RESEARCH ARTICLE

Randomized, Controlled Trial of Exercise on Objective and Subjective Sleep in Parkinson's Disease

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ABSTRACT: Background: Sleep dysfunction is common and disabling in persons with Parkinson's Disease (PD). Exercise improves motor symptoms and subjective sleep quality in PD, but there are no published studies evaluating the impact of exercise on objective sleep outcomes. The goal of this study was to to determine if high-intensity exercise rehabilitation combining resistance training and body-weight interval training, compared with a sleep hygiene control improved objective sleep outcomes in PD.

Methods: Persons with PD (Hoehn & Yahr stages 2–3; aged ≥45 years, not in a regular exercise program) were randomized to exercise (supervised 3 times a week for 16 weeks; n = 27) or a sleep hygiene, no-exercise control (in-person discussion and monthly phone calls; n = 28). Participants underwent polysomnography at baseline and post-intervention. Change in sleep efficiency was the primary outcome, measured from baseline to post-intervention. Intervention effects were evaluated with general linear models with measurement of group × time interaction. As secondary outcomes, we evaluated changes in other aspects of sleep architecture and compared the effects of acute and chronic training on objective sleep outcomes.

Results: The exercise group showed significant improvement in sleep efficiency compared with the sleep hygiene group (group × time interaction: $F = 16.0$, $P < 0.001$, $d = 1.08$). Other parameters of sleep architecture also improved in exercise compared with sleep hygiene, including total sleep time, wake after sleep onset, and slow-wave sleep. Chronic but not acute exercise improved sleep efficiency compared with baseline.

Conclusions: High-intensity exercise rehabilitation improves objective sleep outcomes in PD. Exercise is an effective nonpharmacological intervention to improve this disabling nonmotor symptom in PD. © 2020 International Parkinson and Movement Disorder Society

Key Words: exercise; Parkinson's disease; polysomnography; rehabilitation; sleep

Parkinson's disease (PD) is a progressive neurodegenerative disorder with motor and nonmotor symptoms, including sleep dysfunction. Nonmotor symptoms adversely affect quality of life and are often more bothersome than motor symptoms.[1,2] Sleep disorders affect 74%–98% of PD patients[3,4] and include sleep

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fragmentation, rapid eye movement (REM) sleep behavior disorder, daytime sleepiness, and insomnia.[5] PD patients also have alterations in sleep architecture, with reductions in sleep efficiency (percentage of time in bed that is actually spent asleep), total sleep time, and slow-wave sleep.[6] In addition to negatively affecting quality of life, sleep disorders in PD are associated with depression, psychosis, autonomic dysfunction, worse motor disability, fatigue, and neuroinflammation.[5,7-9]

Despite the significant negative impact of sleep dysfunction in PD, few pharmacologic therapies effectively improve these symptoms, and available treatments can have detrimental side effects.[10] Nonpharmacological therapies such as exercise are therefore promising alternatives for treatment of sleep dysfunction in PD. Studies investigating the influence of exercise on PD have shown beneficial effects on motor symptoms and quality of life and have been found to be safe and feasible.[11-14] Our prior work showed that high-intensity exercise rehabilitation combining resistance training with body-weight interval training improves motor symptoms, quality of life, neuromuscular performance, motor unit integrity, and muscle mitochondrial function in PD.[11] Further, functional MRI showed that this intervention led to heightened resting-state activity of the substantia nigra and the prefrontal cortex.[15] However, there are knowledge gaps in our understanding of the effects of exercise on sleep in PD.

In healthy adults, regular exercise improves objective sleep outcomes such as sleep efficiency, slow-wave sleep, total sleep time, and latency to sleep onset while also improving subjective sleep quality.[16-18] In PD, exercise has been shown to improve subjective sleep quality, but there are no published studies documenting the effects of exercise on objective sleep outcomes, as measured by polysomnography.[19,20] This randomized, controlled exercise rehabilitation clinical trial investigated the impact of high-intensity exercise rehabilitation on objective measures of sleep. We hypothesized that exercise training would increase sleep efficiency in PD compared with a no-exercise sleep hygiene control.

Methods

Participants

This randomized, controlled clinical trial randomized 71 participants. Using a per-protocol efficacy design, 55 participants (27 in exercise [EX] group and 28 in sleep hygiene [SH-C] group) completed the protocol and were therefore included in the final analysis, as described in the CONSORT flow diagram (Fig. 1). Intention-to-treat analyses were also performed as secondary analyses. The study was registered at clinicaltrials.gov (NCT02593955) and was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board. All participants gave written informed consent prior to participation.

Participants were recruited from the UAB Movement Disorders Center and local PD support groups between October 2015 and February 2018. Inclusion required age ≥ 45years, clinical diagnosis of idiopathic PD, Hoehn and Yahr stages 2–3, and stable medication regimen for at least 4 weeks prior to study entry without anticipation of medication change during the study. Potential participants were excluded for meeting or exceeding U.S. Health and Human Services physical activity guidelines (≥150 minutes/week of moderate-intensity aerobic activity or 75 minutes/week of vigorous-intensity aerobic activity and muscle strengthening activities involving all muscle groups 2 or more days/week)[21]; findings suggestive of atypical or secondary parkinsonism, including cerebellar signs, supranuclear gaze palsy, apraxia, prominent autonomic failure, or other cortical signs; multiple strokes with stepwise progression of symptoms; neuroleptic treatment at time of study entry or time of onset of parkinsonism; inability to walk without a cane or walker; deep brain stimulation; contraindication to an exercise program; Montreal Cognitive Assessment score < 18; use of investigational drugs; or untreated sleep apnea. Study screening included home nocturnal pulse oximetry to assess sleep apnea risk. Participants with a desaturation index ≥5 events/hour had to undergo formal clinical sleep testing to evaluate for sleep apnea and, if diagnosed, had to be treated with continuous positive airway pressure (CPAP) for at least 6 weeks prior to study entry. If sleep apnea was diagnosed during the research polysomnography (PSG), the participant was removed from the study and allowed to reenter later following at least 6 weeks of CPAP treatment.

To ensure balance across participants, computer-generated stratified randomization was performed based on age and sex: (1) 10 women aged 45–65 years, (2) 10 women aged >65 years, (3) 20 men aged 45–65 years, and (4) 20 men aged >65 years. If a randomized participant did not initiate the intervention, the participant was replaced within that stratum. Allocation sequence was concealed from the investigator enrolling and assessing eligibility (A.W.A.), and randomization assignment was revealed sequentially after enrollment.

Assessments

All assessments were performed at baseline and following the 16-week intervention period. In addition, at the 16-week point, EX participants underwent 2 PSGs to assess both chronic and acute effects of exercise: one on a non-exercise night (chronic exercise [CEX], 4–6 nights after the final exercise training session) and one on an exercise night (acute exercise: [AEX], night of the final exercise training session). The CEX PSG was

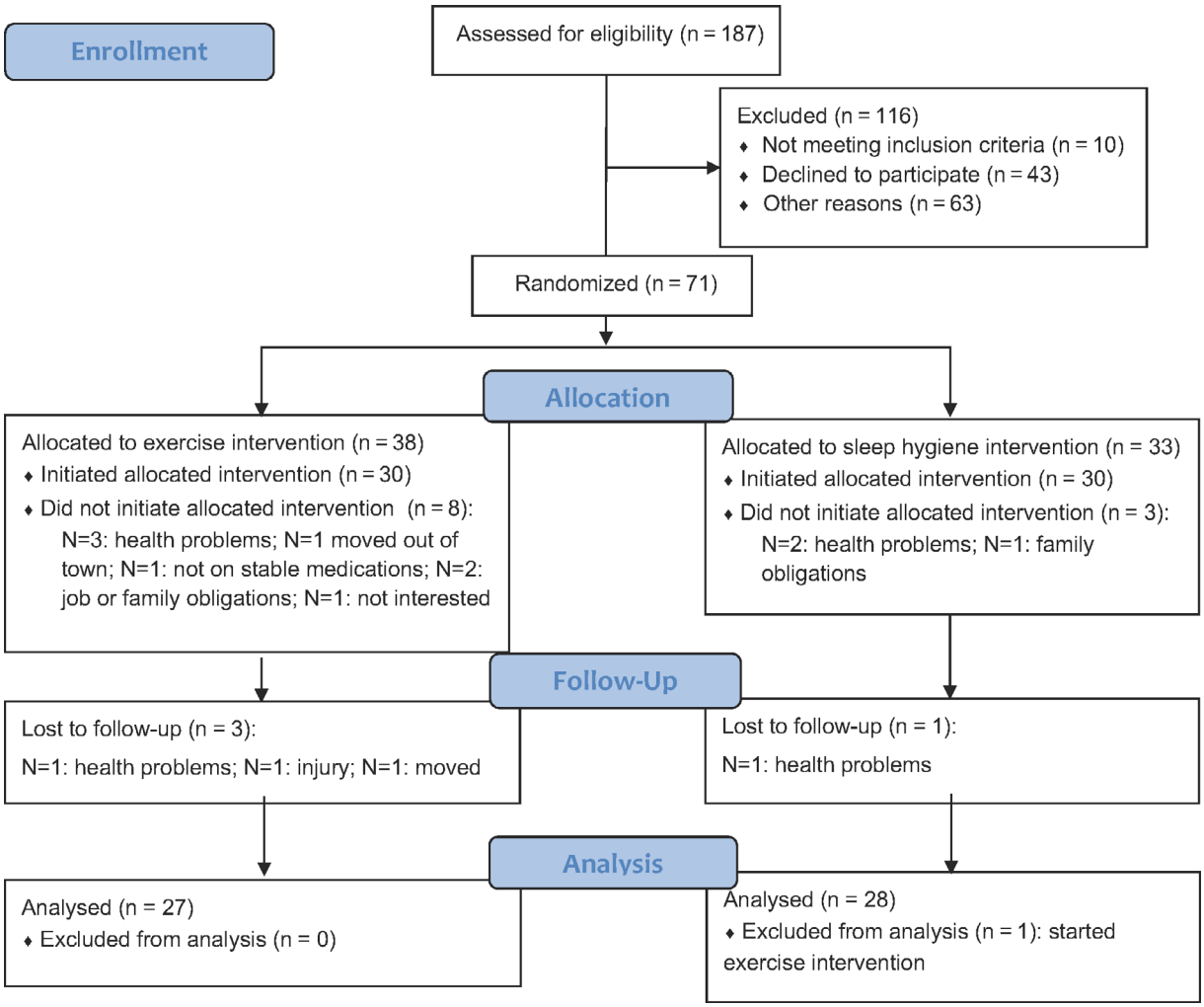

FIG. 1. Consort Flow Diagram. [Color figure can be viewed at wileyonlinelibrary.com]

chosen a priori as the primary outcome because (1) we were most interested in the effects of chronic exercise training on objective sleep outcomes, (2) acute exercise can have differential effects on sleep compared with chronic exercise,[17] and (3) this would be a better comparator with the sleep hygiene participants who did not exercise. As an exploratory outcome, we also evaluated the effects of acute exercise by comparing sleep architecture at baseline, AEX, and CEX.

Polysomnography

Laboratory-based PSG recordings included electroencephalography (leads F3, F4, C3, C4, O1, and O2 referenced to the contralateral mastoid), submental and bilateral anterior tibialis and extensor digitorum communis electromyograms, electrooculogram, airflow monitoring with thermocouple and nasal pressure, respiratory effort using polyvinylidene fluoride belts at the chest and abdomen, pulse oximetry, and video. PSGs were scored by a certified sleep technician and a board-certified sleep medicine physician (A.W.A.). PSGs were labeled with a study code to allow blinding of PSG interpretation.

PSGs were started at approximately 10 PM, and duration of recording was 8 hours. Participants remained on their regular medication schedule. PSGs were evaluated for sleep architecture, including sleep efficiency, total sleep time (TST), wake after sleep onset (WASO; amount of time spent awake after sleep onset), latency to sleep onset, time and percentage of each sleep stage (N1, N2, N3, and REM), latency to first REM period, arousal index, periodic limb movement index, apnea hypopnea index, and REM sleep without atonia. REM sleep without atonia was scored according to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events.[22]

Additional Assessments

Participants were also evaluated with the Movement Disorder Society Unified Parkinson's Disease Rating

Scale (MDS-UPDRS),[23] Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), and the psychomotor vigilance task[24] (PVT-192; Ambulatory Monitoring, Inc., Ardsley, NY). The psychomotor vigilance task (PVT) is a handheld device that objectively measures participant reaction time to a light stimulus that appears at a random interstimulus interval over a 10-minute test. The PVT measures mean reciprocal reaction time (response time) and lapses, both of which are sensitive to sleep deprivation.[25]

Intervention

Exercise intervention

Participants randomized to exercise intervention (EX) had supervised exercise training 3 times a week for 16 weeks at the UAB Center for Exercise Medicine. All exercise sessions were performed prior to 2 PM, and most were in the morning. Participants maintained their typical medication schedule and were encouraged to exercise at the time of day that they felt their PD medications were most effective. Exercise training consisted of a combination of resistance training (RT) and body-weight functional mobility exercises with limited rest intervals that we previously used in PD to challenge strength, power, balance, and endurance.[11] After a familiarization session, resistance training volume and intensity progressed during a ramp-up phase over the first 4 sessions by increasing the number of sets (ie, first day, 1 set; second day, 1 set; third day, 2 sets; fourth day, 3 sets). Thereafter, RT intensity/training loads targeted 10-repetition maximum (10RM) in sessions 1 and 3 each week. For session 2, resistance loads were reduced ~30%, with greater emphasis on maximizing speed of movement during the concentric phase (eccentric phase was controlled/slowed) for 12 repetitions/set. The RT component of the prescription was adapted from our prior dose-response optimization trial in older adults, which we also implemented in our recent exercise-drug interaction trial.[26,27] The full-volume exercise prescription consisted of: (1) 5 movements to improve strength and muscle mass (leg press, knee extension, chest press, overhead press, pull down), each performed for 3 sets of 8–12 repetitions (~30 repetitions at 10RM during sessions 1 and 3; ~36 total repetitions during session 2); (2) trunk exercises to improve postural stability (trunk extension and flexion); and (3) 3–4 body-weight exercises to improve power and balance (eg, step-up, squat, jump squat, lunge, side lunge, push-up, assisted pull-up, assisted dip). Body-weight movements were modified as necessary to match abilities (eg, weight assistance, bench or wall push-ups, etc., as necessary). For body-weight movements, the goal was to accumulate at least 50 repetitions in each of 3–4 exercises/session. Resistance exercise movements and body-weight movements were coupled/alternated while stressing different muscle groups (eg, a set of chest presses followed immediately by step-ups, with the sequence repeated twice more before moving onto the next coupled combination, eg, overhead press and lunge). Heart rate (HR) was recorded throughout each session via a Polar HR monitor and helped to determine the short rest intervals between sets. Experienced trainers certified by the American College of Sports Medicine and/or the National Strength and Conditioning Association supervised all sessions.

Sleep hygiene intervention

Participants randomized to the sleep hygiene intervention (SH-C) received suggestions for improving sleep hygiene through discussion with a board-certified sleep medicine physician (A.W.A.). The participants had an opportunity to express specific sleep complaints and had directed recommendations for improvement. They were provided a handout with tips for improving sleep hygiene and a recommendation for a book that describes sleep relaxation techniques and tips for improving symptoms of insomnia. The duration of these discussions was 30–60 minutes. Participants were also contacted by telephone every 4 weeks to address any questions about sleep hygiene measures and to maintain engagement in the study.

Statistical Analysis

The study was a randomized, controlled interventional design with primary analysis performed per protocol. The primary outcome measure was the change in sleep efficiency within participant, as measured by PSG, from baseline to the post-16-week intervention (non-exercise night; CEX), compared between the 2 intervention groups. Sleep efficiency was defined as the percentage of time in bed actually spent asleep ([total sleep time/total time in bed] × 100). Based on a prior clinical trial,[28] we estimated an SD of 7% and mean difference of 4.8%. Sample size of 27 per group would have 80% power to detect a change in sleep efficiency in EX compared with SH-C. The study was initially designed based on a 1-sided test, but we report 2-sided P values to be more conservative. Secondary analyses included changes in other measures of sleep architecture and subjective sleep outcomes (PSQI, ESS, and FSS) compared between groups. As additional secondary analyses, the differences between the 3 PSGs (baseline, AEX, CEX) in the EX group were evaluated. Intention-to-treat (ITT) analysis was also performed with the inclusion of 5 additional participants to determine if the results could be extrapolated to participants who did not complete the protocol. One SH-C participant had postintervention data but was excluded from the per-protocol analysis because of initiating a high-intensity exercise intervention outside the study

protocol. The other 4 participants (3 EX and 1 SH-C) included in the ITT analysis did not have post-intervention data collected. Therefore, imputation was performed using the mean postintervention value for all participants who completed the protocol (n = 55) for these missing objective and subjective sleep outcome values.

Statistical analyses were performed using JMP Pro 14 (SAS Institute, Inc., Cary, NC). Summary statistics were calculated and tested for normality (Shapiro-Wilk). Group comparisons of baseline demographics and clinical characteristics (EX versus SH-C) were assessed with independent-sample *t* tests for normally distributed data and with nonparametric tests (Mann-Whitney *U* test) for nonnormally distributed data. The primary statistical methods for the intervention effects were general linear models with measurement of group × time interaction. Effect sizes were evaluated with Cohen's *d*. Because the objective sleep outcomes evaluated as secondary outcomes are not independent, we did not correct for multiple comparisons. To control for the potential contribution of change in motor symptoms to the sleep outcomes, a model was run with the dependent variable as change in sleep outcome (ie, sleep efficiency; N3 time, or total sleep time) and predictor variables as change in MDS-UPDRS part III and group. Sleep architecture differences across the times (baseline, postintervention exercise night [AEX] PSG and post-intervention non-exercise night [CEX] PSG) were compared in EX with mixed-model repeated-measures analysis of variance. If significant differences were found between the PSGs, Tukey's honestly significant differences (HSD) multiple-comparison procedure was used to determine which nights were different.

Results

Participant Characteristics and Exercise Adherence

Baseline demographics and clinical characteristics for participants are shown in Table 1. There were no significant group differences in age, sex, duration of disease, MDS-UPDRS score, levodopa-equivalent dose (LED), or dopamine agonist LED. Training progression and adherence were emphasized, and adherence to EX averaged 92.2% ± 12.5% of sessions. Twenty-three of 27 participants (85%) in EX had >90% adherence.

Objective Sleep Outcomes

There were no group differences in sleep parameters at baseline. Participants in EX had significant improvement

TABLE 1. Baseline demographics and participant characteristics

	Exercise group	Sleep hygiene group	*P*
n	27	28	—
Randomization strata, n			
Men aged 45–65	9	9	
Women aged 45–65	5	4	$X = 0.72$
Men aged >65	7	10	$P = 0.87$
Women aged >65	6	5	
Age			
Mean ± SD	65.33 ± 8.17	65.82 ± 5.19	$t = 0.26$
Range	45–78	54–77	$P = 0.79$
Sex, n (%)			
Male	16 (59.3)	19 (67.9)	$X = 0.44$
Female	11 (40.7)	9 (32.1)	$P = 0.51$
DOD (years)			$z = -1.57$
Median (IQR)	6.0 (3.0–9.0)	3.0 (1.0–7.5)	$P = 0.12$
MDS-UPDRS part I			$z = -0.96$
Median (IQR)	7.0 (5.0–11.0)	9 (6.0–12.5)	$P = 0.34$
MDS-UPDRS part II			$t = -1.31$
Mean ± SD	11.11 ± 5.88	9.14 ± 5.28	$P = 0.20$
MDS-UPDRS part III			$t = -1.45$
Mean ± SD	33.48 ± 12.39	28.11 ± 15.02	$P = 0.15$
MDS-UPDRS part IV			$z = 0.14$
Median (IQR)	3.0 (0.75–5.0)	3.0 (0.0–6.0)	$P = 0.88$
MDS-UPDRS total			$t = -1.20$
Mean ± SD	56.46 ± 18.13	50.07 ± 20.91	$P = 0.23$
LED			$z = -1.08$
Median (IQR)	640.0 (440.0–855.0)	482.5 (300.0–748.8)	$P = 0.28$

DOD, duration of disease; LED, levodopa-equivalent dose; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale. Normality tested with Shapiro-Wilks and nonparametric test reported (Wilcoxon z) if not normal.

TABLE 2. Objective and subjective sleep outcomes

	Exercise, n = 27		Sleep hygiene, n = 28		Group × time interaction	Δ between groups[d] Effect size (d) 95% CI
	Preintervention	Postintervention	Preintervention	Postintervention		
Sleep efficiency[a]					**$F = 16.04$**	12.1
Median (IQR)	76.8 (67.5–86.2)	83.1 (76.9–90.7)[b]	80.0 (73.2–86.7)	75.7 (66.6–82.5)[c]	**$P < 0.001$**	**$d = 1.08$**
Mean ± SD	75.1 ± 15.3	82.2 ± 12.0	78.7 ± 10.2	73.8 ± 12.3		**(5.1–18.9)**
WASO (min.)[a]					**$F = 12.56$**	−54.4
Median (IQR)	90.5 (61.5–147.6)	67.8 (42.4–98.1)[b]	78.1 (52.2–114.9)	102.4 (65.5–145.9)	**$P < 0.001$**	**$d = 0.96$**
Mean ± SD	108.1 ± 70.0	70.2 ± 83.9	89.8 ± 49.2	106.4 ± 55.4		**(−89.8 to − 19.0)**
Total sleep time (min)[a]					**$F = 7.28$**	44.5
Median (IQR)	388.7 (322.5–414.0)	403.0 (364.5–436.0)[c]	371.8 (336.9–415.5)	361.5 (321.3–400.7)	**$P = 0.0093$**	**$d = 0.73$**
Mean ± SD	363.5 ± 75.5	393.1 ± 61.1	370.0 ± 54.9	355.1 ± 62.7		**(6.5–82.5)**
Sleep latency[a]					$F = 0.90$	−9.0
Median (IQR)	7.3 (3.9–14.3)	4.2 (2.3–14.2)	9.6 (4.0–14.1)	12.3 (7.2–25.0)[c]	$P = 0.35$	$d = 0.26$
Mean ± SD	12.4 ± 13.5	14.7 ± 39.2	10.5 ± 7.7	21.7 ± 28.3		(−30.9 to 12.9)
−N1 time[a] (min)					$F = 0.27$	11.7
Median (IQR)	38.0 (28.0–55.0)	36.0 (24.5–53.5)	35.0 (27.8–49.8)	35.3 (23.8–46.9)	$P = 0.60$	$d = 0.31$
Mean ± SD	40.0 ± 18.0	49.4 ± 47.5	42.4 ± 22.3	40.1 ± 27.2		(−11.6 to 34.9)
N1%[a]					$F = 0.008$	−0.2
Median (IQR)	10.3 (7.6–15.2)	8.9 (6.1–13.5)	9.9 (6.4–14.0)	9.1 (7.0–13.8)	$P = 0.93$	$d = 0.02$
Mean ± SD	12.0 ± 7.3	11.1 ± 8.7	12.3 ± 8.6	11.6 ± 8.4		(−5.2 to 4.8)
N2 time[a] (min)					$F = 0.007$	1.3
Mean ± SD	199.6 ± 51.3	191.7 ± 47.8	215.9 ± 64.1	206.7 ± 61.6	$P = 0.93$	$d = 0.02$
						(−35.3 to 37.9)
N2%[a]					$F = 2.88$	−5.9
Median (IQR)	56.3 (48.0–62.3)	51.5 (45.0–54.1)[b]	56.4 (48.5–67.4)	58.1 (48.8–66.2)	$P = 0.096$	$d = 0.46$
Mean ± SD	55.0 ± 10.3	49.0 ± 10.6	57.8 ± 12.7	57.6 ± 12.3		(−13.4 to 2.1)
N3 time[a] (min)					**$F = 8.08$**	25.1
Median (IQR)	50.5 (27.5–101.5)	88.5 (54.0–130.5)[b]	54.8 (16.8–85.9)	56.8 (17.5–88.0)	**$P = 0.006$**	**$d = 0.77$**
Mean ± SD	74.3 ± 62.3	99.4 ± 75.6	55.0 ± 42.6	55.0 ± 37.1		**(4.7–45.4)**
N3%[a]					$F = 1.87$	3.3
Median (IQR)	16.9 (8.7–28.4)	23.6 (13.4–29.6)[b]	17.0 (4.5–22.4)	15.8 (5.1–24.4)	$P = 0.18$	$d = 0.37$
Mean ± SD	19.7 ± 14.8	24.3 ± 15.7	14.7 ± 10.9	16.0 ± 11.1		(−2.3 to 8.9)
REM time[a] (min)					$F = 1.76$	*14.1*
Mean ± SD	49.5 ± 24.3	60.2 ± 39.8	56.7 ± 30.3	53.3 ± 33.6	$P = 0.19$	$d = 0.36$
						(−10.4 to 38.6)
REM %[a]					$F = 0.98$	2.7
Mean ± SD	13.3 ± 6.4	15.6 ± 10.3	15.3 ± 7.9	14.9 ± 9.1	$P = 0.33$	$d = 0.27$
						(−3.7 to 9.1)
REM latency (min)[a]					$F = 0.022$	4.2
Median (IQR)	141.8 (100.5–293.1)	139.0 (96.8–256.0)	147.5 (83.5–207.0)	123.8 (86.4–184.3)	$P = 0.88$	$d = 0.04$
Mean ± SD	187.2 ± 111.7	175.1 ± 97.5	148.9 ± 74.5	133.2 ± 71.5		(−66.5 to 74.9)
Arousal Index[a]					$F = 0.22$	−0.7
Median (IQR)	3.9 (3.3–5.9)	3.3 (2.5–5.6)	4.3 (3.1–5.8)	3.9 (3.2–7.5)	$P = 0.44$	$d = 0.21$
Mean ± SD	5.0 ± 3.6	4.5 ± 3.2	5.0 ± 2.7	5.2 ± 3.0		(−2.8 to 1.4)
AHI (events/hour)[a]					$F = 0.25$	−0.6
Median (IQR)	0.2 (0–1.1)	0.3 (0–3.3)	0.4 (0–1.4)	0 (0–2.0)	$P = 0.57$	$d = 0.16$
Mean ± SD	1.5 ± 3.2	1.6 ± 2.7	0.9 ± 1.3	1.6 ± 4.0		(−2.9 to 1.7)
PLMS Index[a]					$F = 0.189$	−2.7
Median (IQR)	1.1 (0.2–7.4)	1.6 (0.5–16.7)	2.3 (0.6–30.9)	8.2 (0.9–31.7)	$P = 0.67$	$d = 0.12$
Mean ± SD	8.2 ± 14.8	11.5 ± 18.5	16.1 ± 22.5	22.2 ± 32.6		(−17.3 to 11.8)
% REM with RWA[a]					$F = 0.49$	−0.04
Median (IQR)	21.0 (1.8–68.0)	25.8 (5.3–70.7)	19.6 (3.9–57.4)	34.1 (5.6–70.9)	$P = 0.49$	$d = 0.20$
Mean ± SD	34.5 ± 35.6	39.1 ± 26.5	30.8 ± 31.3	39.6 ± 33.9		−0.2 to 0.1)
RBD[ae]						
n (%)	11 (42.3)	13 (50)	12 (46.2)	17 (60.7)	NA	NA
PVT mean RRT[a] ↑					$F = 0.048$	0.02
Median (IQR)	3.4 (3.1–3.9)	3.4 (3.2–3.8)	3.5 (3.2–3.8)	3.4 (3.0–4.0)	$P = 0.83$	$d = 0.06$
Mean ± SD	3.5 ± 0.5	3.5 ± 0.5	3.4 ± 0.7	3.5 ± 0.8		(−0.2 to 0.2)
PVT Lapses[a] ↓					$F = 0.001$	0.03
Median (IQR)	2.0 (1.0–4.0)	1.5 (0–4.25)	2.0 (0–4.75)	2.0 (0–7.5)	$P = 0.98$	$d = 0.01$
Mean ± SD	3.2 ± 3.8	2.6 ± 2.8	6.7 ± 16.8	6.1 ± 13.9		(−3.0 to 3.1)
PSQI[a] ↓					**$F = 4.38$**	1.8
Median (IQR)	6.0 (5.0–9.0)	6.0 (4.0–10.0)	8.0 (5.0–10.75)	6.0 (4.0–8.0)[c]	**$P = 0.041$**	**$d = 0.57$**
Mean ± SD	6.9 ± 3.5	7.0 ± 3.5	8.1 ± 3.5	6.4 ± 2.9		**(−0.2 to 3.8)**

(Continues)

TABLE 2. Continued

	Exercise, n = 27		Sleep hygiene, n = 28		Group × time interaction	Δ between groups[d] Effect size (d) 95% CI
	Preintervention	Postintervention	Preintervention	Postintervention		
ESS[a] ↓ Mean ± SD	9.44 ± 4.65	9.46 ± 5.20	7.39 ± 5.06	8.14 ± 5.19	$F = 0.60$ $P = 0.44$	−0.7 $d = 0.21$ (−2.9 to 1.4)
FSS[a] ↓ Mean ± SD	36.23 ± 11.57	34.74 ± 12.85	33.67 ± 11.13	33.33 ± 10.59	$F = 0.11$ $P = 0.737$	−1.1 $d = 0.09$ (−8.9 to 6.7)

For values not normally distributed, median (IQR) and mean ± SD are shown.
[a]No significant difference between values at baseline ($P > 0.05$).
[b]$P < 0.01$ for within-group change from preintervention to postintervention.
[c]$P < 0.05$ for within-group change from preintervention to postintervention.
[d]Mean difference in change between groups. Within-group mean change, effect size, and 95% CI are shown in Supplemental Table 1.
[e]RBD: >27% epochs of REM with RWA.
↑, higher score is better; ↓ lower score is better; AHI, apnea hypopnea index; ESS, Epworth Severity Scale; FSS, Fatigue Severity Scale; N1, stage N1 sleep; N2, stage N2 sleep; N3, stage N3 sleep; PLMS, periodic limb movements; PSQI, Pittsburgh Sleep Quality Index; PVT, psychomotor vigilance task; RBD, REM sleep behavior disorder; REM, rapid eye movement sleep; RRT, reciprocal reaction time; RWA, REM without atonia; WASO, wake after sleep onset.

in sleep efficiency compared with those in SH-C (ie, significant group × time interaction; $F = 16.04$, $P < 0.001$, $d = 1.08$; Table 2, Fig. 2). To examine the potential contribution of changes in motor symptoms on sleep outcomes, change in MDS-UPDRS part III was included as a predictor variable for change in sleep efficiency and after adjustment, the model was significant ($F = 9.22$, $P = 0.0004$). However, MDS-UPDRS part III was not a significant predictor of change in sleep efficiency ($P = 0.44$), but group remained significant ($F = 17.17$, $P = 0.0001$). Therefore, we concluded that the observed changes in sleep were because of the exercise intervention and not because of changes in motor symptoms.

As shown in Table 2 and Figure 2, other measures of sleep architecture also improved in the EX group compared with the SH-C group. These include significant group × time interactions for WASO, TST, and time spent in N3 (slow-wave sleep). There were no significant changes between groups for REM sleep without atonia or PVT-assessed objective vigilance.

Acute and Chronic Exercise Effects

Participants in the EX group had 3 PSGs: at baseline; post-intervention on an exercise night (AEX); and post-intervention on a non-exercise night (CEX). Comparison of sleep efficiency at baseline, AEX, and CEX showed significant differences among nights ($F = 4.04$, $P = 0.0235$; Fig. 3A). Tukey's HSD multiple-comparison procedure showed that sleep efficiency was significantly higher with CEX compared with baseline, without significant difference between baseline and AEX. There were also significant differences among the 3 nights for TST ($F = 3.66$, $P = 0.0328$; Fig. 3B),

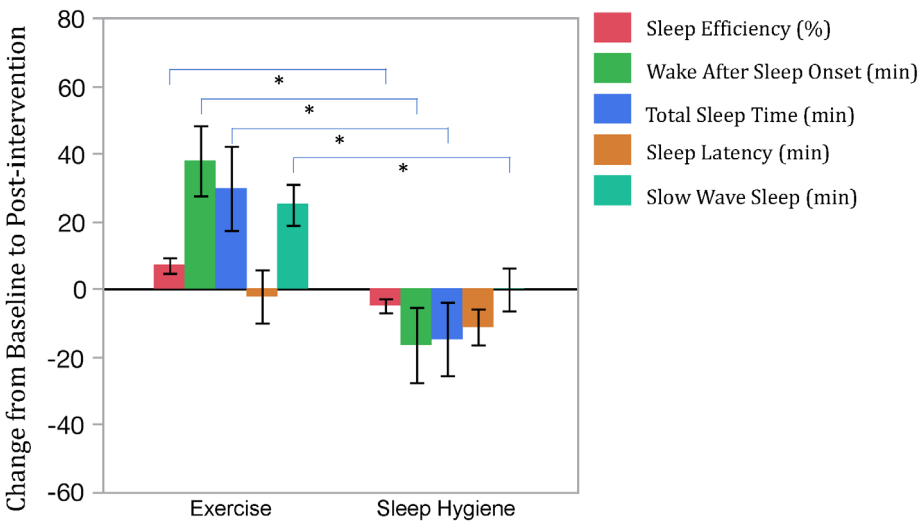

FIG. 2. Objective Sleep Outcomes in Exercise and Sleep Hygiene Participants. In order to show improvement as a positive change, outcomes for which a lower score is better (wake after sleep onset and sleep latency) were multiplied by -1 for this figure. *Significant group x time interaction ($p < 0.01$). [Color figure can be viewed at wileyonlinelibrary.com]

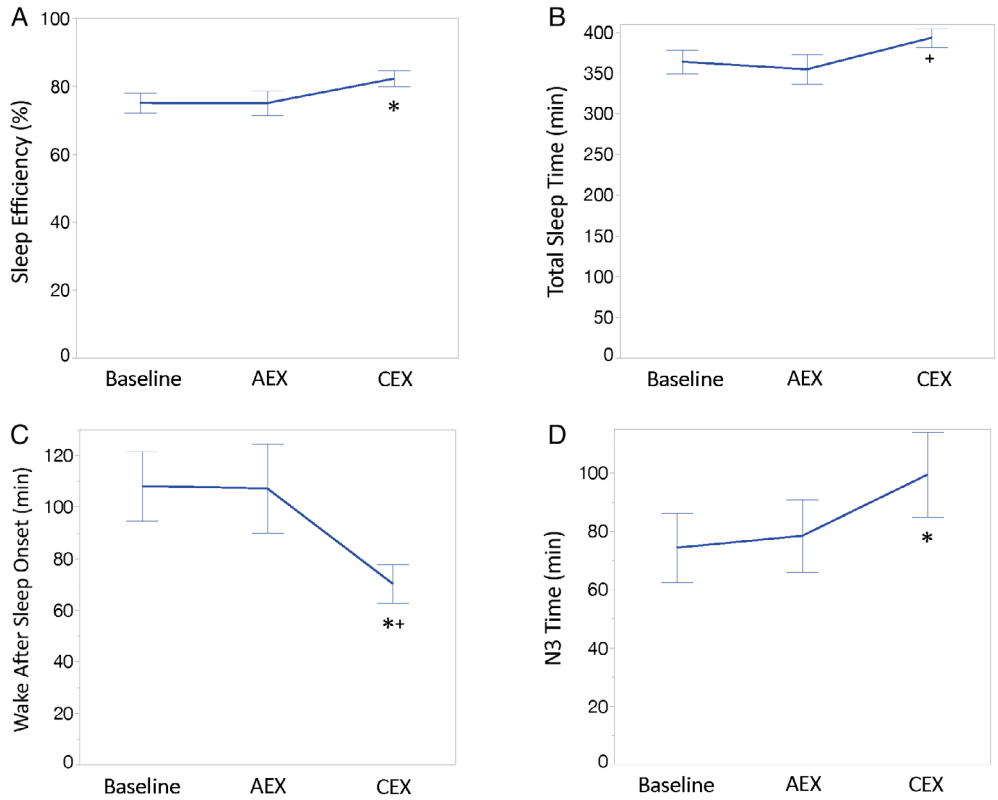

FIG. 3. Objective sleep outcomes on PSGs recorded at baseline, in the trained state on an exercise night (AEX), and in the trained state on a non-exercise night (CEX). **A**: Sleep Efficiency; **B**: Total Sleep Time; **C**: Wake after Sleep Onset; **D**: Time spent inN3. *Significant difference from Baseline based on Tukey's HSD multiple comparisons procedure; +Significantly different from AEX based on Tukey's HSD multiple comparisons procedure. [Color figure can be viewed at wileyonlinelibrary.com]

WASO (F = 5.31, P = 0.008; Fig. 3C), N3 time (F = 9.29, $P < 0.001$; Fig. 3D), N2% (F = 3.96; P = 0.025), and N3% (F = 4.21, P = 0.020). Tukey's HSD multiple-comparison procedure showed that TST was significantly higher with CEX compared with AEX; WASO was significantly better (lower) with CEX compared with baseline PSG and compared with AEX; N2% was significantly lower with CEX compared with baseline, and N3% and time spent in N3 were significantly higher with CEX night compared with baseline. There were no significant differences among the 3 nights ($P > 0.05$) for other measures of sleep architecture. These outcomes are shown in Supplemental Table 2.

Subjective Sleep Outcomes

There was significant improvement in subjective sleep quality assessed by the PSQI in the SH-C group compared with the EX group (significant group × time interaction; Table 2). The SH-C group showed improvement in sleep quality (P = 0.041), whereas EX did not change. To investigate the aspect of subjective sleep quality driving these changes, we evaluated the PSQI subscores (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. These results are shown in Supplemental Table 3. There was significant improvement in the sleep disturbance subscore in the SH-C group compared with the EX group (group × time interaction: F = 5.84, P = 0.019). In addition, there was a reduction in the use of sleep medications subscore in the EX group compared with the SH-C group (group × time interaction: F = 6.60, P = 0.013). None of the other subscores had significant differences over time between groups. Similar to the lack of change in the daytime dysfunction subscore of the PSQI, there were no changes in subjective sleepiness measured by the Epworth Sleepiness Scale or fatigue measured by the Fatigue Severity Scale in either group (Table 2).

Intention-to-Treat Analysis

Outcomes from ITT analysis are shown in Supplemental Table 4. The EX group had significant improvement in sleep efficiency compared with the SH-C group (group x time interaction; F = 5.35, P = 0.024). Significant group × time interactions were also noted for WASO and time spent in N3, with improvement in the EX group compared with the SH-C group. In contrast to the per-protocol analysis, the group × time interactions for TST and subjective sleep quality were no longer significant.

Discussion

This randomized, controlled trial is the first to investigate the effects of exercise rehabilitation on objective sleep outcomes in PD. High-intensity exercise training, when compared with a no-exercise sleep hygiene control, improved sleep efficiency, total sleep time, time spent in N3 (slow-wave sleep), and WASO. In contrast, the sleep hygiene intervention improved subjective sleep quality compared with exercise. Further, the observed effects of exercise on objective sleep were not influenced by changes in motor symptoms (MDS-UPDRS part III). Because pharmacological therapies for sleep dysfunction are often ineffective or have intolerable side effects,[29] our findings demonstrate an important step forward in identifying nonpharmacological therapies for this common and disabling nonmotor symptom.

Prior work investigating the impact of exercise on sleep in PD has been limited.[30] One controlled study showed that resistance training over 12 weeks improved subjective sleep quality, and these self-reported improvements in sleep correlated with improvements in muscle strength.[20] Two other controlled studies, one using a multimodal exercise intervention and another a Qigong meditative movement intervention, also showed subjective sleep quality improvement.[19,31] In healthy older adults, exercise training improves objective sleep measures, including increases in sleep efficiency and total sleep time and reductions in latency to sleep onset.[16,17] To our knowledge, this is the first study to demonstrate exercise-induced objective sleep improvement measured with PSG in PD.

Several potential mechanisms underlying exercise-induced changes in sleep have been proposed, and the effects are likely multifactorial. For example, there is a significant bidirectional relationship between sleep and mood, and exercise can improve mood in PD, which may contribute to sleep improvement.[32] Furthermore, exercise can increase brain-derived neurotrophic factor, which is decreased in sleep dysfunction and important for regulation of slow-wave sleep (stage N3).[33-35] Exercise may also improve sleep by increasing body temperature, thus increasing slow-wave sleep, which has been proposed to be important for thermoregulation.[16,17,36] This mechanism seems less likely an influence in the current study because sleep improved on CEX but not AEX and temperature effects because of exercise are more likely to have acute effects. Additional potential mechanisms of chronic exercise-induced benefits on sleep include reduction of inflammation, increases in growth hormone, alterations in autonomic function/heart rate variability, and changes in neurotransmitters important for sleep regulation.[16,17,37,38] In light of the prevalence of sleep dysfunction, mood disorders, autonomic dysfunction, and neuroinflammation in PD, the influence of exercise may be particularly relevant for this patient population.[1,39]

In comparing objective sleep outcomes in the untrained state (baseline) with chronic and acute effects of exercise, sleep architecture was improved with CEX compared with baseline, whereas the same effects were not seen with AEX. In healthy adults, prior work has shown that both acute and chronic exercise can improve sleep.[16,17,40] However, other studies have demonstrated no difference in total sleep time because of an acute bout of exercise.[41] Importantly, no prior work has evaluated objective sleep outcomes in PD in the trained state (ie, CEX) following a single bout of high-intensity exercise (i.e. AEX). Therefore, the cause of the lack of improvement following acute exercise in the trained PD participants is unclear. This effect could be because of the tendency of acute strenuous exercise to increase proinflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor–α, and IL-6, whereas chronic exercise promotes downregulation of these proinflammatory cytokines.[42] Thus, alterations in levels of cytokines, which play important roles in sleep regulation, could result in relatively worse sleep on a night of acute exercise compared with chronic training.[43] Another possibility is that there are differential effects of acute and chronic exercise on sleep specific to PD. For example, two proposed mechanisms for the beneficial effects of exercise on sleep are alterations in heart rate variability and increases in body temperature.[16,17] Perhaps the autonomic dysfunction of PD (including impairments in thermoregulation and cardiac autonomic function) alters the potential beneficial effects of acute exercise in these patients.[44] Another consideration is that a first-night effect (worse sleep on the first night in the sleep laboratory) could have influenced sleep at baseline and AEX, with CEX not influenced by this effect because of being performed soon after AEX. However, in our prior studies in PD, the first-night effect did not adversely affect objective sleep outcomes.[45] Further study using different exercise prescriptions and intensities followed by PSG longitudinally is required to elucidate the underlying mechanisms.

We were surprised by the improvement in subjective sleep quality in SH-C compared with EX despite only EX showing objective sleep improvement. This disconnect between objective and subjective sleep in PD has been observed in prior work, and therefore subjective sleep outcomes in PD should be interpreted with caution.[5,46] Although it is possible that the sleep hygiene intervention is more beneficial for subjective sleep than the high-intensity exercise intervention, another potential explanation is that our inability to blind participants to their intervention group led to participant bias. For example, the focus of interactions with the research staff was on sleep for SH-C. Therefore, it is possible that SH-C participants were unconsciously biased to report improvement in sleep quality. In contrast, many

interactions with study personnel for EX were related to exercise in the supervised intervention. The subjective improvement in SH-C could thus be because of the placebo effect. Another possibility is that the lack of objective improvement in sleep with AEX may have led to a perception of less improvement in sleep overall among those in the exercise group. An additional potential contribution is that, although there was no significant difference in PSQI at baseline between groups, the median baseline PSQI was 6.0 in EX and 8.0 in SH-C. Therefore, there may have been less room for improvement in the EX group because of a floor effect. In evaluation of the change in PSQI subscores over time, the sleep disturbance subscore improved in SH-C relative to EX. Therefore, although exercise improved objective sleep efficiency measured by PSG, the sleep hygiene intervention seems to have improved the subjective experience of nighttime sleep disturbances. This supports the idea of the benefits of sleep hygiene for subjective sleep in PD, and certainly the subjective experience is an important one for overall quality of life. There may be sleep benefits in the home environment from sleep hygiene that are not detectable in the sleep laboratory. These potential improvements in sleep at home may also explain why some aspects of sleep architecture worsened postintervention in SH-C, in that improvement at home may have reduced sleep drive (because of less sleep deprivation), thus leading to lower sleep efficiency by PSG. Interestingly, participants in EX reported reduced use of sleep medications following the intervention, suggesting there was some subjective recognition of sleep improvement from exercise. Perhaps future studies can investigate the utility of a combination of exercise and sleep hygiene to improve both objective and subjective sleep outcomes. In light of the importance of adequate sleep time on overall health, cognition, and mortality, the findings of the beneficial effects of exercise on objective sleep remains important.[47,48]

One interesting and new finding was that chronic exercise training increased slow-wave sleep (N3) in PD. This is intriguing because N3 has been proposed to be important for cognition, language, and memory consolidation in non-PD populations.[49,50] Furthermore, increased slow-wave sleep is important for executive function and selective slow-wave sleep disruption leads to reduced performance on visuospatial testing.[51,52] Our own work also showed a relationship between cognitive performance and slow-wave sleep in PD.[53] This raises the possibility that exercise interventions can improve cognition in PD by enhancing slow-wave sleep.

This study has several strengths, including the randomized, controlled design; being the only study in PD with PSG evaluation following an exercise intervention; the supervised nature of the intervention; and the excellent adherence to the protocol. There are also some limitations that should be discussed. First, because of the nature of the intervention, it was not possible to blind participants to group assignment, and this may have introduced potential bias. Second, PSG was performed on a single night at each point, thus not accounting for the potential influence of the first-night effect. However, in our prior studies in PD, the first-night effect has not adversely affected sleep.[45] In addition, if the first-night effect were playing a role in sleep improvement in the current study, it would have been expected to affect EX and SH-C groups equally. Another potential limitation is that, compared with EX, SH-C had less in-person contact with study staff. Thus, the social benefits of study participation in EX compared with SH-C could have influenced some results, although this would be expected to also influence subjective outcomes. Finally, we did not include a non-PD control group. Although this may be useful in future studies, the focus of the current study was to identify the effects of exercise on objective sleep outcomes in PD. Furthermore, the effects of exercise on sleep architecture in healthy elderly is well established.[16,17]

In conclusion, this is the first study to demonstrate the impact of high-intensity exercise on objective sleep outcomes in PD. Specifically, PD participants showed improved sleep efficiency, total sleep time, stage N3 (slow-wave sleep), and WASO following a 16-week exercise intervention compared with a sleep hygiene control group. In addition, this is the first report of changes in sleep architecture comparing untrained, trained, and acute exercise (in the trained state) in PD. These findings have important therapeutic implications and are an exciting step forward in identifying nonpharmacological therapies for this common and disabling nonmotor symptom. Further work is needed to better understand the mechanisms underlying the beneficial exercise-induced changes in sleep in PD. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.