

Exercise for falls prevention in Parkinson disease

A randomized controlled trial



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ABSTRACT

Objective: To determine whether falls can be prevented with minimally supervised exercise targeting potentially remediable fall risk factors, i.e., poor balance, reduced leg muscle strength, and freezing of gait, in people with Parkinson disease.

Methods: Two hundred thirty-one people with Parkinson disease were randomized into exercise or usual-care control groups. Exercises were practiced for 40 to 60 minutes, 3 times weekly for 6 months. Primary outcomes were fall rates and proportion of fallers during the intervention period. Secondary outcomes were physical (balance, mobility, freezing of gait, habitual physical activity), psychological (fear of falling, affect), and quality-of-life measures.

Results: There was no significant difference between groups in the rate of falls (incidence rate ratio [IRR] = 0.73, 95% confidence interval [CI] 0.45–1.17, $p = 0.18$) or proportion of fallers ($p = 0.45$). Preplanned subgroup analysis revealed a significant interaction for disease severity ($p < 0.001$). In the lower disease severity subgroup, there were fewer falls in the exercise group compared with controls (IRR = 0.31, 95% CI 0.15–0.62, $p < 0.001$), while in the higher disease severity subgroup, there was a trend toward more falls in the exercise group (IRR = 1.61, 95% CI 0.86–3.03, $p = 0.13$). Postintervention, the exercise group scored significantly ($p < 0.05$) better than controls on the Short Physical Performance Battery, sit-to-stand, fear of falling, affect, and quality of life, after adjusting for baseline performance.

Conclusions: An exercise program targeting balance, leg strength, and freezing of gait did not reduce falls but improved physical and psychological health. Falls were reduced in people with milder disease but not in those with more severe Parkinson disease.

Classification of evidence: This study provides Class III evidence that for patients with Parkinson disease, a minimally supervised exercise program does not reduce fall risk. This study lacked the precision to exclude a moderate reduction or modest increase in fall risk from exercise. Trial registration: Australian New Zealand Clinical Trials Registry (ACTRN12608000303347).

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GLOSSARY

CI = confidence interval; IRR = incidence rate ratio; NSW = New South Wales; PD = Parkinson disease; **PIG** = Poisson inverse gaussian; **RR** = relative risk; **UPDRS** = Unified Parkinson's Disease Rating Scale.

People with Parkinson disease (PD) fall frequently, with 60% falling annually and two-thirds of these falling recurrently.^{1–3} These fall rates are double those in the general older population,³ and the resulting injuries,⁴ pain,⁵ activity limitations,³ and fear of falling³ compromise health and well-being.

While evidence from systematic reviews shows that exercise programs are effective in preventing falls in the general older population,^{6,7} only 5 randomized controlled trials have evaluated exercise programs designed to reduce falls in people with PD. Three underpowered trials^{8–10} reported no

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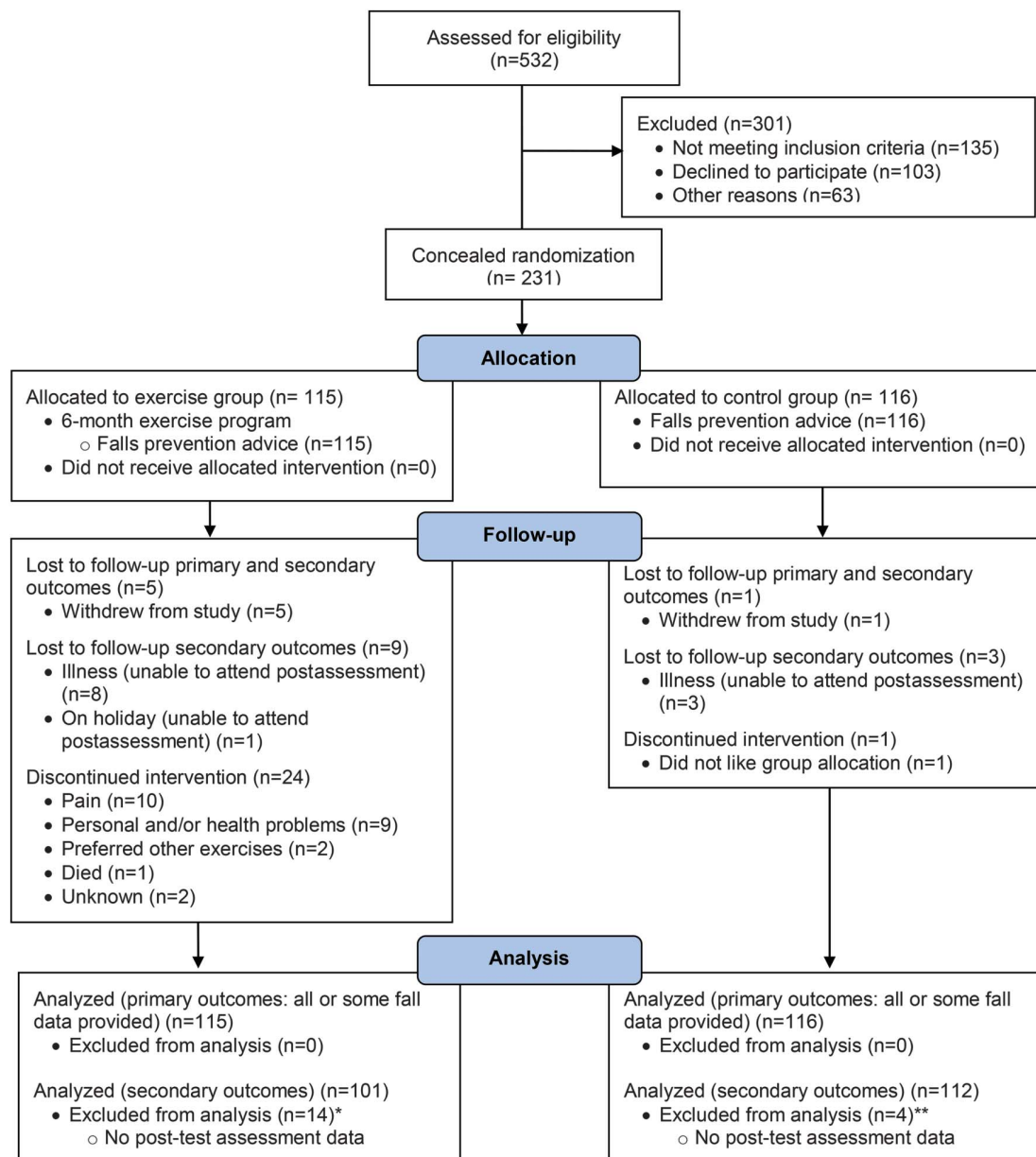
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effect on falls, while 2 trials^{11,12} reported significant reductions in falls when exercises that challenged balance were compared with exercises that did not challenge balance. These positive trials did not, however, target 2 additional independent physical risk factors for falls, i.e., reduced leg strength and freezing of gait,¹ which are also potentially remediable.^{13–16}

The outcomes in the 2 positive fall prevention trials in people with PD were achieved

using fully supervised exercise. A fully supervised mode of exercise delivery is difficult to sustain in clinical practice, while less-supervised models of exercise delivery may offer a more clinically relevant and sustainable intervention strategy. This approach has been found to reduce falls and fall-related injuries by 35% in the general older population.¹⁷ Therefore, we aimed to determine whether a pragmatic, minimally supervised exercise

Figure 1 Flow of participants through the trial



*The 24 exercise participants who discontinued intervention include 4 of the participants lost to both primary and secondary outcomes and 7 of the participants lost to secondary outcomes; **3 exercise and 3 control participants provided posttest questionnaire data but no posttest physical assessment data.

program targeting balance, leg muscle strength, and freezing of gait could reduce falls in community-dwelling people with PD.

METHODS Design. A prospective, assessor-blinded, randomized controlled trial was undertaken from 2008 to 2012. The methods have been described in detail elsewhere.¹⁸ We randomly allocated 231 community-dwelling participants with PD to an exercise group (intervention) or usual-care group (control) (figure 1).

The primary research question was: does a minimally supervised exercise program targeting balance, leg muscle strength, and freezing of gait reduce falls in community-dwelling people with PD as compared with usual care? The secondary research question was: does the exercise program improve fall risk factors, fear of falling, affect, and quality of life?

This study provides Class III evidence that for patients with PD, a minimally supervised exercise program does not reduce falls risk.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by The University of Sydney Human Research Ethics Committee, and written informed consent was obtained from all participants. The trial was registered prospectively with the Australian New Zealand Clinical Trials Registry (ACTRN12608000303347).

Participants. Participants were recruited from metropolitan Sydney and regional and rural New South Wales (NSW), Australia, via Parkinson's NSW consumer support groups, newspaper advertisements, and referrals from neurologists and physical therapists. Eligibility criteria included a diagnosis of idiopathic PD (confirmed by a medical practitioner), age 40 years or older, ability to walk independently with or without a walking aid, stable antiparkinsonian medication for at least 2 weeks, and one or more falls in the past year or at risk of falls based on physical assessment. Participants were deemed to be at risk of falling if they scored 25 cm or less on the Functional Reach Test¹⁹ or if they failed to reach criterion on one of the balance tests in the QuickScreen Clinical Falls Risk Assessments,²⁰ i.e., unable to perform near tandem stand with eyes closed for 10 seconds, unable to complete 8 steps in the alternate step test (18-cm step) in less than 10 seconds, or unable to perform 5 repetitions of sit-to-stand in less than 12 seconds.

Participants were excluded if they had a Mini-Mental State Examination score of <24, unstable cardiovascular disease, or other uncontrolled chronic conditions that would interfere with the safety and conduct of the training and testing protocol. All eligible volunteers received clearance from their medical practitioner.

Randomization and masking. Participants were randomized to intervention or control groups after baseline assessment. Randomization was stratified by fall history (0–9/≥10 falls in the previous 12 months) using a computer-generated random-number schedule with variable block sizes of 2 and 4. Randomization was performed centrally by an investigator not involved in recruitment or assessments (C.S.). Outcome assessors were masked to group allocation.

Intervention group. The intervention group undertook the PD-WEBB program (www.webb.org.au). This program¹⁸ included 40 to 60 minutes of progressive balance and lower limb strengthening exercises 3 times a week for 6 months, and cueing strategies to reduce freezing of gait¹⁵ for participants

reporting freezing. Balance exercises included standing with a decreased base of support, graded reaching activities, and forward/sideways/backward stepping. Strengthening exercises included sit-to-stand, forward and lateral step-ups, semisquats, and heel raises, with load progressively increased via weighted vests.²¹ Participants attended a monthly exercise class led by a physical therapist and performed the remaining exercise sessions at home. The exercises were prescribed and progressed in the class, and 2 to 4 home visits were conducted by the physical therapist over the 6 months. When group sessions were not feasible, participants performed all exercise sessions at home. Eight to 10 of these home sessions were supervised by a physical therapist. For participants with freezing of gait, cueing strategy training was undertaken during an additional 1 or 2 home visits. The intervention group also received a booklet containing standardized fall prevention advice.²²

Control group. The control group received usual care from their medical practitioner and community services. A booklet containing standardized fall prevention advice was provided.²²

Outcome measures. The primary outcome measures were the number of falls and the proportion of fallers recorded during the 6-month intervention period. Falls (defined as unintentionally coming to rest on the ground or other lower surface without overwhelming external force or a major internal event)²³ were recorded by the use of a “falls diary.” Participants received calendars on entry to the study, with instructions to record the following: falls; nursing, medical, and allied health appointments; and hospitalizations. Participants returned completed calendars monthly in prepaid envelopes. Participants were also telephoned monthly to record any changes in medications, use of health resources, and to verify fall details.

Secondary outcomes included the following: the PD Fall Risk score¹; mean knee extensor muscle strength of both legs²⁴; coordinated stability test of balance²⁵; the Short Physical Performance Battery, which includes walking, standing balance, and sit-to-stand tests²⁶; fast walking velocity over 4 m; the 5-repetition sit-to-stand test; the Freezing of Gait Questionnaire²⁷; the Falls Efficacy Scale–International²⁸; a habitual physical activity questionnaire recording the amount of regular exercise and activities of daily living; quality of life using the mental and physical subscores of the SF-12v2 (Short Form 12 version 2), the SF-6D (Short Form 6 dimensions) utility score, a PD-specific quality-of-life questionnaire (PDQ-39)²⁹; and the positive affect subscale of the Positive and Negative Affect Schedule.³⁰

Home exercise logs were kept by participants, and class records were kept by the physical therapists delivering the intervention. Adverse events (defined as a significant injury or medical event causing the participant to seek attention from a health professional or limit their activities for ≥2 days) occurring during exercise were monitored and recorded throughout the study.

Measurements and procedures. Secondary outcomes were collected on entry to the study (baseline) and after the 6-month intervention period (posttest) by 1 of 7 trained assessors in participants' homes. The order of outcome measurements was standardized and conducted when participants were optimally medicated, usually 1 hour after ingestion of PD medications.

Statistical analysis. A statistical analysis plan was developed and certified before unblinding and analysis. An intention-to-treat approach was used for all analyses. A blind review of the falls data revealed that the negative binomial model was not flexible enough to capture both the nonfallers and the large number of multiple fallers. In contrast, the Poisson inverse gaussian (PIG)

Table 1 Demographic and clinical characteristics of the study participants at baseline

Characteristic	Exercise (n = 115)	Control (n = 116)
Sex, male, n (%)	69 (60)	66 (57)
Age, y	71.4 (8.1)	69.9 (9.3)
Height, m	1.7 (0.1)	1.7 (0.1)
Weight, kg	76.3 (15.7)	76.6 (14.9)
Body mass index, kg/m ²	26.3 (4.5)	26.8 (4.4)
Falls in past 12 mo, median no. (IQR) ^a	2 (4)	2 (3)
People who fell in the past year, n (%)	90 (78)	90 (78)
People who fell 2+ times in past year, n (%)	74 (64)	72 (62)
People who fell 10+ times in past year, n (%)	13 (11)	15 (13)
Time since PD diagnosis, y	7.5 (5.8)	8.3 (6.0)
Hoehn and Yahr stage, 0-5	2.7 (0.5)	2.7 (0.6)
Stage 2, n (%)	33 (30)	41 (35)
Stage 3, n (%)	77 (67)	69 (60)
Stage 4, n (%)	3 (3)	6 (5)
UPDRS ⁴⁰		
Motor examination, 0-108	25.8 (8.9)	26.7 (10.1)
Dyskinesia and dystonia, 0-14	1.3 (2.0)	1.0 (1.6)
Motor fluctuations, 0-7	1.6 (1.6)	1.4 (1.6)
Freezing when walking, 0-4	1.0 (1.2)	1.4 (1.2)
Freezing of gait in the past month, n (%)	53 (46)	61 (53)
Mini-Mental State Examination, 0-30	28.6 (1.5)	28.7 (1.4)
Frontal Assessment Battery, 0-18	14.2 (2.4)	14.2 (2.5)
Exercise, h/wk	3.6 (3.5)	4.0 (4.1)
Deep brain stimulation received, n (%)	11 (9.6)	15 (12.9)
Medications		
Daily levodopa equivalent dose, mg	787 (486)	807 (521)
Levodopa, no. of people taking (%)	108 (94.0)	109 (94.0)
Dopamine agonists, no. of people taking (%)	49 (42.6)	52 (44.8)
MAO type B inhibitors, no. of people taking (%)	5 (4.3)	11 (9.5)
COMT inhibitors, no. of people taking (%)	41 (35.7)	36 (31.0)
Other Parkinson medications, no. of people taking (%)	15 (13.0)	27 (23.3)
Coexisting conditions ^b		
0, no. of people (%)	18 (15.7)	25 (21.6)
1, no. of people (%)	38 (33.0)	34 (29.3)
≥2, no. of people (%)	59 (51.3)	57 (49.1)
Relevant prior surgery		
Knee replacement surgery, no. of people (%)	19 (16.5)	13 (11.2)
Total hip replacement surgery, no. of people (%)	12 (10.4)	10 (8.7)
Spinal surgery, no. of people (%)	12 (10.4)	7 (6.0)

Abbreviations: COMT = catechol-O-methyltransferase; IQR = interquartile range; MAO = monoamine oxidase; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale.

Data are mean (SD) unless stated otherwise.

^aMedian (IQR) scores are presented, as scores ranged from 0 to 1,825 in the control group and 0 to 730 in the experimental group.

^bConditions included arthritis, heart disease, high blood pressure, lung disease, diabetes, osteoporosis, depression, chronic back pain, and cancer; the number of coexisting conditions ranged from 0 to 9.

distribution gave a good fit. Therefore, the intervention effect on the number of falls was assessed using PIG regression, with the logarithm of the days of follow-up included as an exposure term in the model. An analysis adjusted for previous multiple faller status was also performed. The proportion of fallers was compared between groups using a χ^2 test.

Prespecified subgroup analyses for the primary outcomes were undertaken to identify any differential impact of the exercise intervention according to fall history (0–9 vs ≥ 10 falls in the previous year), physical function (based on 4-m comfortable walk speed at baseline, dichotomized at the median), disease severity (based on Unified Parkinson's Disease Rating Scale [UPDRS] motor score at baseline, dichotomized at the median), and cognition (based on Frontal Assessment Battery score at baseline, dichotomized at the median). The main analysis for each subgroup was based on interaction tests in PIG models using continuous interaction terms where possible, and dichotomous interaction terms using prespecified cutoffs were used to assist in the interpretation of subgroup analyses.

Between-group comparisons of final test performance for the continuously scored secondary outcome measures were made using general linear models (analysis of covariance) controlling for baseline performance. The R version 2.15.2 package “gamlss”³¹ was used to fit the PIG model to the number of falls; SPSS version 20 statistical software (IBM Corp., Armonk, NY) was used for all other analyses.

Sample size. Because it was our intention to compare fall rates between groups using incidence rate ratios (IRRs) from negative binomial regression models,³² we conducted a sample-size calculation using the nbpower command in the Stata software package.¹⁸ Assuming a control group rate of falls of 1 fall/person month¹ over 5 months of follow-up, 115 participants per group were required to provide 80% power to detect as significant, at the 5% level, a 30% lower rate of falls for exercise participants than control participants (i.e., IRR = 0.70). Five months was used to account for loss to follow-up.

RESULTS Flow of participants through the trial. The trial flow of participants is summarized in figure 1. A total of 231 participants (135 male) with an average age of 71 (SD 9) years were recruited. The 115 exercise participants and 116 control participants were similar in demographic characteristics, levodopa equivalent dosages, and comorbidities at baseline (table 1).

Intervention. Group exercise was offered at 22 locations. Seventy-eight participants attended an exercise class once per month, with an average of 3.5 participants per group (range 2–6). The remaining 37 exercise participants performed all exercise sessions at home. On average, 13% of the exercise sessions were supervised by a physical therapist.

Adherence to exercise protocol. Exercise adherence records were available for 108 (94%) of the 115 exercise participants. The exercise group completed a mean of 72% (SD 38%) of prescribed exercise sessions. Twenty-five participants (22%) performed a modified program to account for pain and coexisting conditions, while 24 participants (21%) discontinued the exercise program.

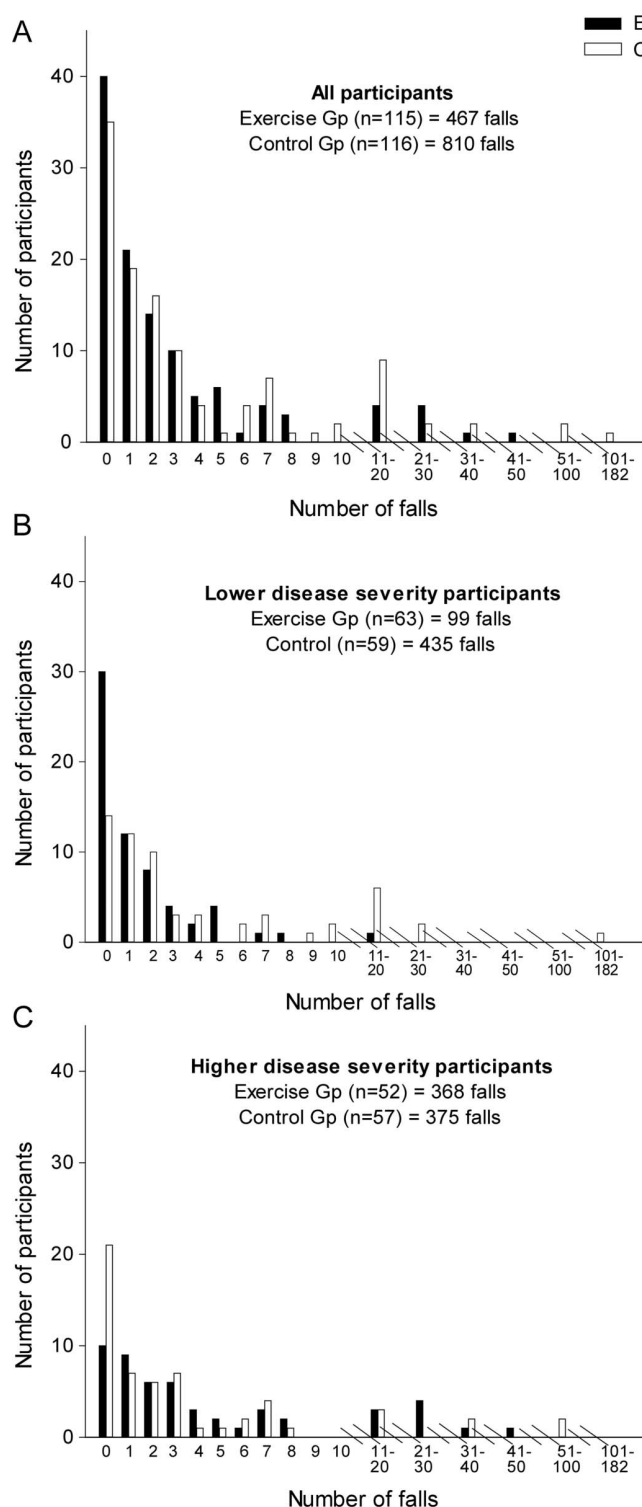
Adverse events. Two participants fell while exercising at home. One fell while putting on the weighted vest and one fell while turning on completion of a stepping exercise. Neither fall resulted in injury requiring medical attention or restriction of activities.

Primary outcomes. Six months of falls data were available for 225 participants (97%) and one or more months of falls data were available for the remaining 6 participants. During the intervention period, 467 falls (4.1 falls/person) were reported in the exercise group and 810 (7.0 falls/person) in the control group (figure 2, table 2). This 27% difference in fall rate in the exercise group compared with the control group was not statistically significant (IRR = 0.73, 95% confidence interval [CI] 0.45–1.17, $p = 0.18$). There was no significant difference in the proportion of fallers with 75 (65%) of the exercise participants and 81 (70%) of the control participants reporting at least one fall (relative risk [RR] = 0.93, 95% CI 0.78–1.12, $p = 0.45$). The results of the primary analyses were essentially unchanged after adjustment for baseline faller status. Medical attention was sought for 21 falls in the exercise group and 19 falls in the control group (table e-1 on the *Neurology*[®] Web site at Neurology.org).

Prespecified subgroup analysis revealed a significant interaction effect for disease severity (rate of falls $p < 0.001$, proportion of fallers $p = 0.001$) (figure 2, table 2). Participants with lower disease severity (motor UPDRS score ≤ 26) demonstrated a 69% reduction in falls in the exercise group (IRR = 0.31, 95% CI 0.15–0.62, $p < 0.001$) and a lower proportion of fallers (RR = 0.69, 95% CI 0.52–0.90, $p = 0.01$) compared with the control group. In contrast, participants with higher disease severity (motor UPDRS score ≥ 27) displayed a trend toward more falls in the exercise group (IRR = 1.61, 95% CI 0.86–3.03, $p = 0.13$) with a higher proportion of fallers (RR = 1.28, 95% CI 1.01–1.62, $p = 0.04$) compared with the control group. A marginally significant interaction effect was found for cognition on rate of falls as a continuous variable ($p = 0.048$), but this interaction was not significant when data were dichotomized ($p = 0.45$) (table e-2). No significant interaction effect was found for fall history or physical function on rate of falls.

Secondary outcomes. At 6 months, the exercise group performed significantly better than the control group on several physical outcomes (Short Physical Performance Battery and sit-to-stand), psychological outcomes (Falls Efficacy Scale International and Positive Affect Scale), and overall quality of life (SF-6D) after adjusting for baseline values (table e-3).

Figure 2 Falls reported by all participants, participants with lower disease severity, and participants with higher disease severity



Post hoc analysis. To assist in understanding the differential impact of the intervention on falls by disease severity, post hoc subgroup analyses were undertaken for the secondary outcomes (table e-4). The only significant interaction effect was found for amount of

regular exercise including prescribed exercises ($p = 0.04$). For participants with lower disease severity, a greater amount of habitual exercise was performed by the exercise group compared with the control group (1.5 h/wk, 95% CI 0.03–3.05, $p = 0.046$), but there was no significant between-group difference (-0.4 h/wk, 95% CI -1.2 to 0.5 , $p = 0.38$) for participants with higher disease severity. Post hoc analysis of adherence data showed that the exercise participants with lower disease severity completed 76% (SD 39%) of prescribed exercise sessions, while those with higher disease severity completed 67% (SD 36%) of prescribed exercise sessions, and this -9% (95% CI -23 to 6) difference in adherence was not statistically significant ($p = 0.24$). Participant characteristics according to disease severity subgroup are presented in table e-5.

DISCUSSION This randomized controlled trial of a 6-month, minimally supervised exercise program targeting physical fall risk factors, i.e., impaired balance, impaired leg strength, and freezing of gait, did not reduce falls, proportion of fallers, or serious fall-related injuries in community-dwelling people with PD. Despite the lack of significant effect on several fall risk factors (PD Fall Risk score, knee strength, coordinated stability test, and Freezing of Gait Questionnaire), this exercise program resulted in improvements in balance and mobility (Short Physical Performance Battery and 5-repetition sit-to-stand), fear of falling, positive affect, and overall quality of life relative to the control group. These findings may be explained by the nature of the balance and strength exercises and are consistent with recent evidence highlighting the task-specific effect of exercise in people with PD.³³ These findings add weight to the evidence supporting the efficacy of exercise for people with PD^{13,34} but, unlike previous trials of supervised exercise,³⁵ were achieved with an exercise program in which more than 87% of the prescribed exercise sessions were undertaken independently.

The nonsignificant effect on overall fall rate found in our study may be explained by the differential effects of the exercise program according to disease severity. Our prespecified subgroup analysis indicated that this exercise program was effective in reducing falls and proportion of fallers in people with milder PD but marginally ($p = 0.04$) increased the proportion of fallers in people with more severe disease. This group had good adherence to the prescribed program but overall did no more exercise per week than the control group. If the overall dose of exercise is important (i.e., prescribed program + usual physical activity), then the dose of exercise more broadly may have been insufficient in our study. It is also possible that

Table 2 Primary intention-to-treat analysis and disease severity subgroup analysis^a

	Exercise	Control	IRR (95% CI), p value	RR (95% CI), p value	Disease severity × intervention interaction
Primary analysis, E = 115, C = 116					
Falls	467	810	0.73 (0.45–1.17), p = 0.18		Continuous, p = 0.02 ^b
Falls/person/6 mo	4.1	7.0	0.79 (0.53–1.19) ^d , p = 0.25		Dichotomous, p < 0.001 ^c
Fallers, n	75	81		0.93 (0.78–1.12), p = 0.54	Continuous, p = 0.03 ^b
Proportion of fallers, %	65	70		0.94 (0.74–1.12), p = 0.71 ^d	Dichotomous, p = 0.001 ^e
Lower disease severity subgroup, E = 63, C = 59					
Falls	99	435	0.31 (0.15–0.62), p < 0.001 ^c		
Falls/person/6 mo	1.6	7.4			
Fallers, n	33	45		0.69 (0.52–0.90), p = 0.01 ^b	
Proportion of fallers, %	52	76			
Higher disease severity subgroup, E = 52, C = 57					
Falls	368	375		1.61 (0.86–3.03), p = 0.13	
Falls/person/6 mo	7.1	6.6			
Fallers, n	42	36		1.28 (1.01–1.62), p = 0.04 ^b	
Proportion of fallers, %	81	63			

Abbreviations: C = control; CI = confidence interval; E = exercise; IRR = incidence rate ratio; RR = relative risk; UPDRS = Unified Parkinson's Disease Rating Scale.

^a Lower disease severity = motor UPDRS score ≤26; higher disease severity = motor UPDRS score ≥27.

^b p < 0.05.

^c p < 0.001.

^d Adjusted for baseline multiple faller status.

^e p < 0.01.

the more severely affected participants were potentially placed at higher risk of falls, through increased exposure to fall risk situations resulting from improved mobility and reduced fear of falling achieved in the program. The lack of a differential effect of the intervention on other secondary outcomes for those of lower and higher disease severity may simply reflect low statistical power of interaction tests. However, given the differential impact according to disease severity on falls themselves, the lack of a differential impact on secondary outcomes may also suggest a role of other fall risk factors that were not measured.

The significant 69% reduction in fall rate for the lower disease severity subgroup achieved in our trial is comparable to the 67% reduction in fall rate in a 6-month, fully supervised trial of tai chi.¹¹ The majority of participants in the tai chi trial had relatively mild PD (i.e., 1–2 on the Hoehn and Yahr scale), while the majority of participants in our trial scored 3–4 on the Hoehn and Yahr scale. In contrast, however, a reduction in falls in people with PD in Hoehn and Yahr stages 3–4 was reported when a 7-week, fully supervised, balance-demanding exercise program was delivered.¹² Taken together, this evidence suggests that minimally supervised exercise programs aimed at reducing falls in

people with PD should be implemented early in the disease process. With the progression of disease affecting both motor and nonmotor systems (as evidenced by the higher fall risk in participants with higher disease severity at baseline, shown in table e-5), people with more severe disease may derive more benefit from a multifactorial, closely supervised intervention. Further adequately powered trials and meta-analyses are required to confirm these suggestions.

Our study has several limitations. The control group did not receive an intervention to control for the Hawthorne effect, and all participants continued their usual medical care including adjustment of medications and deep brain stimulation parameters as required. Nevertheless, these results provide a pragmatic, clinically relevant evaluation of the impact of a minimally supervised exercise program compared with usual care. We chose to focus on physical risk factors and acknowledge that interventions designed to target nonmotor fall risk factors, such as impaired cognition,^{1,36} in combination with exercise may have a more significant impact on falls.³⁷

Future research is required to gain greater insight into successful fall reduction programs as well as the potential for increasing fall risk in some individuals. Given the heterogeneity of PD, interventions aiming

to reduce falls in PD should consider tailoring multifactorial interventions according to motor and non-motor risk factors, absolute risk of falls,³⁸ disease severity, and motor phenotype. In addition, promising pharmacologic therapies³⁹ in combination with multifactorial interventions warrant investigation.

AUTHOR CONTRIBUTIONS

Colleen Canning contributed to the conception and design of the trial, analyzed and interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. Catherine Sherrington contributed to the conception and design of the trial, interpreted the data, and revised the manuscript for important intellectual content. Stephen Lord contributed to the conception and design of the trial, interpreted the data, and revised the manuscript for important intellectual content. Jacqueline Close contributed to the conception and design of the trial, interpreted the data, and revised the manuscript for important intellectual content. Stephane Heritier wrote the statistical analysis plan, analyzed and interpreted the data, and revised the manuscript for important intellectual content. Gillian Heller analyzed and interpreted the data and revised the manuscript for important intellectual content. Kirsten Howard analyzed and interpreted the data and revised the manuscript for important intellectual content. Natalie Allen contributed to the conception and design of the trial, interpreted the data, and revised the manuscript for important intellectual content. Mark Latt contributed to the conception and design of the trial, interpreted the data, and revised the manuscript for important intellectual content. Susan Murray contributed to the design of the study and revised the manuscript for important intellectual content. Sandra O'Rourke contributed to the design of the study and revised the manuscript for important intellectual content. Serene Paul interpreted the data and revised the manuscript for important intellectual content. Joeeun Song analyzed and interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. Victor Fung contributed to the conception and design of the trial, interpreted the data, and revised the manuscript for important intellectual content.

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