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Two-Year Agility Maintenance Training Slows the Progression of Parkinsonian Symptoms

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The authors declare no conflict of interest. The authors state that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

The present study does not constitute endorsement by ACSM.

Abstract

Introduction — Parkinson's disease (PD) is a progressive neurodegenerative condition and it is unclear if long-term non-pharmaceutical interventions can slow the progression of motor and non-motor symptoms and lower drug dose.

Methods — In a randomized trial, after an initial 3-week-long, 15-session supervised high-intensity sensorimotor agility exercise (E) program designed to improve postural instability, the Exercise+Maintenance (E+M, n=19) group continued to exercise three times per week for 2 years, while E (n=16) and the no exercise and no maintenance control (C, n=20) continued habitual living. Eight outcomes were measured before and after the 3-week initial exercise program and then at 3, 6, 9, 12, 18, and 24 months in all patients.

Results — The Group by Time interactions (all $p<0.005$) revealed robust and favorable effects of the initial 3-week agility program on all 6 non-motor (e.g., primary outcome MDS-UPDRS-M-EDL: ~7 points; EuroQoL: ~9 points) and on each of the 2 motor outcomes (timed up and go test: ~6 s; posturography: up to 7 mm improvements in center of pressure path). E+M maintained but did not further improve the benefits produced by the initial 3-week program. In E, the favorable effects of the 3-week agility program lasted for 3 to 12 months. In C, patients declined steadily in all outcomes over 2 years. By year 2, Leva-dopa equivalents increased by 99.4 mg/day (Time main effect, $p = 0.008$).

Conclusion: A high-intensity sensorimotor agility program with but not without a 2-year maintenance program slowed the progression of parkinsonian symptoms.

Key words: follow up, sensorimotor training, balance training, posture, quality of life

Introduction

Parkinson's disease (PD) is associated with a decline in postural control, walking ability, an increased risk for falling, and a deteriorating quality of life (1-3). While pharmacological treatments are still the mainstream to treat motor symptoms, physical exercise can also improve PD patients' postural control and mobility (2-6). Recommendations urge the use of high intensity exercise stimulus to produce rapid and lasting improvements in PD symptoms (4,7,8). However, the results are inconsistent. Even at the same disease stage, treadmill exercise improved gait speed and cardiovascular fitness independent of exercise intensity (9). In addition, high compared with low frequency exercise can unfavorably affect functional outcomes (10). Yet there is also evidence that exposing PD patients to high-intensity exercising training can functionally meaningfully improve early-stage PD patients' symptoms (8). How long such exercise effects last after the exercise stimulus is withdrawn is also unclear. Despite recommendations to measure the effects at least for 24 months, in 16 studies the average follow-up time was 5.5 months (2,5). The only study with a 24-month-long maintenance program reported favorable effects on selected motor symptoms but also numerically almost identical elbow flexion torque at baseline (50.8 Nm) and at 24 months (50.2 Nm) (11). Yet a second booster dose of multidisciplinary intensive rehabilitation exercise at Year 1 after an initial bout at baseline even without a maintenance program, improved, at Year 2, UPDRS III scores, 6-minute walking distance, and timed up and go performance by 3.4 points, 41.1 m, and 1.1 s, respectively (12).

Whether exercise can reduce patients' drug dose is unclear. In one case, L-dopa equivalent increased moderately by 38.4% in the intensive exercise group compared with 327.4% in the no-

exercise controls at the end of the 2-year follow-up period, suggesting that intense exercise without a maintenance program could moderate drug dose (12). Despite the 2-year low-intensity exercise maintenance program, L-dopa equivalent, however, still increased by 29% (11). It is thus unclear if a high-intensity and long-term exercise maintenance program could reduce the increase normally seen in PD patients' medication.

The purpose of the present study was to determine the immediate and long-term effects of a 3-week-long, high-intensity and high-frequency agility program on PD patients' motor and clinical symptoms with and without a 2-year-long high-intensity agility maintenance program. We expected that patients would tolerate the short-term 3-week initial high-intensity agility program and motor and non-motor symptoms would improve and that the maintenance program would sustain these improvements and slow the progression of symptoms. Based on previous studies (11,12), we also expected that the maintenance program would slow the increase in L-dopa equivalent levels.

Methods

Design and patients. This is a three-group, randomized clinical trial involving PD patients who met the UK Brain Bank criteria and were of stages 2-3 on the Hoehn and Yahr scale. Fig. 1 shows the Consort diagram. Form the hospital database and the outpatient clinic we identified 72 patients who met inclusion criteria based on medical records. Of these, 17 were excluded and the remaining 55 randomized into: Exercise+Maintenance (E+M, n=19, 11M); Exercise only group (E, n = 16, 6M), and to a no exercise and no maintenance control group (C, n=20, 12 M; Table 1). At the time of the start of the study and for a two-year period preceding it, none of the

patients were enrolled in rehabilitation. The initial high-intensity and high-frequency agility E program lasted three weeks. The M program lasted two years. All patients were assessed eight times: before and after the 3-week exercise program and at 3, 6, 9, 12, 18, and 24 months. Wait-listed patients in C had the opportunity to enroll in the exercise program after the end of the trial. After the 3-week initial exercise intervention, patients in E and C were not enrolled in an exercise or maintenance program during the two-year period.

Patients were recruited from the hospital database. An initial screening established disease severity by the language-validated version of Movement Disorder Society Unified Parkinson Disease Rating Scale, Motor Experiences of Daily Living (MDS-UPDRS-M-EDL). A preliminary screening included a full neurological exam and a mobility evaluation. The exam ensured that all included patients had mobility difficulty and postural instability based on a qualitative assessment of gait and postural stability, turns, rigidity, inter-joint coordination, trunk posture, and equilibrium while subjects walked forward, backwards, and sideways. In a separate visit, a neuropsychologist evaluated patients' cognitive function. Patients were excluded with brain abnormalities based on a diagnostic MRI, Mini Mental State Examination score <24, a Beck Depression Inventory score >40, severe cardiac disease, uncontrolled diabetes, a history of stroke, traumatic brain injury, seizure disorder, past or current deep brain stimulation, or current participation in a self-directed or formal group exercise program. All patients remained 'on' medication so that the assessments at baseline and after the intervention and each exercise session occurred 1-2h after patients took PD medications.

The principal investigator performed the randomization. He drew a colored ribbon from a covered box and attached one ribbon to each patient's folder (E: red, E+M: blue, C: green). Two physical therapists and a physical therapy assistant administering the tests, were masked to patients' group assignments. In the familiarization session patients practiced each test and watched the Xbox kinect programs, a key element of the intervention. Patients gave written informed consent to participate in the study. The University Hospital's Ethics Committee (IKEB) approved the study protocol. The trial was registered at Clinicaltrials.gov (NCT03193489).

Outcome measures. The primary outcome was MDS-UPDRS-13 M-EDL, which is sensitive to changes in a broad spectrum of PD symptoms (13). We accepted changes >3.1 points as a minimal clinically important difference (14). The lead physical therapist administered this test in person every time to every patient to assess motor signs of PD.

Secondary outcomes measured changes in HRQoL using: 1) Schwab and England Activities of Daily Living Scale (ADL); 2) EuroQol EQ-5D, and 3) the Parkinson's Disease Questionnaire (PDQ-39, minimal clinically important difference: 4.7 points) (15). The Beck Depression Inventory measured depression and the timed up and go test (TUG) quantified mobility. We quantified postural stability by the magnitude of sway measured on a force platform while standing in a wide and a narrow stance with eyes open or closed. Participants stood for 20 s in each of the four conditions administered in order of: 1) eyes open wide and 2) narrow stance followed by standing with eyes closed 3) in a wide and 4) in a narrow stance. The outcome was the 3D path of the center of pressure (in mm). The testing order was standardized among patients and testing sessions. Adverse events were not systematically assessed.

Intervention. The Exercise program comprised a high-intensity agility intervention, detailed previously in the supplementary material of that paper comprising a different group of patient (16). Briefly, E+M and E completed 15, 1-h-long, sessions over 3 weeks and targeted deficits in postural control and mobility. Three therapists delivered the program by having patients exercise in small groups at individual times only in the hospital's physical therapy gym. Therapists demonstrated most exercises, mingled among patients on the exercise floor to closely supervise and spot them for safety. Patients were asked not to enroll in any other activity programs and perform additional exercises at home on their own. Patients exercised without shoes on a 26-mm thick Theraband-carpeted floor. After 10 minutes of warm-up, patients completed a 20-minute block of sensorimotor and visuomotor agility training and a 20-minute block of sensorimotor agility training using the X-box virtual reality exergame (Microsoft xbox 360 core system with kinect, Microsoft Corp.) (17). Each session ended with 10 minutes of cool down. The sensorimotor and visuomotor agility training included: 1) gait training, 2) coordination training, 3) posture training with and without an augmented sensory input, 4) balance exercises with and without a peer, assistive devices, height stimuli, surface modifications, postural changes, shifts between tasks, and directional changes, 5) body scheme exercises, and 6) posture-corrective exercises. We detailed previously exercise dosing, surface manipulations, task numbers, task types, feedback, and other methods to increase and manipulate motor and sensory stimuli, including the sophisticated use of the X-box virtual reality exergame and how patients kept an exercise log to record symptoms, fatigue, and attendance. A video clip in Supplement 1 shows patients exercising (see Video, Supplemental Digital Content 1, PD patients performing exergaming agility exercises, http://links.lww.com/MSS/B403). The non-Exergaming and Exergaming each represented about 50% of the total exercise time. The average heart rate and

rate of perceived exertion was 120.6 beats per minute and 13.6 or about 80% age-predicted maximum heart rate and 'somewhat hard / hard' on the 20-point Borg scale (unpublished data).

Maintenance program. After the 3-week-long, daily, high-intensity Exercise intervention, E+M continued the Maintenance program three times per week for two years in the hospital's physical therapy gym using the same exercises used in the 3-week-long initial exercise program. The three therapists supervised each session attended by small groups of 3-5 patients who exercised at the same time of the day for 1 h. The aim of the maintenance program was to determine if patients can endure a high-intensity rehabilitation program for an extended time period and if such a program can slow disease progression. E did not perform the maintenance phase and C received no Exercise therapy and no Maintenance either.

Statistical analyses. We estimated the number of participants needed for a significant Group (E+M, E, C) by Time (0 and 3wk, 3, 6, 9, 12, 18, 24 months) analysis of variance with repeated measures on Time for a change of 4 points caused by the initial intense intervention (>3.1 functionally meaningful change) (14). Using an alpha of 0.05, 1- beta (power) of 0.8, 3 groups, a correlation of 0.5 between repeated measures, the total sample size needed was 49 patients. Anticipating dropouts, we randomized 55 patients.

Data are expressed as mean ±SD. The variables were normally distributed based on the Shapiro–Wilk test. The main analysis was a Group (E+M, E, C) by Time (0 and 3wk, 3, 6, 9, 12, 18, 24 months) analysis of variance with repeated measures on Time. In case of an interaction, we used a Tukey's post-hoc contrast to determine the means that differed at $p<0.05$. We also compared at

baseline those nine patients who deceased over the two years with those who completed the trial. We computed Pearson correlations between changes in the primary and secondary outcomes to explore potential mechanistic links underlying improvements in patients' mobility and clinical symptoms. The level of significance was set at $p<0.05$. All statistical analyses were conduced with SPSS version 22.

Results

Table 1 shows that the groups were similar at baseline. During the 3-week high-frequency exercise program and also during the 2-year-long maintenance program, attendance and compliance were 100%, dropout was 0%, and there were no adverse events, which were not assessed systematically.

Primary outcome. The 3-week-long agility program improved MDS-UPDRS M-EDL significantly ($p < 0.05$) but similarly by 30.4% (±10.23) or 6.3 points (±3.06) in E+M and by 42.8 % (±9.43) or 7.8 (±1.57) points in E. These changes were greater than the non-significant changes in C (Group by Time interaction, $F12,258=32.7$, $p=0.001$, Table 2, Figure 2A).

E+M sustained the exercise-induced benefits. In E, the exercise-induced improvements were still present at 3 months. C exhibited a gradual worsening over the two years. At year 2, there was a 12.4 points difference in favor of E+M vs. C ($p<0.05$). Over two years, the MDS-UPDRS M-EDL score had decreased by 6 points in C.

Secondary outcomes. The Group by Time interaction for L-Dopa equivalents was not significant ($p=0.662$) and the dose increased by 97.4 mg/day or 11.4% in the three groups combined (Time main effect), $F_{4,168}=3.6$, $p=0.008$ (Figure 3.)

The agility program improved the PDQ by 26.0% (±7.36) in E+M and by 28.9% (±9.31) in E, more than the –6.8% (±16.85) worsening in C (interaction, $F_{12,258}=9.9$, $p=0.001$, Table 2, Figure 2B). E+M kept the exercise-induced improvements in PDQ for two years at a steady level. In E, the exercise effects were still present at 12 month (Figure 2B). At 24 months, E+M vs. E and E+M vs. C had 15.3 and 24.4 points better PDQ score (both $p<0.05$). E still had a 9.1 better score than C ($p<0.05$). Over the two years, the PDQ score had decreased by 20 points in C (Table 2).

The exercise intervention improved the Beck Depression Index ($F_{12,258}=12.5$), the Schwab and England ADL inventory ($F_{12,258}=8.9$), the EQol VAS scores ($F_{12,258}=10.3$), and the EQoL summed scores ($F_{12,258}=21.5$) in E+M (range of improvements: 13% to 21%, all $p \leq 0.001$) and in E (14% to 20%, all $p<0.05$, Table 2). In E, these effects lasted for three months. At 24 months, E+M still showed the exercise-induced gains and E returned to baseline. Compared with E+M at 24 months, the scores in C were all worse in the Beck Depression Index, Schwab and England ADL inventory, the EQol VAS scores and in the EQoL summed scores(all $p<0.05$).

TUG improved by 6.3 s (±2.75) in E+M and by 6.0 s (±2.96) E (all $p<0.05$) compared with the 0.6 s (±0.76) in C (n.s.) (interaction, $F_{12,258}=20.2$, $p<0.001$, Table 2, Figure 2C). These effects lasted for 18 months in E (Figure 2C). At 24 months, E+M had 6.8 s shorter TUG time than C

(p<0.05). TUG remained unchanged over two years in C (n.s.). Exercise decreased COP path in the four conditions similarly in E+M and E (range: 2.0 to 6.9 mm) and E+M sustained the exercise-induced improvements. In E, the exercise effects lasted until month 12 in the four posturography measures. At 24 months, E+M vs. E had 4.7 to 2.5 mm shorter COP path in the four measures (p<0.05) and these differences between E+M vs. C had even larger (range: 4.2 to 6.7 mm, p<0.05).

Correlation analyses. MDS-UPDRS M-EDL at baseline correlated with the change in MDS-UPDRS M-EDL at 3 weeks r=-0.803 and this correlation essentially remained unchanged by 24 months (r =-0.683, n=18, p< 0.05). Because the primary outcome reached a plateau at month 3 during follow up in E+M (n=18, Figure 2A), we determined the relationship between changes in the primary outcome, MDS-UPDRS M-EDL, for the period from baseline to 3 month and the changes over the same period in PDQ (r=0.422), Beck depression score (r=0.198), EQ VAS (r=-0.181), TUG (r=0.126), and the four postural measures (range of r = 0.092 to 0.297). None of these correlations were significant (p>0.05). The correlation between changes in MDS-UPDRS M-EDL and number of PD years was also low (r=0.271).

Characteristics of deceased patients. One, three, and five patients, respectively, died in E+M, E, and C, with 46 of 55 original patients completing the 2-year study. Causes of death were heart attack (n=2), unknown (n=3), tumor (n=2), and stroke (n=2), all unrelated to study. Table 3 shows the baseline comparisons between patients who died and those who were alive at the end of the 2-year program. At baseline, there were differences between these two groups in MDS-UPDRS M-EDL and TUG.

Discussion

High-intensity and high-frequency supervised sensorimotor agility exercise (3wks, 15 sessions) improved PD patients' motor and non-motor symptoms. The subsequent 2-year-long supervised maintenance program sustained but did not further improve the benefits produced by the initial 3-week program in the eight outcomes. The favorable effects of the 3-week agility program without the maintenance program on motor and non-motor symptoms lasted for 3 to 12 months. Patients in the no-intervention control group declined steadily in all outcomes over two years. Exercise therapy with and without the maintenance program did not reduce drug dose.

Acute exercise effects

The data contribute to the emerging picture that a variety of motor interventions can improve PD patients' motor and clinical symptoms (2-5). The ~7.0 points (n=35, effect size 1.2), over twice the 3.1 points of clinically meaningful improvements(14) in MDS-UPDRS M-EDL are similar to the changes of 7.3 in UPDRS III following a 4-week-long multidisciplinary intensive rehabilitation treatment (12). The improvements correlated strongly with the baseline scores, suggesting that the intervention was particularly effective and, as hypothesized, not harmful in patients with low initial scores. Thus, high-intensity and challenging exercise therapy is effective for PD patients with a Hoehn–Yahr stage 1.2 (12) but also for patients at stage of 2-3 (present study, Table 1) to improve perceived and measured mobility, posture, and clinical symptoms. Future studies will determine whether or not high intensity and frequency are prerequisites to induce such acute effects on MDS-UPDRS M-EDL, as lower intensity yoga, dance, and balance training are also effective(2-5) and superior to very low intensity physical and occupational therapy (18).

The 3-week-long intervention uniformly improved secondary outcomes of perceived and objectively measured functions by 13 to 55% (effect sizes: 0.53-2.54, Table 2). Because depression affects quality of life most, it was important to see that exercise improved QoL and the Beck Depression Index (3.3 points). Thus, agility training in addition to aerobic exercise can also improve PD patients' depression (19,20). Changes in the Schwab and England (10 points), TUG (6.1 s), PDQ (13.3 points) and posturography scores suggest improved static and dynamic balance and non-motor symptoms, confirming and for the most part exceeding changes reported previously (2-5) The high response rate in all outcomes is probably related to the suitability of the exercise stimulus, as patients attended all sessions and none dropped out.

Maintenance program

A 2-year-long agility maintenance program slowed the progression of PD symptoms (Figure 2, Table 2). The maintenance program clinically meaningfully (14) further improved the primary outcome by 3.5 points at Month 3 but thereafter this improved level remained unchanged. The favorable initial rapid adaptations to the 3-week program disappeared in E so that at Month 6 there were no differences (2 points, n.s.) in MDS-UPDRS M-EDL scores between E and C (Figure 3, Table 2). The maintenance program did not further increase the gains produced by the initial intense exercise phase in the secondary outcomes but the maintenance program was necessary to sustain the initial gains in all outcomes. The data provide evidence that even short-term exercise programs can moderate PD patients' motor and non-motor symptoms. However, such changes are transient and for lasting neuroprotective and restorative effects to occur, PD patients need to participate in long-term maintenance programs (1-5,21).

Agility and resistance training can both improve motor and non-motor symptoms and maintain such improvements (11,12,22). The difference between our agility and other agility and resistance training programs could be in effectiveness. In our patients the MDS-UPDRS M-EDL scores were 12.4 points lower (better) than control (Figure 2, Table 2) in contrast to the 2.2-point difference reported at Month 24 in favor of the multidisciplinary intensive rehabilitation treatment versus control (12). In this study patients' disease severity was lower (mean Hoehn–Yahr stage of 1.2) (12) than in the present study (range Hoehn–Yahr stage of 2-3). The on-medication MDS-UPDRS III scores at Month 24 after resistance training maintenance program changed little (11). Taken together, it may be necessary to keep exercise intensity high for a prolonged period to slow the progression of PD symptoms and improve MDS-UPDRS M-EDL scores by 12.4-point (Table 2). The agility program did not affect drug dose, which, against our expectation of a relative reduction, increased by 11% (12).

Most PD patients with a diagnosis of stage 2-3 on the Hoehn-Yahr scale present with multiple comorbidities. Those who died compared with those who completed the program differed ($p<0.05$) at baseline only in two variables (MDS-UPDS M-EDL: worse score by 7.2 points; TUG: 2.9 s longer; Table 3). The suggestion emerging from these data requires confirmation as to which variables could be used to predict progression of PD symptoms in stage 2 to 3 PD patients.

The mechanisms of how a prolonged and high-intensity exercise incorporating sensorimotor and visuomotor stimuli might slow the progression of disease in PD patients remain unclear. Short-term intensive balance training challenges postural stability and produced correlated

morphometric changes in gray matter of brain areas and balance behavior (23). Motor-cognitive training decreased PD patients' reliance on frontal brain structures, resulting in improved functioning (24). At the cellular level, animal and human PET data suggest that exercise can improve dopamine signaling, leading to task-specific improvements in postural control (25-27). Such improvements in motor function are accompanied by neuroplastic changes, including improved dopaminergic signaling through an increase in striatal dopamine release, reduced dopamine reuptake, and an elevated dopamine-D2 receptor expression measured at protein and transcript levels. Sustained exercise activates neurotrophic factors, which produce anti-inflammatory and pro-regenerative effects on motor and cognition function in old adults with and without a degenerative condition (28-31). In particular, there is emerging evidence suggesting that rapid reactive movements to external and internal perturbations on unstable surfaces, as done in the present agility training study, could increase the descending neural drive leading to correlated improvements in clinical symptoms and in the magnitude, timing and rate of torque generation (32).

Limitations, conclusions

Without a maintenance-only group we cannot tell if the initial 3-week-long exercise period enhanced the maintenance effects. It is likely that some of the maintenance effects were due to the attention and social contact patients received over the two years in contrast to a lack of attention and contact in the E and C groups. The correlations between changes in the outcomes did not reach significance, making causation among variables not possible. As the outcomes were purely behavioral, we could not examine any potential mechanisms. To achieve and maintain the high exercise intensity, adherence, and compliance, three therapists and a

designated facility were needed, conditions that may not be available in many settings. Finally, without a high-intensity comparison group such as intensive cycling (33,34), in which interaction with unstable surfaces and rapid responses to external and internal perturbations are absent, we cannot tell if in the present and past studies (4,8,12,32,35) the agility or the fitness stimulus did in fact produce the disease-slowing postural and mobility improvements, an issue we are addressing in our ongoing studies. A lack of systematic assessment of adverse events is a limitation but anecdotally and based on patients' exercise diaries we found no evidence for program-related falls in and outside the gym. The deaths for which pathology reports were available were caused by serious medical conditions unrelated to the intervention. In conclusion, a high-intensity sensorimotor agility program with but not without a 2-year maintenance program slowed the progression of PD patients' motor and non-motor symptoms without reducing drug dose.

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The authors declare no conflict of interest. The authors state that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Supplemental Digital Content

Supplemental Digital Content 1. Exergaming.avi. PD patients performing exergaming agility exercises. Tollár et al, 35 s, 5 MB.

Figure Captions

Figure 1. Consort diagram. E, Exercise only for three weeks, E+M, Exercise for three weeks followed by a Maintenance program for two years, and C, Control, no Exercise and no Maintenance.

Figure 2. Effects of a 3-week-long exercise program and a 2-year-long exercise maintenance program on measures of parkinsonian symptoms and mobility. Change scores after 3 weeks of high-intensity individualized agility training (dark gray shading) with (E+M, n=18, filled circles) and without (E, n=13, filled squares) a maintenance exercise program or no exercise and no maintenance control (n=13, open circles) on MDS-UPDRS M-EDL (A), PDQ summed scores (B), and timed-up-and-go (TUG) test (C) followed by a 24-months-long follow-up period. Horizontal thin line denotes baseline above and below which, respectively performance is worse and better. Vertical bars denote 1 + or – standard deviation. *, Group by Time interaction ($p < 0.05$). a, Control (open symbol) different from the other two groups;

b, All three groups differ from one another; c, Exercise+Maintenance group (filled circles) different from Control (open symbols), d, Exercise+Maintenance group (filled circles) different from Control (open symbols) and Exercise group (filled squares).

Figure 3. Changes in drug dose. Effects of 3 weeks of high-intensity individualized agility exercise (E) training with (E+M, n=15, filled circles) and without (E, n=13, filled squares) a maintenance agility exercise program or no exercise and no maintenance control (C, n=17, open circles) on L-Dopa equivalent dose. Compared with baseline (0wk), the drug dose was ~11% higher at Month 24 (24mo) in the three groups combined (Time main effect, p=0.008, not graphed). Vertical bars denote + or – 1 standard deviation, omitted for clarity in the Control (C) group.

Figure 1

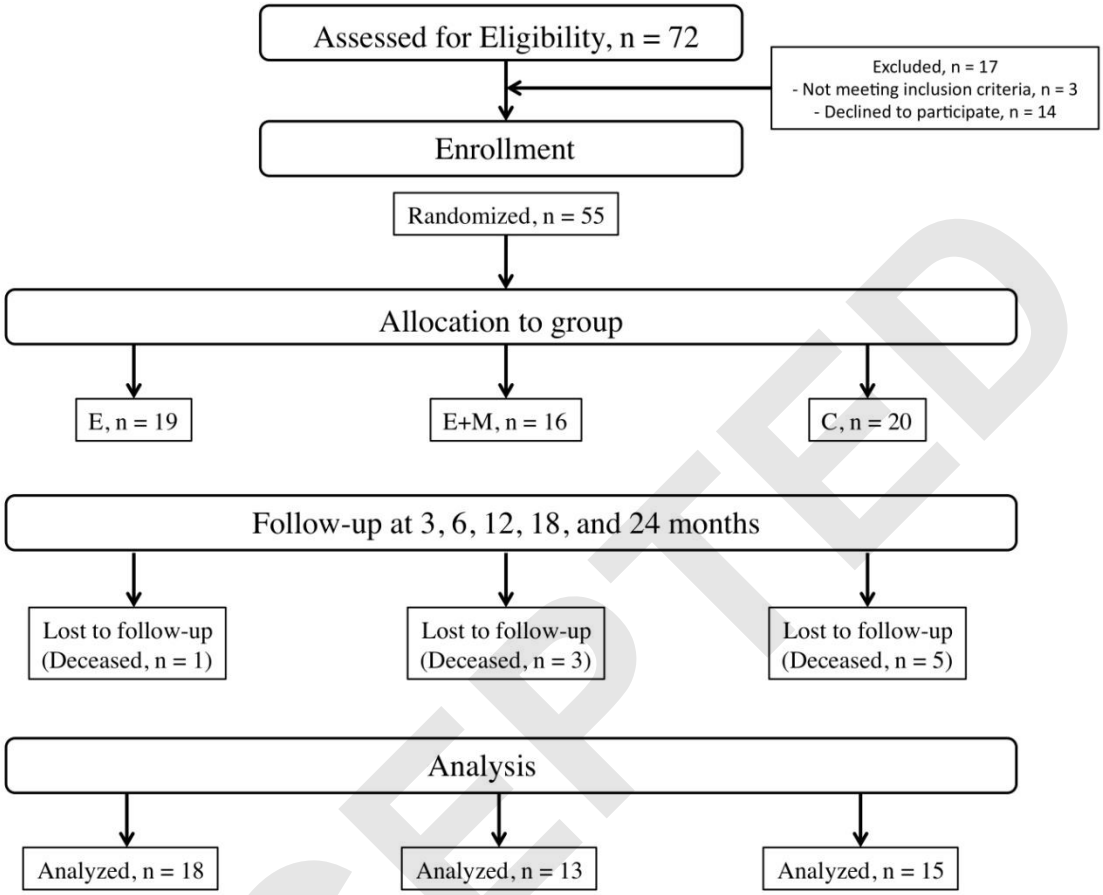

Figure 2

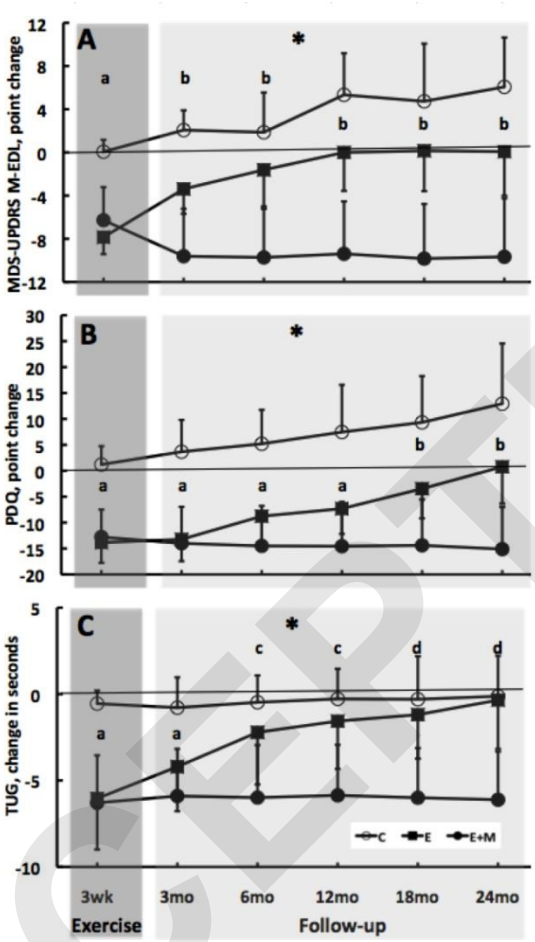

Figure 3

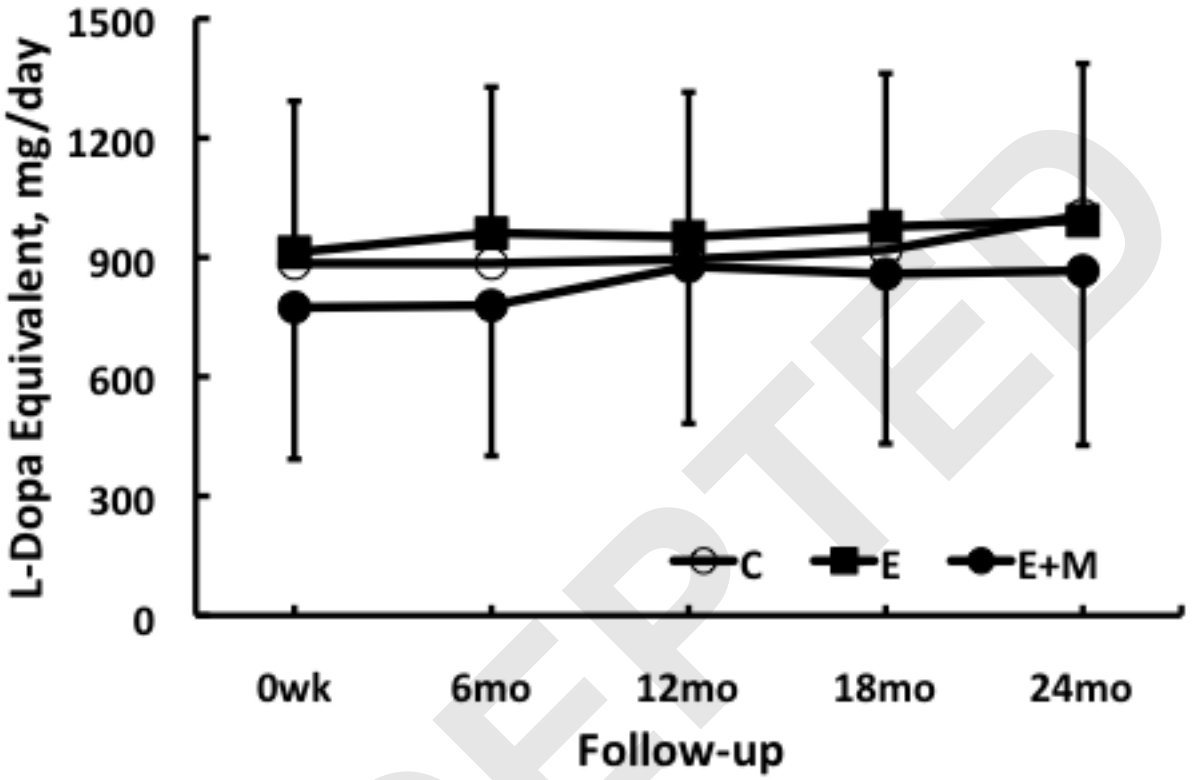

Table 1. Patient characteristics as baseline.

	E+M, n = 19 (11M)		E, n = 16 (6M)		C, n = 20 (12M)		All, n = 55 (29M)	
Variable	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Age, y	67.5	3.91	67.6	3.26	67.6	4.08	67.6	3.75
Height, cm	173.8	6.56	172.0	4.70	174.6	5.70	173.4	5.66
Mass, kg	75.4	11.32	73.9	7.0	78.4	11.19	76.0	10.20
BMI, $kg \cdot m^{-2}$	24.9	2.65	24.9	1.81	25.7	2.75	25.2	2.46
PD years	6.5	2.67	6.8	1.76	7.1	2.75	6.8	2.39
Hoehn - Yahr stage	2.5	0.51	2.31	0.48	2.40	0.50	2.40	0.49
L-Dopa equivalent, mg/day	774.2	381.5	912.6	380.1	884.8	332.0	857.2	364.5
MDS-UPDRS M-EDL	19.5	6.28	19.1	4.54	18.9	7.94	19.1	6.41
PDQ-39								
Mobility	17.9	6.45	15.3	3.57	16.1	9.13	16.5	6.92
ADL	6.8	2.81	5.5	1.93	8.1	4.75	6.9	3.56
Emotions	6.3	3.11	6.3	2.47	7.1	4.75	6.6	3.60
Stigma	5.1	1.90	5.3	1.70	5.7	3.20	5.4	2.38
Social	1.5	1.61	2.3	1.57	1.6	1.85	1.7	1.69
Cognition	4.6	2.36	5.0	2.13	4.7	3.10	4.7	2.56
Communication	2.6	1.92	2.8	2.20	2.7	1.98	2.7	1.99
Body pain	4.1	1.87	3.8	1.61	4.6	2.16	4.2	1.91
Sum of sub-items	51.1	16.99	49.4	8.73	50.5	25.61	50.4	18.67
BDI	19.3	5.60	14.4	3.58	18.0	10.60	17.4	7.59
SE ADL, %*	78.4	11.43	71.2	7.54	68.1	16.20	72.6	11.72
EQ-5D VAS, mm	64.5	13.73	67.5	8.563	61.1	11.52	64.1	11.69
EQ-5D								

Mobility	2.3	0.54	2.7	0.63	3.5**	0.51	2.5	0.56
Self-care	1.6	0.55	2.2	0.51	2.5	0.49	2.1	0.52
Usual activities	1.9	0.59	2.1	0.51	2.4	0.67	2.1	0.59
Pain	1.8	0.58	2.5	0.54	2.7	0.61	2.3	0.58
Anxiety	2.2	0.71	2.2	0.69	2.9	0.61	2.4	0.67
Sum of sub-items	14.2	2.43	12.9	1.45	15.05**	2.42	14.1	2.32
TUG, s	17.0	3.81	15.1	3.31	18.6**	4.18	17.0	4.00
COP path, mm								
Wide stance, EO	8.7	7.60	6.3	5.74	7.2	4.21	7.4	5.97
Wide stance, EC	9.2	5.44	7.0	2.66	7.2	4.18	7.8	4.37
Narrow stance, EO	10.8	6.06	7.3	3.71	8.1	3.75	8.8	4.82
Narrow stance, EC	12.4	8.52	7.8	2.97	10.2	5.94	10.3	6.51

E+M, 3 weeks of intense agility exercise program plus two years of exercise maintenance

E, 3 weeks of intense agility exercise program only followed by assessments for 2 years

C, no exercise only an assessment every three months for 2 years

BMI, body mass index

PD, Parkinsons's disease

MDS-UPDRS M-EDL, Movement Disorders Society-Unified Parkinson's Disease Rating Scale - Motor Experiences of Daily Living

PDQ-39, Parkinson's Disease Questionnaire

BDI, Beck depression inventory (0 to 20, lower value less depression)

SE ADL, Schwab & England Activities of Daily Living Scale (Parkinson's Disease) (0 to 100, 100 denoting no mobility disability)

EQ-5D, EuroQol five dimensions questionnaire, VAS: visual analogue scale

TUG, timed up and go tests (lower value denotes better mobility)

COP, center of pressure

EO, eyes open

EC, eyes closed

*, not normally distributed

**, baseline difference between groups, $p<0.05$

Table 2. Changes in primary and secondary outcome measures after the high-intensity agility program administered daily for 3 weeks and the high-intensity maintenance program administered 3 times per week for 2 years.

		Exercise, weeks		Followup, months				
		0	3	3	6	12	18	24
Variable	Group	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Mass. Kg*	E+M	75.9 ±11.46	-	-	-	74.6 ±10.12	-	74.7 ±9.38
	E	73.8 ±7.31	-	-	-	73.3 ±6.25	-	74.3 ±6.35
	C	79.4 ±11.55	-	-	-	76.7 ±8.88	-	75.4 ±8.08
Leva-Dopa equivalent, mg/day	E+M	774.2 ±381.49	-	-	779.2 ±378.10	877.3 ±395.00	858.6 ±427.09	866.5 ±438.59
	E	912.6 ±380.10	-	-	960.9 ±367.39	951.7 ±363.78	977.1 ±385.48	992.5 ±394.68
	C	884.8 ±331.97	-	-	884.8 ±331.97	895.4 ±330.61	918.6 ±300.33	1006.5 ±375.55
MDS-UPDRS M-EDL*	E+M	19.4 ±6.28	13.1 ±3.67	9.6 ±2.48	9.4 ±2.19	10.0 ±2.20	9.6 ±2.03	9.5 ±1.47
	E	19.1 ±4.54	10.6 ±3.28	15.1 ±2.63	17.4 ±2.94	19.1 ±2.51	19.4 ±2.44	18.9 ±2.15
	C	18.9 ±7.94	18.6 ±7.56	20.1 ±7.04	19.4 ±6.24	22.8 ±6.46	21.1 ±4.43	21.9 ±3.54
PDQ-39*	E+M	49.9 ±16.61	37.1 ±13.15	35.9 ±11.74	35.4 ±10.91	35.3 ±10.17	35.5 ±9.59	34.8 ±10.01
	E	49.3 ±9.65	35.5 ±9.43	36.1 ±9.52	40.5 ±9.20	42.0 ±8.48	45.9 ±8.11	50.1 ± 6.41

	C	39.6 ±18.27	40.8 ±16.79	43.3 ±15.45	44.8 ±13.42	47.1 ±13.70	48.9 ±12.71	59.2 ±25.57
Beck Depression Index	E+M	19.4 ±5.73	16.4 ±4.79	16.4 ±4.79	15.3 ±4.35	15.9 ±4.58	15.5 ±5.04	13.9 ±4.06
	E	14.5 ±3.53	10.9 ±3.63	13.9 ±3.56	12.2 ±3.81	14.8 ±3.11	13.5 ±2.47	15.5 ±1.81
	C	15.3 ±10.42	15.3 ±9.48	15.3 ±10.38	15.2 ±9.29	16.0 ±9.27	18.5 ±7.51	20.7 ±5.86
Schwab & England ADL.	E+M	70.6 ±17.65	78.3 ±12.95	79.4 ±11.62	81.1 ±10.23	81.1 ±9.00	81.1 ±9.00	81.1 ±9.00
ADL, %*, **	E	66.2 ±9.61	78.5 ±6.89	76.9 ±7.51	72.3 ±9.27	68.5 ±5.55	68.5 ±8.01	66.2 ±6.50
	C	72.0 ±18.97	71.3 ±18.47	71.3 ±18.47	70.0 ±16.90	68.7 ±15.98	68.7 ±15.98	67.2 ±14.86
EuroQol, Visual	E+M	65.3±13.66	74.7 ±9.77	74.7 ±9.77	74.7 ±9.77	77.2 ±8.26	76.7 ±8.40	76.1 ±9.16
analog scale, mm*	E	67.7 ±9.27	76.9 ±6.30	76.9 ±6.30	76.2 ±6.50	75.4 ±6.60	74.6 ±6.60	74.6 ±6.60
	C	63.8 ±11.50	62.3 ±10.50	62.3 ±10.50	62.3 ±10.50	61.7 ±9.57	59.7 ±8.55	59.7 ±8.55
EuroQol, Summed	E+M	14.1 ±2.49	10.9 ±1.61	9.6 ±1.54	8.9 ±1.26	8.7 ±1.32	8.8 ±1.25	8.7 ±1.41
Scores of 5 Items*	E	13.1 ±1.32	11.2 ±1.24	10.9 ±1.50	11.7 ±1.18	11.7 ±1.18	12.4 ±1.04	12.5 ±1.45
	C	14.5 ±2.48	13.6 ±2.10	13.4 ±1.88	13.7 ±1.50	13.7 ±1.44	14.3 ±1.29	14.4 ±1.30
Timed-up-and go, s*	E+M	16.9 ±3.91	10.6 ±2.92	11.0 ±2.56	10.9 ±2.79	11.0 ±2.72	10.9 ±2.49	10.8 ±2.41
	E	14.8 ±3.54	8.7 ±1.78	10.6 ±1.35	12.5 ±1.70	13.2 ±1.59	13.6 ±1.68	14.4 ±1.50
	C	17.7 ±3.25	17.2 ±3.04	16.9 ±3.02	17.2 ±3.13	17.4 ±2.39	17.4 ±1.72	17.6 ±2.19
COP path, mm								

Wide stance: Eyes	E+M	8.9 ±7.79	3.4 ±1.22	3.2 ±0.93	3.2 ±0.94	3.2 ±0.97	3.2 ±0.98	3.2 ±1.07
Open*	E	6.8 ±6.23	3.7 ±1.00	4.3 ±0.71	5.3 ±0.84	6.1 ±0.93	7.1 ±0.95	7.8 ±1.02
	C	6.4 ±3.51	6.0 ±5.90	7.1 ±4.35	7.5 ±4.45	8.0 ±3.63	8.8 ±4.49	9.5 ±4.88
Wide stance: Eyes	E+M	8.9 ±5.31	4.4 ±2.02	3.7 ±1.44	3.8 ±0.99	3.8 ±1.03	3.5 ±0.81	3.1 ±0.80
Closed*	E	7.1 ±2.52	3.9 ±1.57	5.4 ±1.25	5.9 ±1.10	6.0 ±1.07	6.5 ±1.02	7.8 ±1.54
	C	6.7 ±4.28	6.6 ±4.64	7.1 ±2.98	7.9 ±2.96	8.6 ±3.60	8.0 ±2.87	9.9 ±3.84
Narrow stance: Eyes	E+M	10.3 ±5.82	4.1 ±1.55	3.9 ±0.80	3.4 ±0.63	4.1 ±1.08	4.3 ±0.74	3.9 ±0.91
Open*	E	7.8 ±3.90	5.8 ±2.78	5.8 ±1.41	5.9 ±1.28	6.4 ±1.80	6.9 ±1.26	6.9 ±1.43
	C	7.6 ±3.78	6.8 ±3.62	7.5 ±2.50	6.8 ±2.40	7.5 ±1.81	8.1 ±2.16	8.0 ±2.05
Narrow stance: Eyes	E+M	12.1 ±8.68	5.3 ±2.46	4.5 ±0.76	4.4 ±0.78	4.7 ±1.07	4.6 ±0.70	4.0 ±0.53
Closed*	E	8.3 ±2.63	5.2 ±2.07	6.2 ±1.31	6.4 ±1.56	6.5 ±2.18	6.5 ±0.99	6.5 ±1.02
	C	9.2 ±5.25	8.6 ±4.28	8.5 ±2.67	8.3 ±2.24	9.2 ±3.47	8.9 ±2.60	9.8 ±2.91

E+M (n=18), 3 weeks of intense agility exercise program plus two years of exercise maintenance

E (n=13), 3 weeks of intense agility exercise program only followed by an assessment every three months for 2 years

C (n=15), no exercise, only an assessment every three months for 2 years

MDS-UPDRS M-EDL, Movement Disorders Society-Unified Parkinson's Disease Rating Scale - Motor Experiences of Daily Living

PDQ-39, Parkinson's Disease Questionnaire

Beck depression inventory (0 to 20. lower value less depression)

Schwab & England Activities of Daily Living Scale (Parkinson's Disease) (0 to 100. 100 denoting no mobility disability)

Timed up and go tests (lower value denotes better mobility)

COP. center of pressure

*, Group by Time interaction, $p<0.001$

**, Not normally distributed, analysis on logged transformed data

Table 3. Baseline comparisons between patients who died and those who completed the 2-year program.

	Completed, n = 46, 17M		Deceased, n = 9, 6M		t test
Variable	Mean	±SD	Mean	±SD	p value
Age, y	67.5	3.86	67.9	3.14	0.778
Height, cm	173.8	5.79	172.3	5.70	0.494
Mass, kg	76.4	10.51	74.0	8.66	0.517
BMI, $kg \cdot m^{-2}$	25.2	2.51	24.9	2.26	0.696
Hoehn - Yahr stage	2.4	0.49	2.4	0.53	0.771
L-Dopa equivalent, mg/day	850.1	362.13	873.5	375.52	0.870
PD years	6.6	2.34	8.1	2.67	0.082
MDS-UPDRS M-EDL	18.0	5.91	25.1	5.78	0.002
PDQ-39 sum score	46.4	15.99	8.9	2.32	0.001
BDI	16.7	7.37	20.8	8.20	0.141
SE ADL, %*	69.8	16.12	61.1	7.82	0.123
EQ-5D VAS, mm	65.5	11.70	57.2	9.39	0.052
EQ-5D sum score	14.0	2.25	14.9	2.67	0.275
TUG, s	16.6	3.72	19.5	4.79	0.046
COP path, mm					
Wide stance, EO	7.5	6.20	7.3	4.92	0.950
Wide stance, EC	7.7	4.36	8.6	4.56	0.549
Narrow stance, EO	8.7	4.78	9.2	5.32	0.803
Narrow stance, EC	10.1	6.46	11.2	7.16	0.651

BMI, body mass index

PD, Parkinsons's disease

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TUG, timed up and go tests (lower value denotes better mobility)

COP, center of pressure

EO, eyes open

EC, eyes closed

*, Not normally distributed