the potential influence of these factors.

This pilot RCT also has several limitations. Sample sizes were small, limiting power and generalizability. However, we observed significant improvement in the yoga versus control group in RLS symptoms and symptom severity, as well as in several other clinically important parameters, again arguing for a potential beneficial effect of the yoga program. Although the EF program was designed to help control for staff attention, setting, and time, class time requirements were higher in the yoga group and EF participants did not receive formal home practice assignments. However, EF group instructions to complete daily treatment logs were specifically framed as homework, and all but one EF participant reported regular engagement in nonpharmacologic approaches recommended in the educational films and reading materials. Nonetheless, because we did not require EF participants to record the time expended on these treatments, we cannot directly compare time expenditures on these home-based activities with those of the yoga group home practice, and thus cannot rule out the potential influence of differential time expenditure on the observed improvements in the yoga versus EF group. In addition, although assessors were blinded to participant treatment status, participants could not be masked. However, treatment expectancies did not differ between-groups, expectations were unrelated to change in outcomes, and adjustment for treatment expectancies did not substantively alter findings, suggesting that placebo effects did not explain the observed findings. Moreover, observed effect sizes were

substantially larger than would be expected with placebo,[89] and significantly greater than those observed in control groups for RLS symptoms, symptom severity, and other clinically important outcomes. Yoga group participants reported longer duration of RLS symptoms at baseline, and were more likely to report a prior RLS diagnosis. However, adjustment for neither symptom duration nor previous diagnosis appreciably altered findings, suggesting that these factors did not account for the observed between-group differences and that yoga may offer a viable therapeutic option even in patients with long-standing RLS. Finally, the study population was drawn from only two sites and was predominantly female and well educated, potentially limiting generalizability to other populations and geographic regions. Participants may also have been particularly receptive to yoga and other nonpharmacologic therapies (as reflected in the comparator group's active participation in the latter), again raising the possibility of selection bias and potentially limiting generalizability to adults less receptive to nonpharmaceutical treatment of RLS. Finally, outcomes were assessed only before and after the 12-week intervention period, precluding determination of potential longer term effects of the yoga program on RLS symptom burden or other clinically important endpoints.

CONCLUSIONS

Findings of this exploratory RCT suggest that yoga may offer a safe, viable, and effective intervention for reducing RLS symptoms and symptom severity, sleep and mood disturbance, and perceived stress in adults with moderate to severe RLS. Larger RCTs are needed to confirm these benefits in this and other adult populations with RLS, to assess the long-term effects of yoga in patients with RLS, and to evaluate potential underlying mechanisms.

ABBREVIATIONS

BMI, Body mass index
CEQ, Credibility Expectancy Questionnaire
EF, Educational film
ES, Effect size
dL, Deciliter
g, Gram
Hg, Hemoglobin
ICD-9, International Classification of Diseases, 9th Revision
IRB, Institutional Review Board
IRLS, International Restless Legs Syndrome Study Group Rating Scale
ITT, Intent to treat
kg, Kilogram
OSU, The Ohio State University
m, Meter
PASE, Physical Activity Scale for the Elderly
QOL, Quality of life
RCT, Randomized controlled trial
RLS, Restless Legs Syndrome
SE, Standard error
SF-36, Medical Outcomes Study Short Form-36
SPSS, Statistical Package for the Social Sciences
WVU, West Virginia University

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DISCLOSURE STATEMENT

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