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Running head: Exercise for People in Early- or Mid-Stage Parkinson Disease

Research Report

Exercise for People in Early- or Mid-Stage Parkinson Disease: A 16-Month Randomized Controlled Trial

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ABSTRACT

Background. Exercise confers short-term benefits for individuals with PD.

Objective. Compare short- and long-term responses among two supervised exercise programs and a home-based exercise control group.

Design. 16-month randomized controlled exercise intervention including: flexibility/balance/function exercise (FBF), supervised aerobic exercise (AE), and home-based exercise (CON).

Setting. University outpatient clinic.

Patients. 121 individuals with PD; Hoehn &Yahr stages 1-3.

Intervention. FBF (individualized spinal and extremity flexibility exercises followed by group balance/functional training), supervised by a physical therapist; AE (treadmill, bike and/or elliptical trainer), supervised by an exercise trainer. Supervision was 3 days/wk for 4 months, and then monthly (16 months total). Controls exercised at home using the National PD Foundation 'Fitness Counts' program, with 1 supervised group clinic-based session/month.

Measurement. Outcomes, obtained by blinded assessors, were determined at 4,10 and 16 months. Primary outcomes: overall physical function (Continuous-Scale Physical Functional Performance, CS-PFP); balance (Functional Reach, FR); and walking economy (VO_2 mL/kg/min). Secondary outcomes: Unified PD Rating scale (UPDRS) Activities of Daily Living (ADL) and Motor Subscales, and quality of life (PDQ-39).

Results. Of 121 participants: 86.8%, 82.6%, and 79.3% completed 4, 10, and 16 months respectively. Results were: CS-PFP: improvement at 4 months was greater in the FBF group than Control (mean difference 4.3; 95% CI: 1.2 to 7.3) and AE (mean difference 3.1; 95% CI:

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0.0 to 6.2). FR was not different between groups at any time point. Walking Economy: AE improved compared to FBF at 4 (mean difference -1.2; 95% CI: -1.9 to -0.5), 10 (mean difference -1.2; 95% CI: -1.9 to -0.5), and 16 months (mean difference -1.7; 95% CI: -2.5 to -1.0). The only secondary outcome that showed significant differences was UPDRS ADL: FBF performed better than Controls at 4 (mean difference -1.47; 95% CI: -2.79 to -0.15) and 16 months (mean difference -1.95; 95% CI: -3.84 to -0.08).

Limitations. Absence of a non-exercise control.

Conclusions. Findings demonstrated overall functional benefits at 4 months for FBF and improved walking economy (up to 16 months) for AE.

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INTRODUCTION

Parkinson's disease (PD) is a chronic progressive disorder affecting about 1% of people over age 60 in industrialized countries, an estimated 4% of people over the age of 80,[1] and is anticipated to affect 8-9 million people worldwide by 2030.[2] Management of PD has been traditionally by pharmacology and/or surgery. Evidence from various exercise approaches[3-11] demonstrates benefits of exercise in preserving aspects of function and quality of life.[12-16] However, a Cochrane review of 2001 noted that "there is insufficient evidence to support or refute the efficacy of any given form of physiotherapy over another in Parkinson's disease", further stating, "Therefore a consensus must be found as to 'best practice' physiotherapy for Parkinson's disease."[17] Despite considerable efforts, there is not yet sufficient evidence. Furthermore, most interventions studied were relatively short-term, benefits were reported immediately after the intervention, and few reported post-intervention follow-up. Available post-intervention data (typically 12-26 weeks)[15] suggest benefits are lost after supervision is terminated. With no strategies in place to facilitate ongoing exercise, this is not surprising because PD is chronic and progressive. Ongoing exercise is likely necessary to combat declines in strength, flexibility, and balance and their functional consequences.

A next important step is to compare interventions, not just in terms of immediate benefits, but also in terms of long-term outcomes. The program with the greatest short-term benefits after supervised exercise may not be the program with greatest benefits over the long-term. Thus this investigation was designed to compare short- and long-term effects of two supervised exercise programs to a control program.

The three exercise approaches investigated were: 1) flexibility/balance/function program (FBF) specifically designed for people with PD; 2) standard aerobic endurance program (AE);

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and 3) as the control, home-based program of exercises recommended by the National Parkinson's Foundation (CON).[18] FBF and AE were supervised 3x/wk for 4 months, with tapered supervision for one month, and then once monthly to 16 months. CON was supervised 1x/month for 16 months.

The FBF intervention was based on exercises used in a previous investigation demonstrating improvement of spinal flexibility and balance in PD.[8] That program was enriched with exercises designed to enhance postural control and overall function.[19] At 4 months, we expected to see the greatest benefits with this program compared to the other two programs. However, we were concerned that participants could have difficulty adhering to this program once supervised intervention was completed.

Endurance exercise has known health benefits[20] and could potentially benefit people with PD. Improved endurance could lead to improvements in overall function, in particular for those functions that require endurance. We did not anticipate that endurance exercise would be as successful in improving those functional activities that require flexibility and balance as would PD-specific exercises. However, long-term adherence might be easier with this exercise regimen. Hence at 10 and 16 months, it was possible that AE participants would perform better than FBF participants.

The exercises outlined in *Fitness Counts*,[18] developed by the National Parkinson Disease Association, were chosen as a control because these exercises are commonly given to patients by their neurologists without specific supervision or follow-up. Because of the limited supervision, we anticipated that this program would be less successful than the supervised exercise programs in improving all outcome measures.

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Because of the degenerative nature of PD, long-term exercise habits are essential; otherwise, the participant is likely to quickly lose any gains achieved. Yet within three months to a year, only 50% or fewer of individuals with a variety of conditions still adhere to an exercise program.[21,22] Barriers to exercise have been examined[23-26] and include poor exercise self-efficacy, poor sense of control over exercise behaviors, unfavorable self-concept, failure to exercise in the past, insufficient knowledge and skill, and anxiety among other factors. Among factors related to exercise adherence,[27-31] perhaps most important is readiness or willingness to change.[32,33] Based on theoretical constructs, investigators have developed approaches to assisting individuals to develop regular exercise habits.[21,23,34-36] These constructs were instrumental in developing the current investigation.

In summary, this exercise investigation compared two supervised exercise programs and a control exercise program both in the short-term (4 months) and long-term (10 and 16 months). Strategies were in place to enhance long-term adherence following the supervised period of exercise. Comparisons were made at 4, 10, and 16 months with the primary endpoints at 4 and 10 months. Our primary hypotheses were:

(1) *Overall function*: FBF and AE would each have greater improvement on the Continuous Scale Physical Functional Performance test (CS-PFP) than CON. This hypothesis was based on the expectation that both improved flexibility / balance and improved endurance would translate to improvements in functional ability.

(2) *Balance*: FBF would have greater improvement on functional reach (FR) than the other groups. This hypothesis was based findings from our prior investigation.[8]

(3) *Movement Efficiency*: FBF would have better economy of walking than the other groups. The causes of reduced economy of walking in people with PD are unknown; however

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we theorized that improved thoracic flexibility from the FBF program might result in improves walking economy.

Our secondary hypotheses were:

(4) FBF and AE would each perform better than Control on the ADL and Motor subscales of the Unified Parkinson's Disease Rating Scale (UPDRS) because of the impact of these two exercise programs on function.

(5) At four months, FBF and AE would perform better on the 39-item Parkinson's disease quality of life scale (PDQ-39) because of three times a week supervised exercise.

METHOD

Study Design

This was a randomized controlled exercise study for people with early- or mid-stage PD. Participants were enrolled between August 2003 and April 2009; the last participants reached 16 months in July 2010.

Participants were randomized to: 1) supervised flexibility/balance/function exercise (FBF), 2) supervised aerobic exercise (AE), and 3) home exercise (CON). Primary outcomes included: physical function as measured by the Continuous Scale Physical Functional Performance test (CS-PFP);[37] balance as measured by functional reach (FR);[38] and walking economy, (energy cost of walking, oxygen uptake, VO_2 in mL/min/kg).[39] Secondary outcomes included: UPDRS Activities of Daily Living (ADL) and Motor Subscales and a measure of quality of life, PDQ-39.[40] Endpoints were at 4 months, the end of the supervised exercise period for AE and FBF), 10 months, and 16 months. Primary endpoints were at 4 and 10 months.

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This investigation was designed with sample sizes sufficient to detect clinically important differences between groups on several relevant outcome measures. Initial sample size estimates (PASS software, NCSS LLC, Kaysville, Utah)[41] were based on reported mean changes and standard deviations (SD) of measures investigated in the previous exercise intervention study utilizing a similar program[8] as well as other change scores available at the time of the grant submission. Included were functional reach and functional axial rotation,[8] CS-PFP,[37] UPDRS (Total, Motor and ADL) scores.[42] Approximately half-way through study accrual, updated information on effect sizes for the CS-PFP, UPDRS, and FR was used to re-estimate the required sample size. Based on a one-way ANOVA design with 3 groups and a minimally detectable effect size (Cohen's *f*) of 0.4 at 16 months (i.e., a ratio of 0.4 of the between-group standard deviation of mean change when comparing 16-month and baseline measures to the within-group standard deviation of change), it was estimated that 26 participants completing the study per group were needed to achieve at least 90% power, with $\alpha = 0.05$ (two-sided). An effect size of 0.4 translates to between group SDs for mean change between baseline and 16 months of 0.68 cm for FR (within-group SD = 1.7cm), 5.92 points for UPDRS Total (within-group SD = 14.8 points), and 3.2 points for CS-PFP (within-group SD = 8 points). Accounting for an estimated 30% attrition rate over 16 months led us to randomize 38 subjects per group.

Participants

All participants had primary PD diagnosed by a movement disorders specialist using the UK Brain Bank criteria,[43] were in Stages 1-3 of Hoehn and Yahr,[44] lived in the community, and ambulated independently. Study exclusions: uncontrolled hypertension, on-state freezing or exercise limitations from other disorders, and Mini-Mental State Examination[45] less than 24. Most participants were recruited by their treating movement disorder neurologist at the

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University of (blinded). Other methods included advertisements, presentations at PD support groups, and meetings with other community neurologists. All participants gave informed consent, approved by the institutional review board of the University of (blinded).

A telephone screen ruled out exclusions related to health. A movement disorders neurologist confirmed the primary PD diagnosis. A submaximal graded exercise test (GXT) was performed to determine whether participants could exercise safely at intensities up to 85% of age-predicted maximal heart rate (HRmax).[39] Eligible volunteers then underwent baseline testing, followed by randomization. Computer-generated randomization assignments were designed by AEB. Randomization was stratified by sex, blocked to assure balance across groups over time, kept in opaque, sealed envelopes and unsealed by a research assistant after baseline testing. Of the 811 volunteers contacted, 162 provided consent, and 121 were randomized (Figure 1).

Baseline Testing and Outcome Measures

All testing took place at the University of (blinded) and was performed by study personnel, blinded to group allocation. The first test session took place at a time of day when participants had their best response to PD medications; subsequent sessions were as close to that time as possible.

In one session, energy expenditure (VO_2 ml/kg) was measured at 4 walking speeds in 0.5 mph increments (walking economy).[6] The maximum speed was based on the participant's fastest tolerable speed during the graded exercise test. A heart rate monitor was worn throughout the test. First a resting measurement was obtained for five minutes with the participant sitting in a chair. Then the participant walked for five minutes at each of 4 different speeds, beginning with

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the slowest speed. VO_2 was measured during the last 2 minutes of each stage using an automated indirect calorimeter system (ParvoMedics TruMax 2400 metabolic cart; Sandy, UT).

In a second session, the CS-PFP was administered by experienced physical therapists.[37] The CS-PFP, a performance-based measure of physical function, quantifies 16 common functional activities. Examples include making a bed, unloading groceries, climbing three steps onto a platform while carrying luggage (simulating getting onto a bus), and getting up and down from the floor. For each task, the individual chooses the amount of weight, speed, distance covered. As such, tasks are performed at the participant's perceived capacity. Tasks are performed consecutively, thus the CS-PFP measures the cumulative effect of functional performance. Tasks are scored using an alogorithm that takes into account weight carried, time to complete the task, and sometimes distance. This test is reliable and valid for people with and without PD.[46,47]

Functional reach, a test of balance in older adults,[38] was measured as described previously.[8] The functional reach test is predictive of falls[48] and can be used reliably with individuals who have PD.[49] Participants performed two practice trials and three test trials.

Secondary outcomes included the UPDRS and PDQ-39. When this study was initiated, the UPDRS was considered the gold standard for quantifying overall severity of PD.[50] The UPDRS total score and ADL and Motor subscores were utilized.[42] The 39-item quality of life scale, developed for people with PD, (PDQ-39) was completed by participants.[40] Changes in levodopa (used in data analysis) were monitored using the levodopa equivalent (LED; mg/day).[51]

Interventions

Interventions took place at one of three sites: The majority of participants exercised on the University of (blinded) campus. However, some participants (Fig. 1) exercised in a facility

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an hour south or 45 minutes northwest of Denver. The personnel who supervised the exercise sessions were all trained by the P.I. (MS), received written materials outlining the exercise protocols in detail,[19,52-55] and co-treated with the PI periodlically to assure consistentcy when implementating exercise protocols.

FBF and AE subjects participated in supervised exercise 3 days/week for 4 months. In month 5, supervision was tapered (described below). Thereafter, participants were asked to participate in a supervised exercise session 1x/mo. CON participants exercised under supervision during an initial individual session and then 1x/mo for 16 months. All participants were encouraged to perform their prescribed exercise program a total of 5-7 d/wk throughout the 16 months.

Supervised FBF consisted of 2 months of flexibility training one-on-one with a physical therapist[52,53] followed by 2 months of small group exercise (up to 6 participants) that included flexibility, balance, and functional exercises.[19] Supervised AE sessions included 5-10 min of warm-up, 30 minutes exercise at 65% to 80% HR_{max}, and 5-10 min of cool-down.[6] Participants were encouraged to use a treadmill, but were permitted to use a stationary bicycle or elliptical trainer. All except one of the participants performed at least some of their exercise on the treadmill. CON consisted of exercises in the home setting utilizing *Fitness Counts* with a single monthly group exercise session supervised by a physical therapist. Details of the exercises are in Table 1 (online only).

All participants, regardless of group assignment, were assisted to develop long-term exercise habits.[55] After randomization and before beginning to exercise, participants met with their trainer to discuss motivation to exercise, potential barriers, and strategies to develop exercise habits. Participants were asked to record supervised and home exercise throughout 16

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months. After 4 months, to transition participants to unsupervised exercise, supervision for FBF and AE was tapered (2 sessions/wk for 2 wk, then 1 session/wk for 2 wk). Everyone participated in a monthly exercise session, exercise diaries were reviewed monthly, and strategies were suggested to enhance adherence. Inquiry about adverse events was made at these sessions but could be reported by subjects at any time.

Analysis

Descriptive analysis included means, standard deviations, and proportions by group at baseline. Comparisons across the treatment groups for categorical variables were made using chi-square tests or their exact counterparts, depending on expected values. Continuous measures or scales were compared using Analysis of Variance (ANOVA). A linear mixed model with main effects for endpoint (baseline, 4 mo, 10 mo, 16 mo), the stratification variable used in randomization (sex), interaction terms between exercise group and endpoint, and levodopa equivalent dose as a time-varying covariate was used to estimate the intervention effect at each time point for each dependent variable. For walking economy, after determining that the VO_2 vs. treadmill speed relationship was linear across measured walking speeds of 0.8 to 3.5 mph, we modeled $V0_2$ as a function of treadmill speed using a linear mixed model with a random intercept and slope. The other factors in the mixed model for walking economy were the same as above, with the addition of an endpoint-by-speed interaction and a group-by-endpoint-by-speed interaction. For all of the mixed models it was assumed that the group means at baseline were equal due to randomization, a generally more powerful approach for longitudinal data analysis of a randomized clinical trial that is recommended for routine application by Fitzmaurice, Laird and Ware.[56] All analyses were done on an intent-to-treat basis.

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Model fit was assessed using -2 log likelihood and its associated chi-square test statistic. Intervention effects on the primary outcomes at 4 and 10 months were the principal focus of this report but differences at the end of the study period (16 mo) were also of interest. Effect sizes based on differences between group means and 95% confidence intervals (CI) are reported along with statistical significance (two-sided p-values). All statistical analysis was performed using SAS/BASE and SAS/STAT software, Version 9.2 of the SAS System for Windows.[57]

Assessment of non-ignorable missingness

Overall, 94 of 121 (78%) of participants had complete data on the primary outcome measures. The mixed-model analyses assume data are missing at random (MAR). Analysis of plots of group means over time stratified by the time of the last test completed[58] indicated the findings were not biased by missing data (results not shown).

RESULTS

Participants included 121 people in Stages 1-3 of Hoehn and Yahr; almost half were in Stage 2. The majority were men, married, retired, and had an annual income over $50,000. There were no statistically significant differences between the 3 groups for any demographic measures (Tab. 2). Retention was high at 4 months (86.8%) 10 months (82.6%) and 16 months (79.3%) (Fig. 1), at least 10% higher overall than planned for in our sample size calculations.

Table 3 includes the adjusted means from the mixed model for each group at each measurement time point. In Table 4 we present the differences between pairs of groups in mean change from baseline. For each group and each outcome, mean change was obtained through the mixed model regression estimates as the adjusted group mean at a given time point minus the adjusted mean at baseline. Differences between groups in change from baseline were obtained using contrasts (i.e., subtraction) of the mixed model regression coefficients. Results in Table 4

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are reported below as the differences, with 95% CI, in mean change from baseline between specific pairs of exercise groups at a given follow-up time.

As hypothesized at four months with respect to overall function, on the CS-PFP the FBF group improved more than the control group (mean difference 4.3; 95% CI: 1.2 to 7.3) and also improved more than the AE group (mean difference 3.1; 95% CI: 0.0 to 6.2). Contrary to our hypothesis, the AE group did not improve more than the control group (mean difference 1.2; 95% CI: -2.0 to 4.3) on the CS-PFP. However, at 10 and 16 months, there were no differences between any groups for CS-PFP. There were no differences in FR at any time point (Table 4), in contrast to our hypotheses. Also in contrast to the hypotheses, at four months, walking economy (i.e., reduced energy cost of walking) improved more in AE than FBF (mean difference -1.2 ml/kg/min; 95% CI: -1.9 to -0.5) (Figure 2) . At 10 months, the difference between AE and FBF persisted: AE had greater improvements in walking economy than FBF (mean difference -1.21 ml/kg/min; 95% CI: -1.92 to -0.49). And at 16 months, AE improved more on walking economy than Controls **(mean difference -1.3 ml/kg/min; 95% CI: -2.0 to -0.6) and FBF (mean difference -1.7 ml/kg/min; 95% CI:** -2.5 to -1.0).

With regard to secondary outcomes, there were no group differences in the change in PDQ-39 or UPDRS motor subscale at any time point. We had hypothesized that both FBF and AE would perform better than Controls on the UPDRS ADL subscale, but only FBF was better than Controls at 4 months (-1.47, -2.79 to -0.15) and at 16 months (-1.95; -3.84 to -0.08).

Overall group-by-time interactions (Table 5). Slope of change across the four time endpoints was estimated using the mixed model regression estimates for each outcome. AE and FBF demonstrated greater improvements for the UPDRS ADL subscale compared with Control

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(for each comparison: slope of -0.2, 95% CI: -0.4 to 0.0). FBF had more favorable effects on the CS-PFP than Control (slope of 0.4, 95% CI: 0.0 to 0.8).

Five study-related non-serious adverse events were reported: three non-injurious falls (one from each group), two reports of soreness/pain (both from the aerobic group). Additionally, 24 non-serious adverse events (not during exercise) were possibly related to the study (2 sprain/strain: 1 FBF, 1 AE; 22 soreness/pain: 9 FBF, 9 AE, 4 CON). One participant died unexpectedly after enrollment but before randomization.

DISCUSSION

This study examined both short (4-month) and long-term (10- and 16-month) benefits of exercise for people with early- or mid-stage PD. We embarked on this investigation to determine whether FBF, an exercise program targeted to people with PD, would confer greater benefits than would AE, a general conditioning or a control program, and importantly to determine whether the hypothesized differences would persist over the long-term after completion of 3x/week supervised exercise. Study procedures were designed to assist participants to maintain benefits of exercise once the supervised portion of the study was completed. Immediately following the supervised exercise period (4 months), FBF was superior to both AE and CON for improving overall function. However, AE was superior at 4, 10, and 16 months for improving economy of walking.

Overall Function: The hypothesis that FBF would generate better improvements in physical function than CON was based on findings from a previous 10-week study of flexibility exercises compared to wait-listed controls[8] in which exercise improved both flexibility and FR. Augmented with balance and functional training, we anticipated that the program would improve overall functional ability. And, indeed, it did. The mean change from baseline of over 6 points

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suggests FBF conferred substantial functional benefits, possibly because of the global nature of the functional training. This change is of particular clinical significance, given that participants in this study were nearing the threshold for disability as evidenced by their low mean CS-PFP scores.[59] However, the difference was not maintained at 10 and 16 months, possibly because participants were not able to adhere sufficiently to this program.

We hypothesized that AE participants also would perform better than controls on the CS-PFP because this continuous functional task requires endurance. However this was not the case, suggesting that endurance training alone is insufficient for improving overall daily function. This has important ramifications when designing exercise programs for people with early and mid-stage PD.

Balance: We anticipated that the FBF participants would perform better on FR, based on the prior investigation utilizing the axial mobility exercise program,[8] but they did not. Possibly lack of significant improvement in the present investigation reflected the relatively high functional reach distances at baseline. Of importance, even at 16 months the mean FR was not less than baseline for any of the three groups suggesting that all groups might have benefited to some extent with respect to balance.

Movement Efficiency: We postulated that people with PD might require more oxygen consumption (hence reduced walking economy) because of the energy expenditure to overcome the overall stiffness associated with PD. In fact, the FBF group did not improve, but the AE group improved significantly and substantially at all three time points.

The finding that AE improved walking economy was unexpected. Energy cost of walking, when normalized to body weight, is relatively unaffected by such factors as sex and level of fitness (i.e., obesity)[60] and was not expected to change in response to endurance exercise

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training. Baseline data from the current study demonstrated abnormally low walking economy (i.e., higher energy cost) in patients with PD when compared with healthy controls.[39] Thus to understand why walking economy improved in response to AE, it will be necessary to investigate the mechanisms for impaired walking economy associated with PD. Several possibilities include:[39,61,62] 1) increased resting energy expenditure, possibly associated with tremors, although this did not explain our observed differences between patients and controls; 2) impaired efficiency of mitochondrial energy production via oxidative phosphorylation; 3) energy cost of ventilation, which has been reported to be increased in patients with PD; and 4) impaired mechanical muscle contraction efficiency, which may be influenced by such factors as muscle fiber type and multi-segment movement coordination. Centrally mediated mechanisms of reduced muscle force production associated with PD[63] also might contribute to the increased energy demand.

The reduced economy of movement, at baseline, compared to individuals without PD[39] raises the possibility that reduced economy of movement contributes to the fatigue experienced by many individuals with PD.[64] We did not specifically measure fatigue, but this possibility should be considered in future investigations of aerobic conditioning.

Secondary Outcomes: FBF was significantly better on UDPRS ADL subscale at both 4 and 16 months. However, the UPDRS ADL change was small and of questionable clinical significance. No other group differences were found. Possibly all participants continued to be active and to benefit from their respective interventions. This interpretation is supported by data from a subset of our participants who participated in a qualitative study one year post-graduation from the 16-month parent study.[65] Individuals from all three of the exercise groups (FBF, AE,

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and CON) indicated that they continued to exercise after completion of the study, although typically at lower intensity than during the study.

All three treatment groups demonstrated remarkably little UPDRS motor change over 16 months. Yet, based on the natural history of PD, the expected rate of increase in the UPDRS motor subscore in levodopa treated patients (ON-state) would have been at least 2-3 points per year.[66] Lack of comparable decline in these data, as well as on other outcome measures, supports the impression that all participants benefited to some degree from their exercise. We also cannot rule out the possibility of a placebo effect, known to be powerful among people with PD.[67]

Retention of 79.3% at 16 months suggests that long-term intervention studies can be carried out successfully in this population. Furthermore the low rate of adverse events suggests that patients with PD can engage in relatively vigorous treadmill exercise. This contrasts with data from a small pilot study, indicating a high rate of falls with treadmill training.[68]

Several limitations should be acknowledged. It would have been unethical to have a 'no-exercise' control group for a 16-month study, given the growing evidence that exercise benefits people with PD. Cross-sectional data are available across stages of PD for the functional measures used in this study;[59] however longitudinal data are lacking for these measures. Such data will allow further interpretation of data in this investigation.

Our study was conducted in Colorado, one of the fittest states in the country. These individuals may be more likely to exercise than people in other areas of the country, even if they are assigned to the control group, possibly affecting applicability of our results to other populations.

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With regard to outcomes, when this study was initiated there was no expectation that exercise might ameliorate the UPDRS motor subscores. Hence, we did not collect data in the 'OFF-medication' state. However, we did control for levodopa equivalents, which should have adjusted for any bias due to medication effects. Other measures might provide better estimates of balance in people with PD than does FR; evidence in this regard likewise became available after this study was initiated.[69]

With regard to the interventions, the three groups received different degrees of individualized attention and group experience which could have confounded the findings. On the other hand, the interventions studied are clinically relevant, which was the motivation for implementing them as described.

Finally, we do not have meaningful data on participants' adherence. Although we used exercise diaries, accuracy was insufficient for meaningful interpretation. In future studies, we recommend regular use of activity monitors to objectively characterize overall activity (e.g., 1wk/mo).[70,71]

From a clinical perspective, findings suggest that both programs may be important for people with early and mid-stage PD. Findings support using the FBF program with individuals early in PD to improve overall function and AE to improve long-term aerobic endurance. A refresher FBF program could be implemented, should flexibility and function begin to decline. The necessary dose and timing of such a combined intervention is yet to be established. Based on the lack of meaningful decline of any measures over the 16-month study, it appears that '*Fitness Counts'* (Control) also confers some benefits, though to a lesser extent than the supervised programs. Possibly participating in a study with monthly sessions was sufficient for these individuals. Qualitative reports from graduates of the 16-month study[65] emphasize that people

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need ongoing support to maintain regular exercise. We strongly recommend that clinicians find ways to assist individuals with PD to develop and maintain long-term exercise habits, including appropriate exercise programns as well as continued re-evaluation and support.

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Dr Schenkman, Dr Schwartz, and Dr Kohrt provided concept/idea/research design. Dr Schenkman, Dr Baron, Dr Schwartz, and Dr Kohrt provided writing. Dr Hall, Dr Schwartz, Dr Mettler, and Dr Kohrt provided data collection. Dr Schenkman, Dr Baron, Dr Schwartz, Dr Mettler, and Dr Kohrt provided data analysis. Dr Schenkman and Dr Mettler provided project management. Dr Schenkman provided fund procurement. Dr Schwartz and Dr Kohrt provided facilities/equipment. Dr Mettler provided clerical support. Dr Hall provided consultation (including review of manuscript before submission). The authors gratefully acknowledge members of the research team who made this study possible and the participants with Parkinson disease, without whom there would have been no study.

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Table 1. Exercise Interventions

	Flexibility / Balance / Function (FBF)	**Aerobic Endurance (AE)**	**Control (CON)**
Supervision	Physical therapist	Exercise trainer	Research Assistant, under guidance of physical therapist
Duration of exercise sessions	45-50 minutes	45-50 minutes	45-50 minutes
Recommended frequency	5-7x/wk	5-7x/wk	5-7x/wk
Setting for supervised exercise	Clinic	Exercise facility with participants from various studies; no specific time or group	Clinic
Weeks 1-8			
Location and frequency of exercise	Clinic 3x/wk Additional sessions at home 2-4x/wk recommended	Clinic 3x/wk Additional sessions at home 2-4x/wk recommended	Home 5-7x/wk recommended Clinic 1x/month
Individual versus group for supervised exercise	Individual	Exercise facility with participants from various studies; no specific time or group	Group (up to 6 participants),
Type of exercise	• Spinal and extremity flexibility exercises based on relaxation to increase range • Exercises begin in supine, and progress to standing • Once learned, entire program is practiced each session	• Warm up for 5-10 min. • Aerobic exercise at 65-80% HRmax on treadmill, elliptical trainer, or bike, 30 min. • Cool down, 5-10 min.	• Flexibility and strengthening exercises in sitting and standing • Daily walking (no specific guidelines)
Weeks 9-16			
Location and frequency of exercise	Clinic 3x/wk Additional sessions at home 2-4x/wk recommended	Clinic 3x/wk Additional sessions at home 2-4x/wk recommended	Home 5-7x/wk recommended Clinic 1x/month

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Individual versus group for supervised exercise	Group (up to 6 participants)	Exercise facility with participants from various studies; no specific time or group	Group (up to 6 participants)
Type of exercise	• Warm up with abbreviated flexibility exercises as in weeks 1-8 • Ball exercises for core control and balance • Group exercises incorporating flexibility into balance and function (e.g., stooping, reaching, balance beam, throwing, uneven surfaces, movement to music	• Same as weeks 1-8	• Same as weeks 1-8
Weeks 17-21			
Location and frequency of exercise	Clinic 2x/wk for 2 weeks; 1x/wk for 2 weeks Additional sessions at home for a total 5-7x/wk (recommended)	Clinic 2x/wk for 2 weeks; 1x/wk for 2 weeks Additional sessions at home for a total 3-5x/wk (recommended)	5-7x/wk recommended Clinic 1x/month
Individual versus group for supervised exercise	Group (up to 6 participants),	Exercise facility with participants from various studies; no specific time or group	Group (up to 6 participants),
Type of exercise	Same as weeks 9-16	Same as weeks 1-8	Same as weeks 1-8
Weeks 22-68			
Location and frequency of exercise	Home 5-7x/wk Clinic, 1x/mo	Home or local health club 5-7x/wk Clinic, 1x/mo	Home 5-7x/wk Clinic, 1x/mo
Individual versus group for supervised exercise	Group (up to 6 participants)	Exercise facility with participants from various studies; no specific time or group	Group (up to 6 participants)
Type of exercise	• Same as weeks 17-21	• Same as weeks 1-16	• Same as weeks 1-16

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		Mean (SD)			p	
Modified Hoehn & Yahr Score		2.3 (0.4)	2.2 (0.5)	2.3 (0.4)	0.724	***
Age		66.3 (10.1)	63.4 (11.2)	64.5 (10.0)	0.467	***
Education		16 (3.2)	15.9 (3.4)	15.8 (2.9)	0.978	***
Years Diagnosed with PD at enrollment		4.5 (3.8)	3.9 (4.2)	4.9 (3.7)	0.537	***
Folstein Mini-Mental Score		28.8 (1.5)	28.3 (1.8)	28.8 (1.1)	0.215	***
UPDRS Activities of Daily Living Score		9.6 (4.8)	8.5 (4.8)	9.4 (4.9)	0.544	***
UPDRS Motor Score		25.9 (8.9)	24.4 (9.1)	24.3 (10.5)	0.717	***
UPDRS Total Score		37.5 (13.7)	34.6 (13.0)	35.5 (13.9)	0.621	***
CS-PFP	Total	44.6 (15.9)	49.6 (15.4)	48.9 (17.2)	0.320	***
Functional Reach (inches)	Forward	12.5 (3.1)	13.6 (3.1)	12.9 (3)	0.266	***
Resting VO_2	ml/kg/min	3.4 (0.6)	3.6 (0.6)	3.5 (0.9)	0.518	***
PDQ-39		21.5 (9.6)	18.5 (13)	23.2 (13.6)	0.176	***

* p-value from chi-square test
** Exact chi-square p-value
*** p-value from ANOVA

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Table 2. Baseline Characteristics

		Group				
		CON	AE	FBF		
	n =	41	41	39		
		n (%)			p	
Sex	Male	26 (63.4)	26 (63.4)	24 (61.5)	0.980	*
	Female	15 (36.6)	15 (36.6)	15 (38.5)		
Race	American Native	1 (2.4)	0	0	0.189	**
	Asian/Pacific Islander	0	2 (5.1)	0		
	African American	1 (2.4)	0	0		
	Caucasian	38 (92.7)	37 (94.9)	40 (97.6)		
	Hispanic	1 (2.4)	0	0		
	Other	0	0	1 (2.4)		
Assistive Device	Walker	1 (2.4)	2 (5)	0	0.899	**
	Straight Cane	3 (7.3)	3 (7.5)	4 (10.5)		
	Other	2 (4.9)	1 (2.5)	1 (2.6)		
	None	35 (85.4)	34 (85)	33 (86.8)		
Community Type	Rural	2 (4.9)	3 (7.5)	3 (7.9)	0.464	**
	Medium (2500-50000)	4 (9.8)	4 (10)	2 (5.3)		
	Large city (50000+)	13 (31.7)	21 (52.5)	16 (42.1)		
	Suburb	22 (53.7)	12 (30)	17 (44.7)		
Living Status	Alone	4 (9.8)	2 (5)	6 (15.8)	0.285	*
	With Spouse, Relative, or Friend	37 (90.2)	38 (95)	32 (84.2)		
Marital Status	Married	35 (85.4)	36 (90)	29 (76.3)	0.555	**
	Widowed	2 (4.9)	0	1 (2.6)		
	Divorced/Separated	3 (7.3)	3 (7.5)	5 (13.2)		
	Employed	1 (2.4)	1 (2.5)	3 (7.9)		
Work Status	Retired	24 (58.5)	22 (55)	23 (60.5)	0.134	**
	Keeping House	2 (4.9)	1 (2.5)	1 (2.6)		
	Not Employed	1 (2.4)	1 (2.5)	6 (15.8)		
	Employed	14 (34.1)	16 (40)	8 (21.1)		
Income	<$20,000/year	0 (0)	2 (5.9)	3 (8.6)	0.358	**
	$20,001-50,000/year	11 (31.4)	6 (17.6)	9 (25.7)		
	>50,000/year	24 (68.6)	26 (76.5)	23 (65.7)		
Modified Hoehn & Yahr Score						
	1	0 (0)	2 (4.9)	0 (0)	0.836	**
	1.5	2 (4.9)	1 (2.4)	1 (2.6)		
	2	20 (48.8)	21 (51.2)	21 (53.8)		
	2.5	15 (36.6)	13 (31.7)	13 (33.3)		
	3	4 (9.8)	4 (9.8)	4 (10.3)		

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PDQ-39		21.5 (9.6)	18.5 (13)	23.2 (13.6)	0.176	***

* p-value from chi-square test
** Exact chi-square p-value
*** p-value from ANOVA

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Table 3. Linear Mixed Model-Based Means

Mean (SE)		Baseline All Groups (n=121)	4 months CON (n=35)	4 months AE (n=34)	4 months FBF (n=36)	10 months CON (n=33)	10 months AE (n=32)	10 months FBF (n=34)	16 months CON (n=31)	16 months AE (n=31)	16 months FBF (n=33)
CS-PFP (higher is better)	Total	48.8 (1.9)	50.7 (2.1)	51.9 (2.2)	55 (2.1)	51.1 (2.4)	51.3 (2.4)	50.3 (2.3)	49.6 (2.4)	50.5 (2.4)	52.9 (2.4)
Functional Reach (inches) (higher is better)	Forward	13.3 (0.4)	13.7 (0.5)	14 (0.5)	13.4 (0.5)	13.6 (0.5)	13.4 (0.5)	13.2 (0.5)	13.4 (0.5)	13.8 (0.5)	13.6 (0.5)
UPDRS Score (lower is better)	ADL	8.1 (0.6)	9.1 (0.7)	7.8 (0.7)	7.6 (0.7)	9.2 (0.8)	7.5 (0.8)	8.4 (0.8)	9.5 (0.8)	7.8 (0.8)	7.6 (0.8)
	Motor	23.7 (1.2)	23.8 (1.5)	21.8 (1.5)	23.6 (1.5)	24.4 (1.5)	22.9 (1.6)	23.7 (1.5)	24.2 (1.8)	21.9 (1.8)	23.7 (1.7)
	Total	33.3 (1.6)	34.4 (1.9)	30.8 (2)	32.5 (1.9)	35.7 (2.2)	32.1 (2.2)	33.9 (2.2)	35.6 (2.4)	31.4 (2.4)	32.6 (2.4)
VO_2 (ml/kg/min)	Intercept	5.2 (0.3)	5.6 (0.4)	4.5 (0.5)	5.6 (0.4)	4.9 (0.4)	4.4 (0.5)	5.7 (0.4)	5.0 (0.4)	3.6 (0.5)	5.3 (0.5)
(lower is better)	Adjusted Slope	3.0 (0.1)	2.7 (0.2)	2.9 (0.2)	2.9 (0.2)	3.1 (0.2)	3.0 (0.2)	2.9 (0.2)	3.1 (0.2)	3.2 (0.2)	3.2 (0.2)
PDQ-39 (lower is better)	Total	17.2 (1.5)	16.3 (1.8)	14.5 (1.8)	18.4 (1.8)	18.4 (2.0)	16.4 (2.0)	15.3 (1.9)	21.0 (2.2)	17.1 (2.3)	17.2 (2.1)

The model Likelihood Ratio Test chi-square <0.001 for all models

Models include the following design variables and covariate adjustments:

Gender (categorical, 2 levels)

Time (categorical, 4 levels)

Group by Time Interactions (6 dummy variables)

Levodopa equivalents (continuous)

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Table 4. Estimated Mean Differences Between Groups (Treatment Effect)

		AE v. Control			FBF v. Control			AE v. FBF			AE & FBF v. Control		
		Estimated Difference Mean (SE)	95% CI	p	Estimated Difference Mean (SE)	95% CI	p	Estimated Difference Mean (SE)	95% CI	p	Estimated Difference Mean (SE)	95% CI	p
Change in Means at 4 months													
CS-PFP	Total	1.2 (1.6)	-2.0 to 4.3	0.465	4.3 (1.5)	1.2 to 7.3	0.006	-3.1 (1.6)	-6.2 to 0.0	0.048	2.7 (1.3)	0.1 to 5.4	0.046
Functional Reach	Forward	0.3 (0.5)	-0.6 to 1.2	0.519	-0.3 (0.4)	-1.2 to 0.6	0.456	0.6 (0.5)	-0.3 to 1.5	0.168	0.0 (0.4)	-0.8 to 0.8	0.960
UPDRS Score	ADL	-1.3 (0.7)	-2.6 to 0.1	0.060	-1.5 (0.7)	-2.8 to -0.2	0.029	0.2 (0.7)	-1.2 to 1.5	0.794	-1.4 (0.6)	-2.5 to -0.2	0.019
	Motor	-2.0 (1.5)	-5.0 to 1.0	0.191	-0.2 (1.5)	-3.2 to 2.7	0.877	-1.8 (1.5)	-4.8 to 1.2	0.244	-1.1 (1.3)	-3.7 to 1.5	0.393
	Total	-3.6 (1.8)	-7.1 to -0.1	0.042	-1.9 (1.7)	-5.3 to 1.5	0.279	-1.7 (1.7)	-5.2 to 1.7	0.321	-2.7 (1.5)	-5.7 to 0.2	0.071
VO_2 (ml/kg/min)	Intercept + Slope	-1.0 (0.3)	-1.7 to -0.4	0.002	0.2 (0.3)	-0.4 to 0.8	0.544	-1.2 (0.4)	-1.9 to -0.5	0.001	-0.4 (0.3)	-0.9 to 0.1	0.122
PDQ-39	Total	-1.8 (1.7)	-5.2 to 1.6	0.299	-1.1 (1.7)	-4.5 to 2.3	0.506	-0.6 (1.7)	-4.0 to 2.8	0.707	-1.5 (1.5)	-4.4 to 1.5	0.325
Change in Means at 10 months													
CS-PFP	Total	0.3 (2.0)	-3.8 to 4.3	0.892	-0.7 (2.0)	-4.7 to 3.3	0.722	1.0 (2.0)	-3.0 to 5.0	0.624	-0.2 (1.8)	-3.7 to 3.3	0.901
Functional Reach	Forward	-0.2 (0.6)	-1.3 to 0.9	0.714	-0.4 (0.6)	-1.5 to 0.7	0.453	0.2 (0.6)	-0.9 to 1.3	0.706	-0.3 (0.4)	-1.2 to 0.6	0.456
UPDRS Score	ADL	-1.7 (0.9)	-3.5 to 0.2	0.083	-0.8 (0.9)	-2.7 to 1.0	0.373	-0.8 (0.9)	-2.7 to 1.0	0.382	-1.2 (0.8)	-2.9 to 0.4	0.129
	Motor	-1.6 (1.7)	-4.9 to 1.8	0.353	-0.8 (1.6)	-4.0 to 2.5	0.648	-0.8 (1.7)	-4.1 to 2.5	0.625	-1.2 (1.4)	-4.0 to 1.7	0.422
	Total	-3.7 (2.3)	-8.2 to 0.9	0.111	-1.9 (2.2)	-6.3 to 2.6	0.407	-1.8 (2.3)	-6.3 to 2.7	0.426	-2.8 (2.0)	-6.7 to 1.1	0.160
VO_2 (ml/kg/min)	Intercept + Slope	-0.6 (0.3)	-1.3 to 0.1	0.079	0.6 (0.3)	0.0 to 1.2	0.069	-1.2 (0.4)	-1.9 to -0.5	0.001	0.0 (0.3)	-0.6 to 0.5	0.972
PDQ-39	Total	-2.0 (2.1)	-6.1 to 2.1	0.340	-3.1 (2.0)	-7.2 to 0.9	0.128	1.2 (2.1)	-3.0 to 5.3	0.577	-2.6 (1.8)	-6.1 to 1.0	0.153
Change in Means at 16 months													
CS-PFP	Total	0.9 (2.0)	-3.1 to 4.8	0.660	3.3 (1.9)	-0.5 to 7.2	0.091	-2.4 (2.0)	-6.3 to 1.4	0.216	2.1 (1.7)	-1.3 to 5.5	0.221
Functional Reach	Forward	0.4 (0.5)	-0.6 to 1.4	0.442	0.3 (0.5)	-0.7 to 1.2	0.616	0.1 (0.5)	-0.9 to 1.1	0.777	0.3 (0.4)	-0.5 to 1.2	0.463
UPDRS Score	ADL	-1.7 (1.0)	-3.6 to 0.2	0.078	-1.9 (0.9)	-3.8 to -0.1	0.041	0.2 (0.9)	-1.6 to 2.1	0.805	-1.8 (0.8)	-3.5 to -0.2	0.029
	Motor	-2.3 (1.8)	-5.9 to 1.4	0.217	-0.5 (1.8)	-4.1 to 3.1	0.774	-1.8 (1.8)	-5.4 to 1.8	0.331	-1.4 (1.6)	-4.5 to 1.7	0.376
	Total	-4.2 (2.5)	-9.1 to 0.7	0.094	-3.0 (2.4)	-7.8 to 1.8	0.220	-1.2 (2.4)	-6.1 to 3.6	0.622	-3.6 (2.1)	-7.8 to 0.6	0.094

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VO_2 (ml/kg/min)	Intercept + Slope	-1.3 (0.3)	-2.0 to -0.6	0.0001	0.4 (0.3)	-0.3 to 1.1	0.230	-1.7 (0.4)	-2.5 to -1	<.0001	-0.5 (0.3)	-1.0 to 0.1	0.108
PDQ-39	Total	-3.9 (2.5)	-8.8 to 1.0	0.114	-3.8 (2.3)	-8.5 to 0.8	0.102	-0.1 (2.4)	-4.9 to 4.7	0.975	-3.9 (2.1)	-8.0 to 0.2	0.064

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Table 5. Estimated Slope Differences Between Groups

		AE v. Control			FBF v. Control			AE v. FBF			AE & FBF v. Control		
		Estimated Difference Mean (SE)	95% CI	p	Estimated Difference Mean (SE)	95% CI	p	Estimated Difference Mean (SE)	95% CI	p	Estimated Difference Mean (SE)	95% CI	p
CS-PFP	Total	0.1 (0.2)	-0.3 to 0.5	0.546	0.4 (0.2)	0.0 to 0.8	0.047	-0.3 (0.2)	-0.7 to 0.1	0.173	0.3 (0.2)	-0.1 to 0.6	0.136
Functional Reach	Forward	0.0 (0.1)	-0.1 to 0.1	0.638	0.0 (0.1)	-0.1 to 0.1	0.502	0.1 (0.1)	0.0 to 0.2	0.257	0.0 (0.0)	-0.1 to 0.1	0.911
UPDRS Score	ADL	-0.2 (0.1)	-0.4 to 0.0	0.020	-0.2 (0.1)	-0.4 to 0.0	0.023	0.0 (0.1)	-0.2 to 0.2	0.925	-0.2 (0.1)	-0.3 to -0.1	0.008
	Motor	-0.3 (0.2)	-0.6 to 0.1	0.137	-0.1 (0.2)	-0.4 to 0.3	0.753	-0.2 (0.2)	-0.6 to 0.1	0.234	-0.2 (0.2)	-0.5 to 0.1	0.293
	Total	-0.5 (0.2)	-0.9 to -0.1	0.021	-0.3 (0.2)	-0.7 to 0.1	0.192	-0.2 (0.2)	-0.7 to 0.2	0.290	-0.4 (0.2)	-0.8 to 0.0	0.036
PDQ-39	Total	-0.3 (0.2)	-0.7 to 0.1	0.172	-0.3 (0.2)	-0.7 to 0.1	0.193	0.0 (0.2)	-0.4 to 0.4	0.939	-0.3 (0.2)	-0.7 to 0.1	0.124

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Figure 1. Consort diagram

Figure 2. Walking economy at speeds from .8 miles/hr to 4 miles/hr. VO_2 in mL/min/kg is presented for each group at four time points (baseline, 4, 10, and 16 months) illustrating the improvement (less oxygen required) for AE, but not for the other two groups. Walking speeds (increased by .5 mph for four speeds) are determined for each participant by the maximum walking speed achieved during the GXT.

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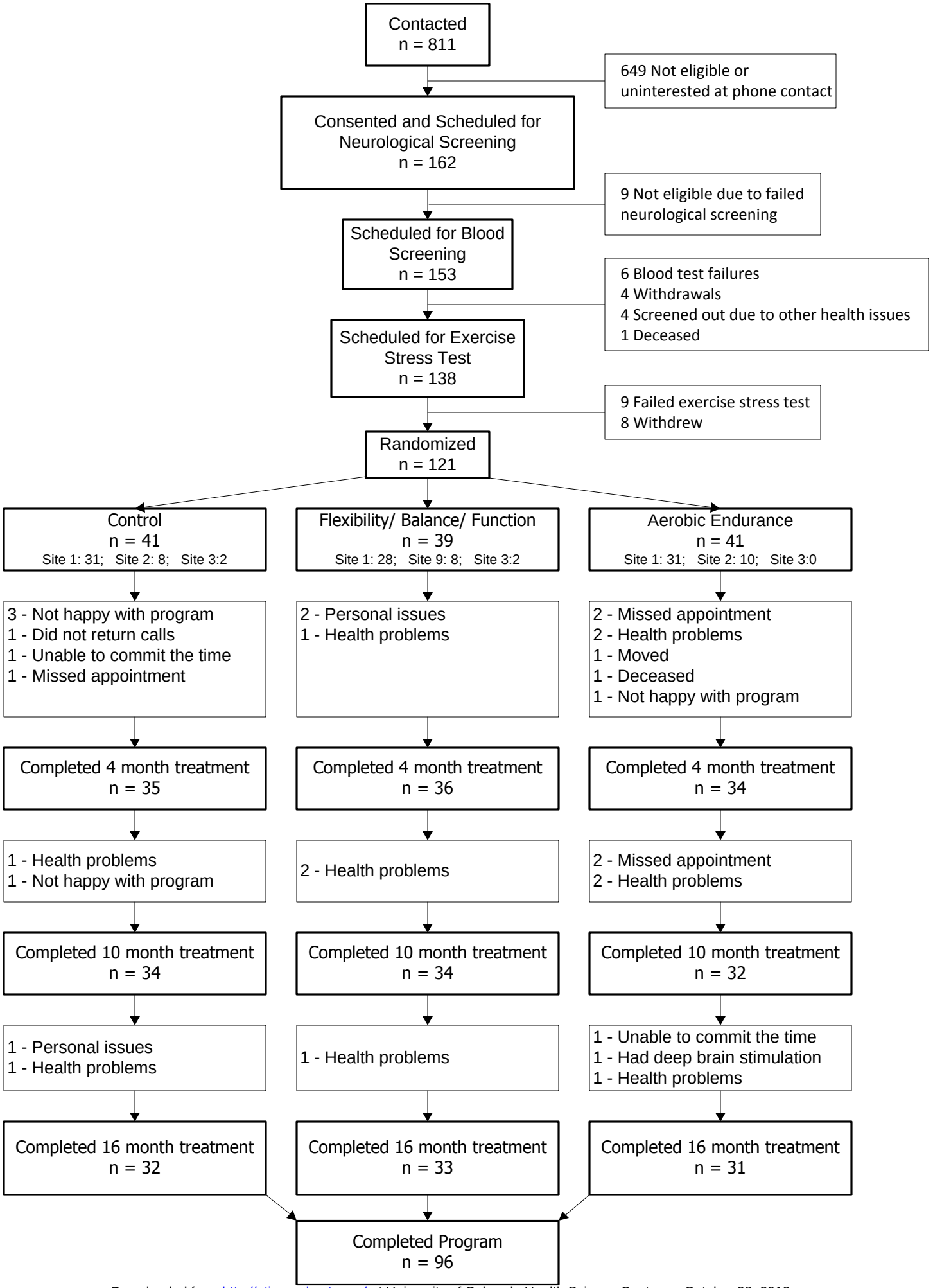

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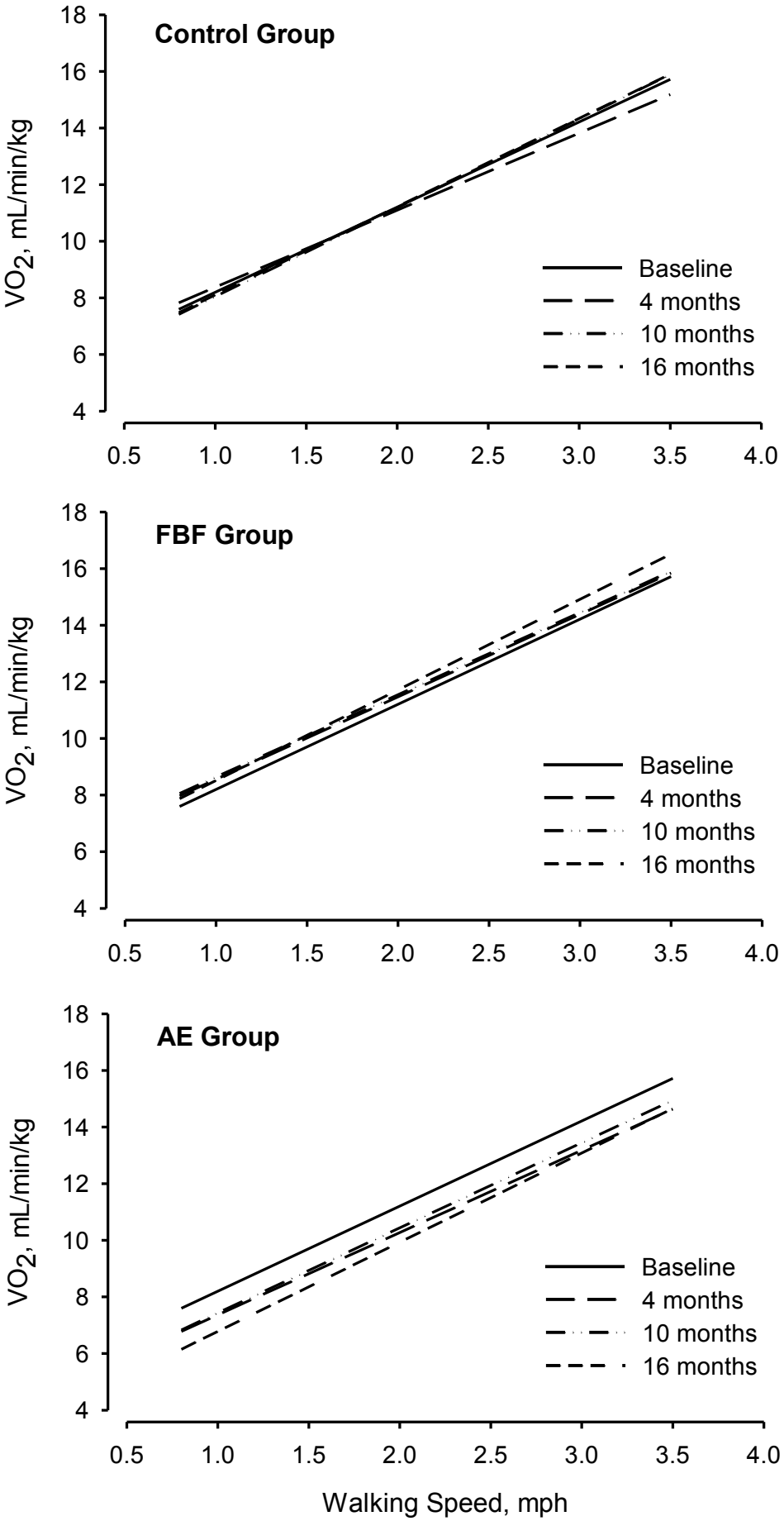

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Exercise for People in Early- or Mid-Stage Parkinson Disease: A 16-Month Randomized Controlled Trial

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