

Randomized Clinical Trial of 3 Types of Physical Exercise for Patients With Parkinson Disease

Lisa M. Shulman, MD; Leslie I. Katznel, MD, PhD; Frederick M. Ivey, PhD; John D. Sorkin, MD, PhD; Knachelle Favours, MPH; Karen E. Anderson, MD; Barbara A. Smith, RN, PhD; Stephen G. Reich, MD; William J. Weiner, MD; Richard F. Macko, MD

Objective: To compare the efficacy of treadmill exercises and stretching and resistance exercises in improving gait speed, strength, and fitness for patients with Parkinson disease.

Design: A comparative, prospective, randomized, single-blinded clinical trial of 3 types of physical exercise.

Setting: The Parkinson's Disease and Movement Disorders Center at the University of Maryland and the Baltimore Veterans Affairs Medical Center, Geriatric Research Education and Clinical Center.

Patients: A total of 67 patients with Parkinson disease who had gait impairment were randomly assigned to 1 of 3 arms of the trial.

Interventions: (1) A higher-intensity treadmill exercise (30 minutes at 70%-80% of heart rate reserve), (2) a lower-intensity treadmill exercise (50 minutes at 40%-50% of heart rate reserve), and (3) stretching and resistance exercises (2 sets of 10 repetitions on each leg on 3 resistance machines [leg press, leg extension, and curl]). These exercises were performed 3 times a week for 3 months.

Main Outcome Measures: The primary outcome measures were gait speed (6-minute walk), cardiovascular fit-

ness (peak oxygen consumption per unit time [$\dot{V}O_2$]), and muscle strength (1-repetition maximum strength).

Results: All 3 types of physical exercise improved distance on the 6-minute walk: lower-intensity treadmill exercise (12% increase; $P=.001$), stretching and resistance exercises (9% increase; $P<.02$), and higher-intensity treadmill exercise (6% increase; $P=.07$), with no between-group differences. Both treadmill exercises improved peak $\dot{V}O_2$ (7%-8% increase; $P<.05$) more than did the stretching and resistance exercises. Only stretching and resistance improved muscle strength (16% increase; $P<.001$).

Conclusions: The effects of exercise were seen across all 3 exercise groups. The lower-intensity treadmill exercise resulted in the greatest improvement in gait speed. Both the higher- and lower-intensity treadmill exercises improved cardiovascular fitness. Only the stretching and resistance exercises improved muscle strength. Therefore, exercise can improve gait speed, muscle strength, and fitness for patients with Parkinson disease. The combination of treadmill and resistance exercises may result in greater benefit and requires further investigation.

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Author Affiliations: University of Maryland School of Medicine, Departments of Neurology (Drs Shulman, Ivey, Reich, Weiner, and Macko), Medicine (Drs Katznel and Sorkin), and Psychiatry (Dr Anderson), and University of Maryland School of Nursing (Dr Smith), Baltimore, and Division of Gerontology and Geriatric Medicine, Baltimore Veterans Affairs Medical Center, Geriatric Research Education and Clinical Center (Dr Katznel, Ivey, Sorkin, and Macko and Ms Favours), Maryland.

THE ONSET OF GAIT IMPAIRMENT is a critical juncture in Parkinson disease (PD) that occurs in the transition from Hoehn and Yahr stage 2 to Hoehn and Yahr stage 3 and is associated with functional decline.¹ Current therapies, including dopaminergic medication and surgery, are inadequate to preserve mobility as PD progresses. There is growing interest in the use of exercise training to improve mobility and function. A literature review performed in December 2011 shows that there were 75 clinical trials of physical training for PD, with 75% of these trials published since 2005. The results of these trials have been promising, showing improvements in PD-

related impairments, function, and quality of life.²⁻⁴ However, studies of exercise for PD have been characterized by methodological problems, including unblinded raters, the absence of a control or

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comparator group, and inadequate sample sizes. Among the 75 trials, there was an average of only 29 participants per trial, including unexercised patients and healthy controls. Evidence-based guidelines for exercise for PD are lacking owing to these limitations as well as to the marked variability of study design and exercise type.

People with PD have reduced physical activity and fitness compared with healthy controls.⁵ However, the relative benefits of aerobic exercise, gait training, and musculoskeletal conditioning for mobility and fitness are unknown. The primary objective of this clinical trial was to compare the efficacy of 3 types of physical exercise to improve gait, fitness, and strength in patients with PD: (1) higher-intensity treadmill, (2) lower-intensity treadmill, and (3) stretching and resistance. The secondary objectives were to investigate the efficacy of exercise to improve disability and nonmotor symptoms in PD.

METHODS

PARTICIPANTS

Study participants were recruited from the University of Maryland Parkinson's Disease Center between February 2007 and May 2010 to participate in a prospective, randomized, single-blinded, parallel-group clinical trial of efficacy of 3 types of physical exercise for PD. The criteria for eligibility were as follows: a diagnosis of PD characterized by asymmetrical onset of at least 2 of 3 cardinal signs (resting tremor, bradykinesia, or rigidity) with no atypical signs or exposure to dopamine-blocking drugs; a Hoehn and Yahr stage of 1 to 3 ("on" for motor fluctuators); the presence of mild to moderate gait or balance impairment (a rating of 1-2 on Unified Parkinson's Disease Rating Scale [UPDRS] item 29 [gait] or item 30 [postural stability]); an age of 40 years or older; and a Folstein Mini-Mental State Examination score of 23 or greater. Exclusion criteria were as follows: unstable medical/psychiatric comorbidities, orthopedic conditions restricting exercise, or performance of more than 20 minutes of aerobic exercise more than 3 times per week (to avoid prior training effect). This protocol was approved by the institutional review board at the University of Maryland School of Medicine. Informed consent was obtained from each participant.

All eligible participants received a screening treadmill exercise test to determine cardiopulmonary safety and neuromotor capacity to participate⁶ (eAppendix, <http://www.jamaneuro.com>). Participants needed to achieve 3 minutes of treadmill walking at more than 0.5 km/h (0.3 mph) for study entry. A random number generator allocated eligible participants into 1 of 3 exercise groups in a 1:1:1 ratio: (1) higher-intensity treadmill, (2) lower-intensity treadmill, or (3) stretching and resistance. The total duration of our study was 4 months (3 months for training and 4 weeks for baseline and posttraining assessments). Initial evaluations included a determination of a participant's medical history and physical and neurologic examinations. Baseline and posttraining assessments were performed by physicians and staff blinded to participants' treatment group. All evaluations were performed while the participants were "on" or within 3 hours of medication. Tests of cardiovascular fitness and physical performance were conducted on separate days to avoid fatigue.

ASSESSMENTS

The assessment of peak oxygen consumption per unit time ($\dot{V}O_2$) was conducted⁶ using a Quark CardioPulmonary Exercise Metabolic Analyzer (Cosmed) (eAppendix). Treadmill tests started at a self-selected walking speed and a 0% grade. The grade was increased 2% every minute until the participant reached voluntary exhaustion. Oxygen consumption, carbon dioxide production, and minute ventilation were measured breath by breath, and the values were averaged for 20-second intervals. Because

the reliability of fitness testing was not previously established for PD, participants performed 2 fitness tests (1 week apart) before and after training, with the highest of the 2 values accepted as the $\dot{V}O_2$ peak (intraclass correlation coefficients of 0.90-0.96).⁶

Gait assessments were performed within 2 weeks before and after training. The 6-minute walk (6MW) was the predetermined primary outcome measure (performed within 1 week of training). Participants were instructed to cover as much distance as possible in 6 minutes, turning every 30 m (100 ft), as prompted by orange cones set across a clear space. Other gait measures were two 10-m walks (self-selected and fastest comfortable pace) and a 15-m (50-ft) fast gait.

Muscle strength was assessed with a 1-repetition maximum strength test performed before and after training in all study groups for leg press and leg extension (the maximum weight a person can move 1 time through a full range of motion). Following warm-up, 5 trials separated by 3-minute rests were conducted to arrive at a 1-repetition maximum strength value. Strength in each leg was tested separately using pneumatic training equipment built for single leg movement (Keiser).

Disability and physical activity assessments included the Schwab and England Activities of Daily Living Scale, the Timed Up and Go test, and the Step Activity Monitor (Cyma Corp). The Step Activity Monitor assesses ambulatory function with 48-hour recordings of stride number, using a microprocessor-linked step monitor with sensitivity adjusted for individual calibration. The Step Activity Monitor was fastened above the participant's ankle during the first and last week of training.

The severity of PD was assessed using Hoehn and Yahr staging and the UPDRS total and motor subscale, which were performed by a movement disorders specialist (L.M.S.) who was blinded to group assignment. Nonmotor symptom assessments of PD included the Beck Depression Inventory, the 16-item Parkinson Fatigue Scale, the Parkinson Disease Questionnaire (to determine health-related quality of life), and the Falls Efficacy Scale (to determine participant's confidence to prevent falls).

EXERCISE TRAINING

All exercise groups trained 3 times per week for 3 months, for a total of 36 sessions at the Baltimore Veterans Affairs Medical Center under direct supervision of exercise physiologists with study physicians available. Vital signs were taken before, during, and after the assigned exercise. All participants were supported in a nonweight-bearing harness to eliminate risk of falls.

Higher-Intensity Treadmill Training

Participants started at a duration of 15 minutes and a heart rate of 40% to 50% of maximal heart rate reserve determined by use of the Karvonen formula.⁷ The intensity and duration of the exercise were increased by 5 minutes, 0.2 km/h (0.1 mph), and 1% incline every 2 weeks as tolerated to reach 30 minutes at 70% to 80% of heart rate reserve.

Lower-Intensity Treadmill Training

Participants started at a duration of 15 minutes, 0% incline, and their self-selected pace. The treadmill incline and speed remained the same for 3 months. The duration of training increased by 5 minutes every 2 weeks to reach 50 minutes at 40% to 50% of heart rate reserve. The duration of the lower-intensity sessions was extended, compared with the higher-intensity sessions (50 vs 30 minutes), to make the total work performed by the 2 treadmill groups comparable.

Stretching and Resistance Training

Participants performed resistance (muscle strengthening) exercises of the lower body followed by stretching of the upper and lower body. Resistance exercises included 2 sets of 10 repetitions on each leg on 3 resistance machines: the leg press, leg extension, and leg curl (Keiser). Weight was increased as tolerated. Stretching exercises comprised 1 set of 10 repetitions each of trunk rotation, hip abduction, and stretches of hamstrings, quadriceps, calves, and ankles performed on padded tables under supervision of an exercise physiologist (eAppendix).

STATISTICAL ANALYSIS

Descriptive statistics (means, standard deviations, ranges, and proportions) were determined for all study variables. Preplanned analyses included comparisons of between-group changes and within-group changes. One-way analysis of variance for continuous variables and χ^2 or Fisher exact tests for categorical variables were used for baseline comparisons of the 3 exercise groups. The change in each outcome variable (before and after training) was modeled in an unadjusted 1-factor (group) analysis of variance, to investigate the effect of the interventions on gait and non-motor symptoms of PD. Our before-after analyses were performed on the 67 participants studied at baseline and after 12 weeks of training. Post hoc analyses (Fisher protected least significant difference) were used to identify significant differences in changes in the 3 intervention groups. Inferences were checked by nonparametric (Kruskal-Wallis) methods. All analyses were performed using SAS Enterprise Guide 4.2 (SAS Institute). A 2-tailed *P* value of less than .05 was considered statistically significant (eAppendix and eTable 1).

RESULTS

Of 945 participants assessed for eligibility, 91 (10%) were screened. Of these 91 participants, 80 (88%) were randomly assigned to an exercise group; of these 80 participants, 67 (84%) completed the protocol (**Figure**). The numbers of participants who dropped out because of attrition were as follows: 6 from the stretching and resistance group, 4 from the lower-intensity treadmill group, and 3 from the higher-intensity treadmill group.

There were no serious adverse events, the exercise sessions never required interruption, and there were no changes of antiparkinsonian medications. The reasons for dropping out of the study included medical conditions (8 participants for orthostatic hypotension, back/joint pain, toe infection, deep brain stimulation battery replacement, or sacral fracture following a fall at home), family demands (4 participants), and commute to study (1 participant). The demographic characteristics of the study participants are described in **Table 1**. Randomization of 22 to 23 participants per group resulted in no overall differences in demographic characteristics or PD severity at baseline among the 3 study arms.

EFFICACY OF EXERCISE

Within-group differences for selected exercise groups were seen for outcomes of gait speed, fitness (peak $\dot{V}O_2$), muscle strength, and UPDRS motor subscale. Between-group differences were only seen for fitness (higher- and lower-intensity treadmill being more effective than stretching

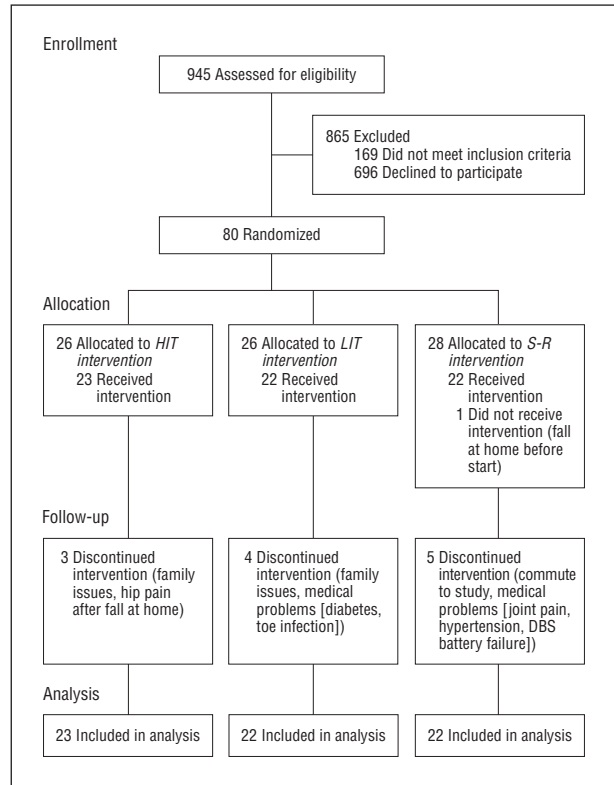


Figure. Consolidated Standards for Reporting Trials flow diagram of comparative, prospective, randomized, single-blinded clinical trial of 3 types of physical exercise for participants with Parkinson disease. DBS indicates deep brain stimulation; HIT, higher-intensity treadmill; LIT, lower-intensity treadmill; S-R, stretching and resistance.

and resistance) and muscle strength (stretching and resistance being more effective than higher- and lower-intensity treadmill).

Gait Assessments

For the primary outcome measure, within-group comparisons showed that all 3 exercise groups improved distance on the 6MW, although only lower-intensity treadmill and stretching and resistance reached statistical significance (**Table 2**). The greatest increase in distance followed lower-intensity treadmill training (48 m [161 ft] or 12% improvement, within-group *P* = .001). Stretching and resistance resulted in a 9% improvement with an increase of 32 m (107 ft) (*P* < .02). Higher-intensity treadmill training showed a 6% improvement, an increase of 23 m (77 ft) (*P* = .07). Only lower-intensity treadmill training resulted in significant improvement or a trend of improvement on all gait assessments.

Assessment of $\dot{V}O_2$ Peak

Both types of treadmill training improved cardiovascular fitness, whereas stretching and resistance had no effect. There was no evidence of differential effect between the 2 treadmill groups, but both treadmill groups had significantly better improvement than the stretching and resistance group. Peak $\dot{V}O_2$ (in milliliters per ki-

Table 1. Demographic Characteristics and Baseline Ratings of Study Participants With Parkinson Disease

Characteristic	Overall (n = 67)	HIT (n = 23)	LIT (n = 22)	S-R (n = 22)	P Value ^a
Sex, No. (%)					
Male	50 (75)	16 (70)	16 (73)	18 (82)	.62
Female	17 (25)	7 (30)	6 (27)	4 (18)	
Race, No. (%)					
African American	4 (6)	2 (9)	1 (5)	1 (5)	.89
White	60 (90)	19 (83)	21 (95)	20 (91)	
Hispanic	2 (3)	1 (4)	0 (0)	1 (5)	
H&Y stage, No. (%)					
2	53 (79)	19 (83)	18 (82)	16 (73)	.91
2.5	4 (6)	1 (4)	1 (5)	2 (9)	
3	10 (15)	3 (13)	3 (14)	4 (18)	
Age, y					
Mean (SD)	65.8 (10.7)	66.1 (9.7)	65.8 (11.5)	65.3 (11.3)	.97
Range	42-86				
UPDRS total					
Mean (SD)	46.6 (13.3)	45.2 (12.2)	46.6 (12.6)	48.2 (15.5)	.76
Range	15-89				
UPDRS motor subscale					
Mean (SD)	32.1 (9.9)	30.3 (9.8)	31.6 (9.2)	34.5 (10.7)	.36
Range	11-59				
Duration of disease, ^b y					
Mean (SD)	6.2 (3.8)	5.9 (3.9)	6.3 (3.5)	6.3 (4.0)	.92
Range	1-18				
MMSE score					
Mean (SD)	27.4 (0.9)	27.4 (0.7)	27.2 (1.1)	27.6 (0.8)	.31
Range	24-28				
S&E disability scale					
Mean (SD)	81.3 (8.7)	82.6 (5.4)	80.0 (10.7)	81.4 (9.9)	.62
Range	50-100				

Abbreviations: HIT, higher-intensity treadmill; H&Y, Hoehn and Yahr; LIT, lower-intensity treadmill; MMSE, Mini-Mental State Examination; S&E, Schwab and England; S-R, stretching and resistance; UPDRS, Unified Parkinson's Disease Rating Scale.

^aRepresenting the significance of an omnibus test that was performed to determine whether the values are the same in all 3 groups. A nonsignificant *P* value means that there is no evidence of differences between groups.

^bOnset of symptoms.

logram per minute) increased by 7% to 8% in higher- and lower-intensity treadmill groups ($P < .005$).

Assessment of Muscle Strength

Muscle strengthening based on 1-repetition maximum testing showed that stretching and resistance resulted in greater muscle strengthening than either the higher- or lower-intensity treadmill exercises (between-group difference, $P < .05$). On both the leg press (compared with higher-intensity [$P = .32$] and lower-intensity [$P = .73$] training) and the leg extension (compared with higher-intensity [$P = .34$] and lower-intensity [$P = .48$] training), stretching and resistance increased strength by 16% (within-group difference, $P < .001$) compared with 2% to 8% for treadmill training (within-group difference was not statistically significant).

Disease Severity and Disability

There was no change in UPDRS total following exercise in any group. Stretching and resistance were the only exercises that improved the UPDRS motor subscale (-3.5 points; $P < .05$). None of the exercise groups improved measures of disability or home ambulatory function (eTable 2).

Nonmotor Assessments

No changes were found in any nonmotor outcomes for any exercise group, including depression, fatigue, quality of life, and Falls Efficacy Scale (eTable 2).

COMMENT

This comparative trial of 3 types of exercise for PD showed within-group benefits across all 3 types of exercise. Differences between groups were only seen in outcomes of fitness and muscle strengthening, not in gait assessments. The treadmill exercises, but not the stretching and resistance exercises, improved cardiovascular fitness. The stretching and resistance exercises, but not the treadmill exercises, improved muscle strength. All 3 types of exercise improved gait, with the most consistent improvements following lower-intensity treadmill training. Therefore, all types of exercise do not produce the same results, and certain exercises are more effective than others for selected outcomes.

Both higher- and lower-intensity treadmill exercises resulted in improvements in gait speed and fitness. Overall, the lower-intensity treadmill exercise (walking at a comfortable pace for a longer duration) resulted in the

Table 2. Outcomes of 67 Participants With Parkinson Disease Following Exercise

Assessment	Participants, No.	Mean (SE)			Within-Person Percentage Change	P Value ^a
		Pretraining	Posttraining	Change		
Gait assessment						
6MW, ft ^b						
HIT	22	1374.2 (57.4)	1451.2 (62.5)	77 (31.1)	6.3 (2.5)	.07
LIT	19	1446.7 (95.2)	1607.7 (111.6)	161 (51)	11.6 (3.7)	.001 ^c
S-R	19	1395.5 (75.6)	1502.4 (81.6)	107 (47.8)	9.1 (5.5)	.019 ^d
10-m Comfortable pace, s						
HIT	23	9.97 (0.5)	9.52 (0.5)	-0.45 (0.2)	-4.5 (2.2)	.16
LIT	22	9.23 (0.5)	8.61 (0.3)	-0.62 (0.2)	-5.4 (2.3)	.06
S-R	22	9.37 (0.6)	9.41 (0.8)	0.04 (0.5)	-0.1 (4.3)	.91
10-m Fast pace, s						
HIT	23	7.73 (0.5)	7.33 (0.4)	-0.4 (0.2)	-4.6 (1.9)	.049 ^d
LIT	22	7.33 (0.4)	6.85 (0.4)	-0.48 (0.3)	-6.2 (3.5)	.02 ^d
S-R	22	7.18 (0.5)	7.08 (0.5)	-0.1 (0.2)	-1.2 (2.3)	.63
50-ft Fast pace, s						
HIT	23	13.84 (0.8)	13.27 (0.9)	-0.57 (0.4)	-3.8 (2.8)	.09
LIT	22	13.01 (0.8)	12.09 (0.8)	-0.93 (0.3)	-6.7 (2.1)	.008 ^d
S-R	22	12.87 (0.8)	12.84 (0.8)	-0.03 (0.3)	0.1 (2.4)	.93
Cardiovascular assessment						
Peak $\dot{V}O_2$, mL/kg/min						
HIT	23	20.85 (0.8)	22.39 (0.9)	1.54 (0.4)	8.1 (2.1)	.003 ^c
LIT	22	23.58 (1.2)	25.11 (1.4)	1.53 (0.7)	6.7 (2.7)	.004 ^c
S-R	21	22.94 (1)	22.89 (1)	-0.052 (0.4)	-0.2 (1.7)	.92
Muscle strength,^e lb						
Leg press						
HIT	18	824.17 (57.4)	847.56 (55.4)	23.39 (14.5)	3.5 (1.8)	.32
LIT	15	949.0 (78.6)	958.0 (75.6)	9.0 (26.2)	1.6 (2.1)	.73
S-R	21	878.76 (65.3)	1021.9 (83.6)	143.1 (26.5)	15.7 (2.4)	<.001
Leg extension						
HIT	18	236.39 (22.5)	243 (21.9)	6.61 (5.2)	7.7 (6.4)	.34
LIT	13	266.15 (21.8)	271.92 (19.7)	5.77 (11.4)	3.6 (3.9)	.48
S-R	21	239.52 (19.3)	271.52 (19.4)	32 (5.7)	15.8 (2.9)	<.001

Abbreviations: HIT, higher-intensity treadmill; LIT, lower-intensity treadmill; S-R, stretching and resistance; $\dot{V}O_2$, oxygen consumption per unit time; 6MW, 6-minute walk.

^aWithin-group comparison.

^bTo convert feet to meters, multiply by 0.3.

^c $P < .005$.

^d $P < .05$.

^eRight and left legs combined; to convert pounds to kilograms, multiply by 0.45.

most consistent improvements in gait speed and demonstrated that it was not necessary to greatly increase walking intensity to achieve benefits. A recent study⁸ comparing tai chi, resistance training, and stretching for PD showed between-group differences between tai chi and resistance training on balance testing and stride length, but not gait speed. Previous studies of treadmill training for PD have varied the duration and type of intervention, including body weight support,⁹⁻¹¹ weight loading,^{10,12} and visual/auditory cueing.^{13,14} As a group, treadmill trials for PD have shown consistent improvements for gait and fitness. There are few comparisons between higher- and lower-intensity treadmill exercises for PD. Pohl et al¹⁵ studied the immediate effects of 30 minutes of high- and low-speed treadmill training compared with conventional gait training and a sedentary control. Both high- and low-speed treadmill training resulted in similar improvements in gait speed, with no improvements in the nontreadmill groups. Body weight-supported treadmill training at high vs low intensity was

also studied, but only descriptive analyses were performed, with high-intensity treadmill training showing greater effects on some gait parameters.¹¹

When very high intensity forced cycling was compared with voluntary cycling, the $\dot{V}O_2$ peak improved in both groups, but upper limb dexterity and the UPDRS motor subscale only improved with forced exercise.¹⁶ This study¹⁶ and high-intensity exercise studies in PD animal models¹⁷ suggest that very high intensity exercise may not only be superior but necessary to achieve benefits. Our study results refute this by demonstrating the most consistent gait improvements with the lower-intensity treadmill exercise. The forced exercise cycling study¹⁶ had limitations, including low sample size (N = 10) and inadequate blinding of raters. The underlying premise of forced exercise is that exaggerated afferent input is necessary to normalize neuronal activity in the basal ganglia thalamocortical circuit,¹⁶ suggesting that physical training can improve global function, in contrast to the approach of lower body training for lower body gait per-

formance. Low-intensity exercise is more practical and more accessible to a larger proportion of patients with PD. Notably, our lower-intensity treadmill intervention resulted in consistent improvements in cardiovascular fitness. The lower-intensity treadmill exercise was greater than our participants' baseline activity, and this training, which is feasible for most patients, was sufficient to improve mobility.

It is not clear why the lower-intensity treadmill exercise was superior to the higher-intensity treadmill exercise. The participants who used the higher-intensity treadmill were encouraged to increase the velocity and increase the incline as tolerated. One explanation is that, when the velocity is increased, gait mechanics may become strained, "sloppy," and less efficient as patients try to keep pace. In contrast, the participants who used the lower-intensity treadmill exercised at their comfortable gait speed but for longer duration. Thus, the key differentiating factor may be training duration or the effect of training velocity on gait biomechanics, particularly for participants with reduced physiologic reserve. Prior to exercise training, oxygen consumption ($\dot{V}O_2$) at a comfortable pace averaged 64% of $\dot{V}O_2$ peak (>70% of $\dot{V}O_2$ peak in one-third of the participants), indicating severe impairment in economy of gait.¹⁸ Although the lower- and higher-intensity treadmill groups both improved cardiovascular fitness, the participants in the lower-intensity treadmill group trained for 67% more time than the participants in the higher-intensity treadmill group.

The mean baseline distance of the 6MW (422 m [1406 ft]) was similar to previous reports for patients with PD.¹⁹⁻²¹ Based on reports of a minimally important difference in the 6MW for older adults, the increase of distance following lower-intensity treadmill exercise (48 m [161 ft]) is a substantial meaningful change, and the increases following stretching and resistance exercises (32 m [107 ft]) and higher-intensity treadmill exercise (23 m [77 ft]) are greater than a small meaningful change.²² Similar thresholds for clinically important change in the 6MW were found for patients with cardiac²³ and pulmonary disorders.²⁴

Stretching and resistance exercises resulted in substantial benefits, with an improvement in the 6MW that exceeded the results of the higher-intensity treadmill exercise. Although the stretching and resistance exercises and the treadmill exercises improved gait, the mechanisms for doing so appear to be different because only resistance training improved strength and because only treadmill training improved fitness. Most previous studies^{20,25-27} of resistance training for PD have also shown improvements in strength and 6MW. In our study, only stretching and resistance improved the UPDRS motor subscale, which suggests that UPDRS items are more responsive to muscle strengthening than gait training. The reduction of 3.5 points on the UPDRS motor subscale exceeds the 2.5-point threshold of a minimally important difference.²⁸

Improvements in gait speed and fitness did not translate into improvement in daily function. Neither ambulation at home (Step Activity Monitor) nor activities of daily living performance (Schwab and England Activities of Daily Living Scale) improved in spite of improvement in the 6MW, a distance representative of community-

based activities of daily living tasks. Previous exercise trials in PD also show more consistent improvement in gait speed than in disability,^{29,30} performance measures,^{27,31-33} or home ambulation.^{34,35} It is unclear whether the extent of improvements is inadequate to improve function or whether the measures are insensitive to these changes.

Our study failed to show improvement in a range of nonmotor outcomes. Exercise trials in PD have been inconsistent in their effects on mood, quality of life, and falls self-efficacy.^{14,29,31,32,36-40} Patients with PD who enroll in exercise studies may have less nonmotor symptoms at baseline (less depression and fatigue and a better quality of life) and, therefore, may be less likely to improve. In a post hoc analysis, we compared the quality of life ratings (from the 12-item Short Form Health Survey) of our participants with those of patients with PD from our center who fit our study's eligibility criteria. The Mental Health Summary Score was higher in the study participants, indicating a better quality of life with regard to mental health (51st vs 48th percentile), whereas the quality of life with regard to physical health was the same for both the study participants and the patients with PD from our center (42nd percentile).

A limitation of our study is that our results are presented without correction for multiple comparisons, increasing the possibility of type II error. Our study's strengths include randomization, blinded raters, continuous exercise supervision, and extensive experience of the study team with exercise trials. However, the advantage of rigorous monitoring for standardization and safety is counterbalanced by the limitation of less practicality for general application in clinical practice or longer clinical trials. Results based on treadmill training cannot be applied to overground walking without further study. In contrast to pharmacologic studies, all exercise trials are limited by unavoidable unblinding of participants. Comparative studies are one approach to manage, but not eliminate, placebo effects. Comparative active arms, such as those used in our randomized clinical trial, are informative but do not address whether physical training is better than no physical training for PD. In our experience, most study participants wanted to be assigned to the higher-intensity treadmill, believing that intense exercise would be most effective. The improvements seen with the lower-intensity treadmill exercise and the stretching and resistance exercises go against the observed patient bias. Although we attempted to make the total work performed by the treadmill groups comparable, the stretching and resistance exercises were not designed for workload equivalence, and many complex variables interfere with eliminating this confounding factor.

In summary, all 3 types of physical exercise improved gait and mobility. However, each type of exercise resulted in a different profile of benefits. The lower-intensity treadmill exercise was the single most effective training exercise for gait and fitness. The fact that the lower-intensity treadmill exercise is the most feasible exercise for most patients with PD has important implications for clinical practice. Although treadmill and resistance training are beneficial for gait, fitness, and muscle strength, these benefits were not accompanied by im-

improvements in disability and quality of life. Treadmill and resistance training were associated with different mechanisms of efficacy (cardiovascular fitness and muscle strengthening, respectively), suggesting the potential for synergy by combining these 2 approaches. Future directions for study include trials of combinations of exercise types, longer training periods, and investigation of the potential for exercise to modify the trajectory of disease progression over time.

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Correspondence: Lisa M. Shulman, MD, Department of Neurology, University of Maryland School of Medicine, 110 S Poca St, Room 3-S-127, Baltimore, MD 21201 (lshulman@som.umaryland.edu).

Author Contributions: *Study concept and design:* Shulman, Katzel, Ivey, Sorkin, Smith, and Macko. *Acquisition of data:* Shulman, Katzel, Ivey, Anderson, Weiner, and Macko. *Analysis and interpretation of data:* Shulman, Katzel, Ivey, Sorkin, Favors, Anderson, Smith, Reich, and Macko. *Drafting of the manuscript:* Shulman, Katzel, Sorkin, Favors, and Macko. *Critical revision of the manuscript for important intellectual content:* Katzel, Ivey, Sorkin, Anderson, Smith, Reich, Weiner, and Macko. *Statistical analysis:* Sorkin and Favors. *Obtained funding:* Shulman, Katzel, and Macko. *Administrative, technical, and material support:* Shulman, Katzel, Ivey, Sorkin, Smith, Weiner, and Macko. *Study supervision:* Shulman, Katzel, and Ivey.

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Online-Only Material: The eAppendix and eTables are available at <http://www.jamaneuro.com>.

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