MSJ Experimental Translational Clinical

Original Article

Randomized controlled trial of exercise interventions to improve sleep quality and daytime sleepiness in individuals with multiple sclerosis: A pilot study

Multiple Sclerosis Journal – Experimental, Translational and Clinical

2: 1–9

DOI: 10.1177/2055217316680639

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Abstract

Background: Nearly 70% of individuals with multiple sclerosis (MS) experience sleep disturbances. Increasing physical activity in people with MS has been shown to produce a moderate improvement in sleep quality, and exercise has been shown to improve sleep quality in non-neurologically impaired adults.

Objective: The purpose of this pilot randomized controlled trial study was to examine the effect of two exercise interventions on sleep quality and daytime sleepiness in individuals with MS.

Methods: Twenty-eight individuals with relapsing–remitting or secondary progressive MS were randomized into one of two 12-week exercise interventions: a supervised, moderate-intensity aerobic exercise (AE) program or an unsupervised, low-intensity walking and stretching (WS) program. Only individuals who were $\geq 70\%$ compliant with the programs were included in analysis ($n = 12$ AE; $n = 10$ WS).

Results: Both groups demonstrated a moderate improvement in sleep quality, although only the improvement by the WS group was statistically significant. Only the AE group demonstrated a significant improvement in daytime sleepiness. Change in sleep quality and daytime sleepiness was not correlated with disease severity or with change in cardiovascular fitness, depression, or fatigue.

Conclusion: The mechanisms for improvement in sleep quality and daytime sleepiness need further investigation, but may be due to introduction of zeitgebers to improve circadian rhythm.

***Keywords*:** Exercise, sleep quality, daytime sleepiness, multiple sclerosis

Date received: 16 August 2016; accepted: 1 November 2016

Introduction

Sleep complaints are very common in individuals with multiple sclerosis (MS). Approximately 50% of individuals with MS have a diagnosable sleep disorder, and 67% report a sleep disturbance.[1–3] Despite the high incidence of sleep disorders in individuals with MS, sleep difficulties are often undiagnosed and untreated.[4–6] This lack of attention to sleep disturbances is unfortunate as poor sleep quality has been an independent predictor of reduced quality of life in individuals with MS.[7,8] Poor sleep quality has been associated with a reduction in physical function, psychological well-being, ability to perform self-care and activities of daily living (ADL), interpersonal relationships, and occupational function in individuals with MS.[9] Furthermore, sleep disturbances have been associated with an increase in perceived fatigue in individuals with MS.[10–16]

Exercise has beneficial effects on physical and psychological symptoms of MS, including improvements in walking mobility, balance, fatigue, and depressive symptoms.[17] Exercise has also been shown to have a moderate benefit in improving self-reported sleep quality, shortening sleep latency, and reducing use of sleep aid medication in adults with sleep problems,[18] but the impact of exercise on sleep quality in people with MS has not been considered.

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A moderate improvement in sleep quality has been demonstrated in individuals with MS who participate in a behavioral intervention to increase physical activity compared with a control group, although this improvement only approached statistical significance.[19] Therefore, the purpose of this study was to examine the efficacy of a supervised moderate-intensity aerobic exercise program and an unsupervised low-intensity walking and stretching program on sleep quality and daytime sleepiness in people with MS.

Materials and methods

This study was approved by the institutional review board of the University of Kansas Medical Center (KUMC) and was registered with clinicaltrials.gov (NCT01783665). Study participants were recruited from an MS specialty clinic located at KUMC, advertisement through the Mid America Chapter of the National Multiple Sclerosis Society (NMSS), and personal referral from consented individuals, area physicians, or study personnel. Written informed consent was obtained from all study participants prior to enrollment. To be included in the study, participants had to be: (1) 18 years or older, (2) have relapsing–remitting or secondary progressive MS, (3) be able to ambulate independently with or without an assistive device, and (3) score ≥ 24 on the Mini-Mental State Exam (MMSE)[20] for individuals to complete informed consent. The exclusion criteria included: (1) history of alcohol/drug abuse or nervous system disorder other than MS, (2) severe physical, neurological, or sensory impairments that would prevent individuals from being able to complete testing or conduct the interventions, (3) developmental history of learning disability or attention-deficit/hyperactivity disorder, (4) relapse and/or corticosteroid use within four weeks of assessment, (5) unable to give consent, (6) uncorrected vision loss that would interfere significantly with testing, (7) untreated known sleep disorder (such as sleep apnea), (8) acute ischemic cardiovascular event or coronary artery bypass surgery less than three months ago; (9) either unable to physically perform the exercise test using the recumbent stepper or demonstrate absolute indications for terminating exercise that follows the American College of Sports Medicine (ACSM) guidelines; or (10) uncontrolled blood pressure with medication (BP > 190/110 mmHg).

After obtaining written informed consent, each participant was scheduled for baseline assessment. The Pittsburgh Sleep Quality Index (PSQI)[21] was used to assess sleep quality, and the Epworth Sleepiness Scale (ESS)[22] to assess daytime sleepiness. The PSQI is a well-validated and reliable measure of sleep quality that consists of 19 self-rated questions. These 19 questions form seven component scores, each of which is rated on a scale of 0 to 3 with 0 indicating no sleep difficulty and 3 indicating severe sleep difficulties. The seven component scores are summed to form a global score ranging from 0 to 21. On the ESS, participants used a four-point Likert scale to rate how likely they would be to fall asleep in eight different scenarios of daily activities. A higher score indicates higher daytime sleepiness.

Cardiorespiratory fitness was assessed using the Total Body Recumbent Stepper (TBRS) submaximal exercise test and the TBRS peak VO_2 prediction equation.[23,24] Heart rate (HR) and BP were assessed prior to testing. Participants were fitted with a Polar HR monitor (Polar Electro Oy, Kempele, Oulu, Finland) for continuous measurement. Using the seated recumbent stepper (NuStep T5XR, NuStep, Ann Arbor, MI, USA), the participants were asked to move their arms and legs in an alternating pattern at a constant speed of 100 steps per minute. All participants began the TBRS submaximal exercise test at 30 watts and per protocol, the resistance was increased every three minutes until test termination criteria were met: (1) participants reached 85% of age-predicted maximum HR, (2) the participant asked to stop the test, or (3) exercise test completion.

Other secondary measures that were collected included depression, which was assessed using the Beck Depression Index-Fast Screen (BDI),[25] fatigue assessed using the Modified Fatigue Impact Scale (MFIS),[26] and disease severity using the Multiple Sclerosis Functional Composite (MSFC).[27] Medical history, medication list, and demographics were collected.

Following baseline assessment, participants were randomized into either the moderate-intensity aerobic exercise (AE) program or the low-intensity walking and stretching (WS) program (Figure 1). Each exercise program consisted of 12 weeks of exercise, three times a week, for a total of 36 exercise sessions. Block randomization with two conditions (disease type and sex) per block was used to ensure an equivalent number of participants in the treatment groups. Research personnel conducting baseline and post-exercise reassessments were blinded to treatment group allocation.

The AE program consisted of a supervised moderate-intensity aerobic exercise intervention. Each session

began with 10–15 minutes of upper and lower body stretching exercises followed by a five-minute warm-up period on the recumbent stepper machine. During the warm-up period, the participants exercised at a low intensity of 25 watts. After the warm-up period, the examiner increased the watts until the target heart rate (THR) was reached. The THR range was calculated using the Karvonen equation.[28] The exercise intensity was set at 50%–59% of the HR reserve for the first six weeks and then increased to 60%–69% of HR reserve for the remaining six weeks. Exercise intensity was monitored throughout the 30 minutes of AE to maintain the participant's HR within the targeted range. HR was monitored throughout the session using the Polar HR monitors. After 30 minutes, the wattage was decreased to 25 for a five-minute cool-down period. The participant then repeated the stretching exercises for 10–15 minutes. Vital signs and compliance with exercise sessions were recorded in weekly exercise logs for each participant.

The walking and stretching (WS) program consisted of an unsupervised, low-intensity program. Each participant in this group was instructed to perform stretching exercises for 10–15 minutes before and after walking for 30 minutes at a low-intensity of below 40% of their HR reserve. An HR monitor watch (OMRON® HR-210) was given to all participants to monitor their HR during the 30 minutes of walking, and written instructions were provided to ensure compliance with the low-intensity program. Compliance with the WS program was assessed using weekly exercise logs.

Twenty-eight participants completed baseline and were randomized into each intervention groups (14 in each group; Figure 1). During the three-month intervention, six individuals withdrew from AE intervention (five because of a change in their work or travel schedule and one because of exacerbation of a prior knee injury that was unrelated to the exercise intervention). The individuals who

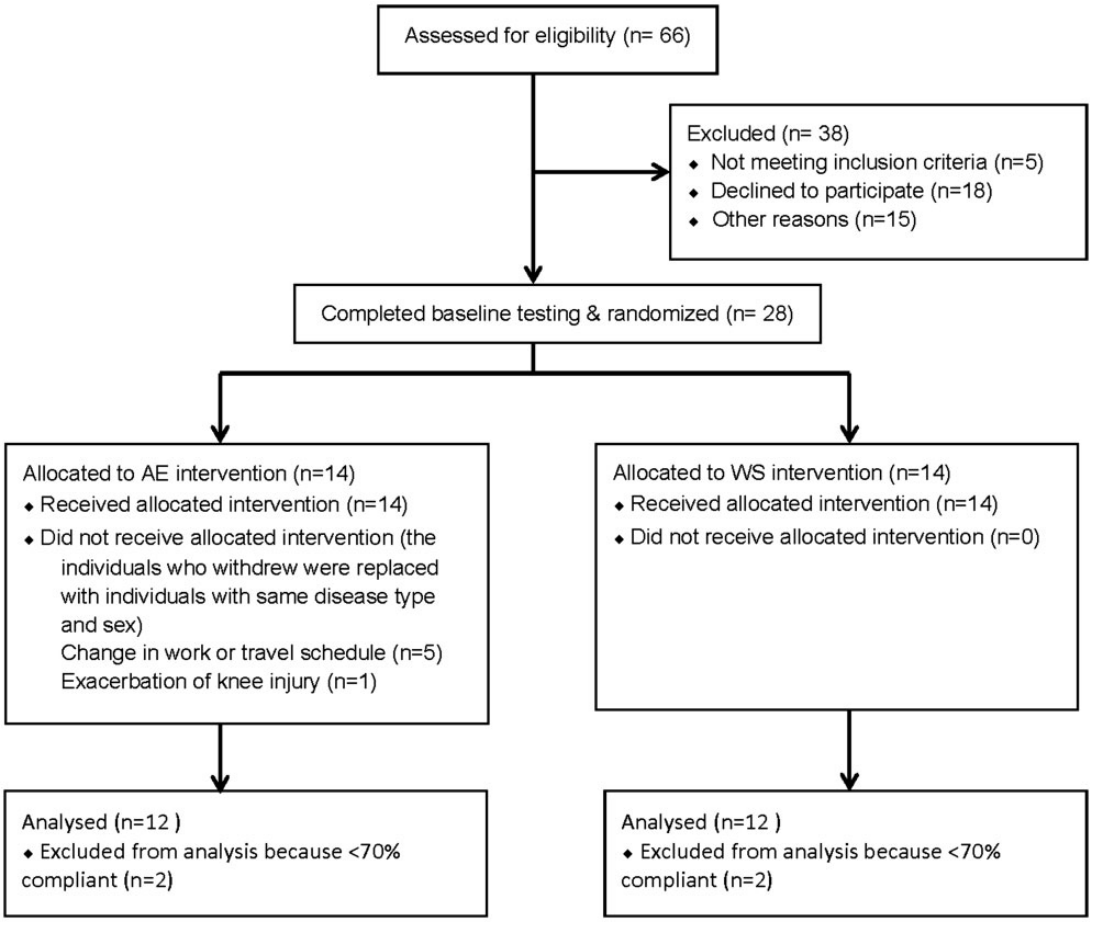

Figure 1. CONSORT flow diagram.
CONSORT: Consolidated Standards of Reporting Trials; AE: aerobic exercise; WS: walking and stretching.

withdrew from the study were replaced with individuals with same disease type and sex. In addition, only participants who were ≥ 70% compliant with the intervention programs were included in the data analysis (two were removed from the AE group and four were removed from the WS group). Therefore, data analysis was conducted on 12 individuals in the AE group and 10 in the WS group.

All data were analyzed using IBM SPSS Statistics version 22. Assumptions of normality were tested using the Shapiro-Wilk test and normal Q-Q plots. Independent *t*-tests and chi-square analyses were used to explore if there are differences in demographics between the two groups at baseline. Mixed-model analyses of variance (ANOVAs) were performed to explore the interaction between the exercise intervention and time of the intervention on the PSQI and ESS (time as within-subject measure, group as between-subject measure). Effect size for the *F*-statistic (partial eta; η_p^2) was reported and interpreted as small = 0.01, moderate = 0.06, and large = 0.14.[29] Percentage change scores and effect size (ES; Cohen's *d*) were also used to examine the magnitude of change in the outcome measures from before to after the interventions. Cohen's *d* was interpreted as small $d = 0.2$, medium $d = 0.5$, and large $d = 0.8$.[29] Spearman's correlations were used to assess the relationship between change in PSQI and change in ESS with variables known to be associated with sleep and daytime sleepiness for each group. Alpha level was set at 0.05.

Results

The AE group consisted of 12 individuals with a mean age of 48.9 ± 13.6 years. Eleven were females, and 10 had relapsing–remitting MS and two had secondary progressive MS. The WS group (mean age = 50.9 ± 12.2 years old) consisted of eight females and two males, and nine had relapsing–remitting MS, and one had secondary progressive MS. There were no significant differences between the groups in sex, disease type, age, disease duration, disease severity, global cognitive function, or depression; Table 1).

Table 1. Descriptive statistics of the participants.

Group	AE	WS
Sex	11 females 1 male	8 females 2 males
MS type	10 RR 2 SP	9 RR 1 SP
Age (years)	48.9 (13.6)	50.9 (12.2)
MSFC	0.395 (0.89)	0.868 (0.68)
Disease duration (years)	10.8 (8.4)	9 (5.6)
MMSE	29.3 (0.9)	28.6 (1.4)
BDI	2.3 (2.1)	4.6 (3.7)

Data reported as mean (standard deviation).
RR: relapsing–remitting, SP: secondary progressive,
MSFC: Multiple Sclerosis Functional Composite,
MMSE: Mini-Mental State Exam,
BDI: Beck Depression Inventory;
AE: aerobic exercise; WS: walking and stretching.

Primary outcome measures

The group by time interaction was not significant for the global PSQI score ($F = 0.602$; $p = 0.447$; $\eta_p^2 = 0.031$; Table 2; Figure 2), indicating there was not a difference in change in the PSQI between groups. However, the main effect of time was significant ($F = 9.634$; $p = 0.006$; $\eta_p^2 = 0.336$), indicating that both groups demonstrated a reduction in PSQI score from baseline to post-intervention assessment. The WS group demonstrated a statistically significant moderate reduction in PSQI score (−19.8% change, ES = 0.51, $t(8) = 2.577$, $p = 0.033$; Table 3). Although not statistically significant, the AE group demonstrated a moderate reduction in PSQI score (−18.4% change, ES = 0.49, $t(11) = 1.773$, $p = 0.104$; Table 3).

There was a significant group by time interaction for the ESS ($F = 6.765$, $p = 0.018$, $\eta_p^2 = 0.263$; Table 2; Figure 2), with the AE group demonstrating a statistically significant 28.6% reduction in daytime sleepiness (ES = 0.63; $t(11) = 2.830$, $p = 0.016$; Table 3) and the WS group demonstrating a 7.9% increase in daytime sleepiness (ES = 0.11, $t(8) = -0.800$, $p = 0.447$).

Secondary outcome measures

The group by time interaction for predicted peak VO_2 trended toward significance ($F = 3.792$, $p = 0.066$, $\eta_p^2 = 0.159$; Table 2). The AE group demonstrated a 12.4% increase in predicted peak VO_2 (ES = 0.67, $t(11) = -2.469$, $p = 0.031$) while the WS group demonstrated a 2.6% decrease (ES = 0.19, $t(9) = 0.508$, $p = 0.624$). There was no significant group by time interaction for the MFIS total score ($F = 0.852$, $p = 0.368$, $\eta_p^2 = 0.043$; Table 2) indicating there was not a difference in change in the MFIS between groups, but the main effect of time was significant ($F = 9.803$, $p = 0.006$, $\eta_p^2 = 0.340$,)

Table 2. Time by group interaction for the primary outcomes measures.

		F-statistic	*p* value	Partial Eta η_p^2
Primary outcome measures				
PSQI	Time	9.634	0.006	0.336
	Time*group	0.602	0.447	0.031
	Group	2.044	0.169	0.097
ESS	Time	3.297	0.085	0.148
	Time*Group	6.765	0.018[a]	0.263
	Group	1.912	0.183	0.091
Secondary outcome measures				
Predicted peak VO_2	Time	1.284	0.270	0.060
	Time*Group	3.792	0.066	0.159
	Group	0.996	0.337	0.046
MFIS	Time	9.803	0.006[a]	0.340
	Time*Group	0.852	0.368	0.043
	Group	0.010	0.922	0.001
BDI	Time	1.431	0.246	0.070
	Time*Group	0.201	0.659	0.010
	Group	2.146	0.159	0.101

[a]Indicates statistical significance.
PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, MFIS: Modified Fatigue Impact Scale, BDI: Beck Depression Inventory.

with the AE group showing a statistically significant reduction in fatigue following exercise (−17.3%, ES = 0.51, $t(11) = 2.792$, $p = 0.018$) and the WS group demonstrating a small effect on reduction in fatigue (−10.0%, ES = 0.24, $t(8) = 1.767$, $p = 0.115$). There was no significant group by time interaction for BDI ($F = 0.201$, $p = 0.659$, $\eta_p^2 = 0.01$; Table 2), indicating there was not a difference in change in the BDI between groups, and both groups showed a small non-significant reduction in depressive symptoms (AE −10.4% change, ES = 0.11, $t(11) = 0.490$, $p = 0.635$; WS −17.4%, ES = 0.18, $t(9) = 0.223$).

Change in PSQI and change in ESS was not significantly correlated with MSFC or change in predicted peak VO_2, MFIS, or BDI for either group (Table 4).

Discussion

This study demonstrates for the first time that individuals with MS who participated in either a supervised moderate-intensity exercise program or an unsupervised low-intensity exercise program experienced moderate improvements in sleep quality, but only the supervised moderate-intensity exercise program produced a moderate effect on daytime sleepiness.

This study extends the promising results from Pilutti et al.[19] that found that individuals with MS who participated in a behavioral intervention to increase physical activity demonstrated a moderate improvement in sleep quality on the PSQI compared to individuals in a control group. Considering exercise is low cost, widely available, and has minimal side effects when conducted appropriately, exercise should be considered an alternative or adjunctive therapy to address poor sleep quality in individuals with MS.

Individuals were excluded from participating in the study if they had a known untreated sleep disorder. A large national study found that more than 70% of individuals with MS screened positive for one or more sleep disorders,[5] indicating that many individuals in the current study likely had unrecognized and undiagnosed sleep disorders. This assumption further supports the strength of this study that exercise, regardless of mode or intensity, produced improvements in sleep quality of the participants despite the likelihood that many of them had an undiagnosed sleep disorder. Future studies should consider screening individuals for common sleep disorders (insomnia, sleep apnea, and restless leg syndrome[5,6]) to determine the impact of exercise combined with standard treatment of the sleep disorder.

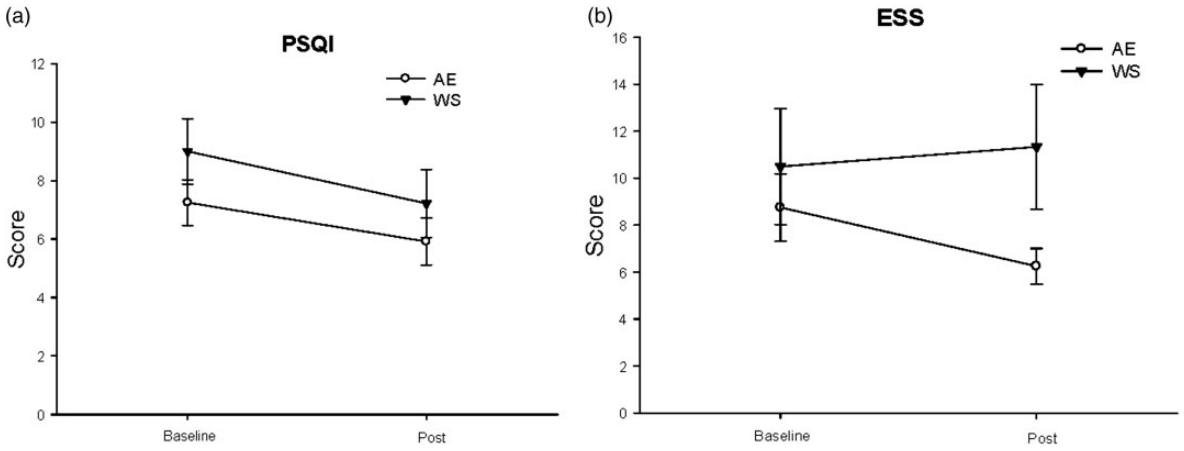

Figure 2. Performance on (a) PSQI and (b) ESS at baseline and post-exercise assessment.
PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; AE: aerobic exercise; WS: walking and stretching.

Table 3. Within group change for the primary outcome measures.

	AE				WS			
	% change	Cohen's *d*	*t*	*p*	% change	Cohen's *d*	*t*	*p*
PSQI	–18.4	0.49	1.773	0.104	–19.8	0.51	2.577	0.033[a]
ESS	–28.6	0.63	2.830	0.016[a]	7.9	0.11	–0.800	0.447

[a]Indicates statistical significance.
PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale; AE: aerobic exercise; WS: walking and stretching.

Table 4. Correlation analysis for change in PSQI and change in ESS with variables of interest.

		MSFC	SubMaxVO_2 % change	BDI % change	MFIS % change
AE group					
PQSI % change	*r*	0.367	–0.272	–0.081	0.489
	p	0.241	0.392	0.824	0.106
ESS % change	*r*	–0.081	–0.191	–0.450	0.149
	p	0.802	0.552	0.192	0.645
WS group					
PSQI % change	*r*	0.100	–0.008	–0.097	0.259
	p	0.797	0.983	0.804	0.500
ESS % change	*r*	0.267	0.437	–0.352	–0.017
	p	0.455	0.206	0.319	0.966

PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, MSFC: Multiple Sclerosis Functional Composite, BDI: Beck Depression Inventory, MFIS: Modified Fatigue Impact Scale; AE: aerobic exercise; WS: walking and stretching.

The mechanism for sleep quality improvement for both groups and improvement in daytime sleepiness for the AE group remains unclear and should be interpreted with caution because of the lack of a control group. Hyperarousal of the nervous system and a heightened stress response are thought to contribute to anxiety[30] and symptoms of insomnia.[31] Perhaps improvements in anxiety and/or stress are

underlying the change in sleep quality. The significant reduction in fatigue that both groups exhibited may also have contributed to the improvement in sleep quality as sleep and fatigue have been strongly associated;[11,16] however, there was no association between change in sleep quality and change in fatigue for either group. Future studies are needed to determine the mechanism or mechanisms contributing to the improvement in sleep quality and daytime sleepiness.

The improvement in daytime sleepiness for the AE group but not the WS group may be due to a large effect (although nonsignificant) of the AE program on improving cardiorespiratory fitness compared to the WS program. A study by Reid et al.[32] found a near significant relationship ($p = 0.058$) between improvement in sleep quality and improvement in fitness level determined by maximum HR for a group of older adults with insomnia who participated in a 16-week aerobic exercise program. Although Reid et al.[32] report the aerobic group experienced a significant reduction in daytime sleepiness, they unfortunately did not report the correlation between change in daytime sleepiness and improvement in fitness level. None of the six studies included in a systematic review[18] on the impact of exercise on sleep quality in middle-aged and older adults included the ESS as an outcome measure. Our study did not find an association between change in cardiorespiratory fitness level with change in sleep quality or change in daytime sleepiness. This seems to support the assertion by Reid et al.[32] that the effect of exercise on sleep quality and daytime sleepiness is likely mediated by another mechanism other than cardiorespiratory fitness.

It is possible that the interaction that occurred with the research personnel and the other participants during the supervision of the aerobic exercise program contributed to the results. In general, supervision and the interpersonal interactions that occur during supervision have a positive effect on the outcomes regardless of the intervention itself.[33] Studies from the different patient populations have demonstrated that supervised exercise interventions lead to better patient-centered outcomes compared to non-supervised interventions.[34,35] The effect of supervision on the outcomes depends on several factors such as the supervisor's behavior, interpersonal skills, attitude toward the patient, ability to apply a particular treatment, and their skill to show empathy.[33] Future studies should balance the interpersonal contact between the groups to reduce that confounding effect.

Another explanation for the improvement in daytime sleepiness for the AE group could be that being on a schedule for attending the exercise may have served as a zeitgeber for this group and may have contributed to regulating their circadian rhythm and internal clock. Retirement or lack of employment, reduced mobility, and reduced interactions have all be shown to contribute to sleep disruptions in older adults,[31] and these similar lifestyle changes are also common in individuals with MS. Because the WS group was less constrained by scheduling exercise sessions when the equipment and personnel were available, there may have been less benefit of a schedule on their daytime sleepiness.

One of the major limitations of this study is the small sample size, which limits the interpretation of the results but sets the basis for future studies in this area. The lack of a control group is another limitation and makes interpretation of the results less clear. Future studies investigating the impact of exercise on sleep quality should consider a delayed treatment design. Another limitation is the lack of detailed information on the medication lists provided by many of the participants. This made analysis of the influence of medication on change in sleep quality and daytime sleepiness difficult. Future studies should assess whether medication influenced or mediates the benefit of sleep on sleep quality and daytime sleepiness as well as determine if exercise changes the need to take medication or the dose of medication.

In conclusion, individuals with MS who participated in either a supervised moderate-intensity or unsupervised low-intensity exercise program demonstrated moderate improvements in sleep quality. Only the supervised moderate-intensity participants improved daytime sleepiness. The mechanism for these improvements warrants further investigation, but may be due to the introduction of zeitgebers to improve circadian rhythm. Exercise may be a non-pharmacological, inexpensive, safe method to improve sleep quality in people with MS.

Acknowledgments

The authors thank Richard Hill, DPT; Garrett Blattner, DPT; Shannon Lynch, DPT; Payden Dowling, DPT; Stephanie Funk, DPT; Logan Hubbard, DPT; Shanna Couch, DPT; Korbyn Steadman, DPT; Amanda Gion, DPT; Kari Langsenkamp, DPT; Marsha Eck, DPT; Jessica Gee, DPT; Alexandra Cousin, SPT; Matthew Obermeier, SPT; and Rachel Stueve, SPT; and the

Mid America Chapter of the National Multiple Sclerosis Society for their assistance with this study.

The study is registered on ClinicalTrials.gov: 'The Effect of Aerobic Exercise on Cognitive Function and Sleep Quality in Individuals with Multiple Sclerosis' (NCT01783665).

Conflicts of interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Sharon Lynch has participated in multicenter clinical trials in MS funded by Biogen, Genzyme, Teva, Sanofi, Novartis, Opexa, Roche, the National Institutes of Health (NIH), the NMSS, Acorda, Sun Pharma, Vaccinex, and Actelion. Jared Bruce provides unbranded talks for the Novartis Speakers Bureau and has served on the Novartis MS and Cognition Medical Advisory Board. The other authors have nothing to declare.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by an NMSS Pilot Grant (PP2068) awarded to CFS. A portion of this study was supported by the NIH Clinical and Translational Science Award grant (UL1 TR000001, formerly UL1RR033179), awarded to KUMC and internal funds provided by the KUMC School of Health Professions and the Department of Physical Therapy and Rehabilitation Science awarded to CFS. SB was supported in part by K01HD067318 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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