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A phase II randomised controlled trial of a 6 month self-managed community exercise program for people with Parkinson's disease.

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ABSTRACT

Background Evidence for longer-term exercise delivery for people with Parkinsons Disease (pwP) is deficient.

Aim Evaluate safety and adherence to a minimally supported community exercise intervention and estimate effect sizes (ES).

Methods Two arm parallel phase II randomised controlled trial with blind assessment. PwP able to walk ≥100meters and with no contraindication to exercise were recruited from the Thames valley, UK and randomised (1:1) to intervention (exercise) or control (handwriting) groups, via a concealed computer-generated list. Groups received a six month, twice weekly program. Exercise was undertaken in community facilities (30minutes aerobic and 30minutes resistance) and handwriting at home, both were delivered through workbooks with monthly support visits. Primary outcome was a 2minute walk, with motor symptoms (MDS-UPDRS III), fitness, health and wellbeing measured.

Results Between December 2011 and August 2013, n=53 (n=54 analysed) were allocated to exercise and n=52 (n=51 analysed) to handwriting. n=37 adhered to the exercise, most attending ≥1 session/week. Aerobic exercise was performed in 99% of attended sessions and resistance in 95%. Attrition and adverse events (AE) were similar between groups, no Serious AEs (n=2 exercise, n=3 handwriting) were related, exercise group related AEs (n=2) did not discontinue intervention. Largest effects were for motor symptoms (2minute walk ES= 0.20 (95%CI=-0.44:0.45) and MDS-UPDRS III ES=-0.30 (95%CI=0.07:0.54)) in favour of

exercise over the 12month follow-up period. Some small effects were observed in fitness and wellbeing measures (ES >0.1).

Conclusion pwP exercised safely and the possible long-term benefits observed support a substantive evaluation of this community program.(ClinicalTrials.Gov:NCT01439022).

INTRODUCTION

Short term exercise has been shown to benefit or stop deterioration in symptoms offering potential personal, societal and economic benefits for the management of Parkinson's disease (PD),[1 2] but many people with Parkinson's disease (PwP) undertake less exercise than other age-matched people, and less than recommended to maintain good health.[3, 4] Whilst exercise may improve health and wellbeing and reduce motor and non-motor symptoms in PwP,[3-6] there is a lack of evidence for the long-term benefits.[6-10] This is in part due to the difficulties of effectively delivering exercise over the longer-term; existing researched interventions are predominantly not cost-effective or sustainable.[11] Thus there is a need for more evidence on how to best deliver a solution that is effective long term.

Exercise referral schemes run throughout the UK are standardised, widely commissioned and have been shown to be effective for cardiac conditions and older people offering a pragmatic solution for PwP.[12, 13] However, PwP are underrepresented within standard UK exercise referral schemes, [14, 15] and report significant barriers.[16]

With the help of fitness professionals, PwP and clinicians, a supported self-managed community exercise program for people with long-term neurological conditions was developed to fit within existing community fitness centres delivered in gyms by professional with expertise in clinical exercise.[17, 18] The intervention was guided by behaviour change theory that considered an individual's capability, opportunity and motivation and incorporated appropriate evidence for safe effective exercise and self-determination theory. [16-19] In this phase II exploratory trial, we evaluated the program's utility focusing on the

extent to which people safely participated and adhered to the six month exercise program. We also sought to estimate effects sizes on fitness, motor and non-motor symptoms, and health and wellbeing measures.

METHODS:

DESIGN

A two arm parallel single blind phase II randomised controlled trial of community delivered exercise for pwP. Participants recruited to the study were allocated the next available study number by the blinded assessor. The study number related to a computer-generated randomization list drawn up by the Oxford Primary Care Clinical Trials Unit (Nuffield Department of Primary Care Health Sciences) that randomized individuals (1:1) into either intervention (Exercise) or control groups (handwriting). The randomisation list used minimisation to balance groups for gender and whether or not individuals used medication for PD at baseline. The list was held by the principal investigator who informed those supporting the intervention of group allocation. Group allocation was concealed from the assessor until the end of the study.

SETTING

Participants were recruited from Oxfordshire, Berkshire and Buckinghamshire, UK and assessments were carried out at the Movement Science Laboratory, Oxford Brookes University, Oxford, UK.

PARTICIPANTS

The study received National Health Service ethical approval (NRES Committee South Central - Southampton A: 11/SC/0267), was registered with ClinicalTrials.Gov (NCT01439022), and was conducted in accordance with the declaration of Helsinki.

People with idiopathic PD were recruited from neurology clinics at the John Radcliffe, Royal Berkshire and Heatherwood and Wexham Park hospitals (via the Dementias and Neurodegeneration research network), GP practices (via Thames Valley Primary Care Research Network) and though local Parkinson's UK meetings.

Inclusion criteria were: (i) diagnosis of idiopathic PD (as defined by the UK PD Society Brain Bank criteria);[20] (ii) able to walk ≥100 meters (with or without walking aid). Exclusion criteria were: (i) A diagnosis of dementia; (ii) history of additional prior neurological condition; (iii) severe depression or psychosis or a mental state that would preclude consistent active involvement with the study over its duration; (iv) cardiac precautions that would prevent the subject from participating in the intervention; (v) any known contraindication to exercise; (vi) reduced cognitive function of any cause (mini-mental state examination <23); (vii) an orthopaedic condition that limited independent walking. Participants' medication was continued as normal and was recorded.

INTERVENTION

Supplement 1 contains details of the intervention according to TIDiER Guidelines.[21] Briefly, both the intervention (exercise) and control groups (handwriting) were prescribed activity sessions lasting 60minutes twice a week over a period of six months. After the six month assessment no further instruction for exercise (or handwriting practice) was given.

Exercise group

The exercise sessions took place at community leisure facilities in Oxfordshire and Berkshire and were supported by monthly visits from a professional experienced in clinical exercise. The exercise program was delivered through an exercise booklet and consisted of 30minutes of aerobic training (55-85% age predicted heart rate max (220-age)) followed by 30minutes of resistance training.

Handwriting group

The handwriting sessions took place in the participants home and were supported by monthly visits by the same staff that supported exercise sessions. The program was delivered through handwriting workbooks and consisted of 'warm-up' hand exercises followed by a variety of writing exercises, finishing with hand exercises.

ASSESSMENT

Demographic information, medical history relating to PD, including current medication use, and cognition (mini-mental state examination) was ascertained at the baseline assessment.

All outcome measures were performed at baseline (entry), 3months (halfway intervention), 6months and (end intervention) and 12months. Measurements were made by the same assessor blinded to intervention allocation and trained in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS).[22] If a patient had On and Off

periods, assessments were carried out during ON state. Participants followed their usual Parkinson's medication regime, but were asked to refrain from the consumption of alcohol, cigarettes, food and caffeine and to avoid exercise for a period of three hours prior to the assessment.

Outcome Measures

A detailed description of outcome measures can be found in the supplement 1.

Motor: The primary outcome measure was the 2minute walk test.[23] Mobility was also measured using the timed up and go test (TUG),[23] and dexterity using the 9 hole peg test[24]. Global motor function was assessed using the motor examination of the MDS-UPDRS (III).[25]

Fitness: Aerobic fitness was determined using a stepwise incremental exercise test. The work rate protocol consisted of 2minute steps starting with unloaded cycling, then increasing to 50watts, and thereafter by 25watts. Participants were verbally encouraged to carry on for as long as they could and the test was terminated when the participant reached volitional exhaustion. Rate of oxygen consumption was calculated as the average oxygen consumed over the last 30secs of the test (VO^2_{max} $l.min^{-1}$).[26] Leg power was measured using a 'power meter',[27] the maximum power achieved from each leg separately was recorded and reported as an average. Grip strength was measured using a hand held dynometer, the maximum force of each hand was recorded and reported as the average. [28]

Health and wellbeing: Health related quality of life was measured using the Euro-QOL (EQ5D-5L)[29] and SF36,[30] scores are reported for the EQ5D-5L index score and SF36 physical and mental scores. Non-motor symptoms were assessed using the Parkinson's disease non-motor symptom questionnaire[31] and self-reported fatigue using the Fatigue Severity Scale (FSS).[32] Health status was measured using Body Mass Index and resting blood pressure and physical activity using the Physical Activity Scale for the Elderly.[33]

Intervention fidelity

Adherence and fidelity was obtained from the exercise booklets. For aerobic exercise, time (in minutes) and exercise equipment used was reported, along with rating of perceived Exhaustion (RPE) and heart rate at the end of the exercise. Resistance training was recorded as the weight (kg) used for the exercise and the number of the repetitions for each exercise, with training volume calculated (weight (kg) x number of repetitions). Engagement with the control intervention was determined by number of handwriting session attempted.

Data analysis

Whilst this was a phase II trial and not designed to determine efficacy, sample size was based on the estimated effect on 2minute walk distance. To detect a clinically meaningful change of 12meters in the 2minute walk would require an effect size of 0.55, with a power of 80% and alpha of 0.05, 80 participants (40 in each group) would be required. Allowing for attrition, we aimed to recruit a total of 100 participants.

Data were analysed based on the intention-to-treat principle. Descriptive statistics were calculated for demographic characteristics and compliance data. Independent samples T-test or X^2 test was used to assess differences between group mean and frequencies at

baseline. Progression in training volume was investigated using linear regression in SPSS (v19). For outcome data the Linear Mixed Models (LMM) procedure of SAS 9.4 was used to determine the mean changes in measures, as response variables, according to two intervention regimes (exercise and handwriting) and three repeated measurements, using baseline as a covariate. Further and based on the differences of least square (Marginal) means between two groups (exercise vs. handwriting) provided by LMM analysis, powers, effect sizes (Cohen's d) and their 95% non-central confidence limits were calculated.

RESULTS

Recruitment, randomisation and participant flow

Between December 2011 and August 2013 the trial recruited 105 participants within the proposed time line. We could not record the number of people screened in the eight GP surgeries and PD Clinics (John Radcliffe, Royal Berkshire and Heatherwood and Wexham Park Hospitals) or the total number of people informed of the study via either presentation at group meetings or newsletter articles at seven local Parkinson's UK groups (Oxford, Newbery, Bracknell, Wokingham, Reading, Hazlemere and High Wycombe). The study was also promoted on Parkinson's UK and Michael J Fox websites.

In total 170 people, contacted through one or more of these routes, expressed an interest in the study; 107 were assessed for eligibility with only two not meeting criteria, leaving 105 people. Table 1 shows pre intervention assessment data, whilst there was no statistical difference between groups, scores for 2minute walk and MDS-UPDRS III tended to be better in the exercise group. Only one person, in the exercise group, used a walking aid. VO_2 data

was unavailable on eleven people from each group due to contraindications. One participant did not receive the allocated intervention, allocated to handwriting group but received exercise, and was included in analysis as part of exercise group. The allocations error was due a misunderstanding of the allocation by the staff delivering intervention. The error was discovered after the completion of the intervention.

Attrition after randomisation was similar between groups, and participant flow can be found in figure 1. Two people were excluded after randomisation (1 from each group) for no longer meeting eligibility criteria due to a revised/additional diagnosis (Lewy-body dementia, multiple system atrophy). Retention was similar between groups with ≥80% retention for both groups at the 3month and 6months dropping to 67% in the exercise group and 63% in handwriting group at 12months. Unrelated medical reasons were the main cause of lost to follow-up at the primary (6month) assessment point. Most of these occurred prior to the 3month appointment resulting in participants dropping out of the trial. Five participants experienced serious adverse events (n=2 exercise group, n=3 handwriting group) during the trial, these were deemed unrelated to either intervention (fall resulting in hospitalisation n=2, acute pancreatitis n=1, death n=2).

Intervention fidelity.

Exercise group: In total 17 individuals discontinued intervention (figure 1), 8 individuals due to medical reasons and one individual was excluded due to additional diagnosis of Lewy-Body dementia. Participants were deemed to have discontinued intervention if they attended none or only the initial session (n=9), reasons can be found in figure 1. There were two related adverse events; these were an abnormal heart rate response to exercise and

orthostatic hypotension, both participants continued with the intervention following medical clearance. All discontinued intervention occurred within the first 3months.

Intervention fidelity was further investigated in the 37 participants that did not discontinue the exercise program. Most people (n=32) attended one or more sessions a week on average and the median number of session attended was 40 out of the 48 prescribed sessions.

In 1341 out of the 1350 sessions attended (99%) the aerobic component was performed for a mean (SD) time of 30.2 (± 3.6) minutes per session. The exercise bike was the most popular mode of aerobic exercise (676 sessions), followed by treadmill (353 sessions) and mixed modes (309 sessions), cross trainer or rowing machine made up ~1% of sessions. The mean (SD) heart rate during the aerobic component was 116 ± 20 bpm with 93% of aerobic sessions performed with in the target zone.

Considering the resistance component; in 95% of attended sessions the two arm pull down exercise was performed, 93% arm raises, 91% leg press, 85% sit-to-stands, 80% 'wood chop' and 25% leg extensions. Linear regression revealed a significant increase ($p<0.05$) in resistance training volume (resistance weight x number of repetitions) during the exercise program for all exercise except arm raises. Beta co-efficient indicated two arm pull down resistance training volume increased by 3.0 (SE 0.7) kg per session (R^2 0.12, $p <0.0001$), leg press volume 10.0 (SE 1.1) kg per session (R^2 0.24, $p<0.0001$), sit to stand 2.7 (SE 0.3) kg per session (R^2 0.20, $p<0.0001$), 'wood chop' 2.3 (SE 0.66) kg per session (R^2 0.10, $p<0.0001$) and leg extension volume 1.7 (SE 0.6) kg per session (R^2 0.08, $p=0.04$).

Handwriting group: In total 11 individuals had discontinued intervention by the 6month follow-up, most did not given a reason (n=6) and there were three discontinued intervention due to medical reasons (figure 1). Two SAE were recorded that did not result in discontinue intervention; a fall that occurred during the intervention and a death which occurred after the intervention in the follow-up period. There were no related adverse events in the handwriting group. The median number of handwriting sessions performed was 40 out of the 48 prescribed sessions and most people (n=36) did more than one session a week on average.

Outcome

Follow-up assessments were completed September 2014. Outcome data is reported in table 2, small to moderate effect sizes (0.1 – 0.3) were found for a number of outcomes.[34] Effect sizes are between group and considered all three follow-up assessments, the largest effect was found on MDS-UPDRS III -0.30 (95%CI 0.07:0.54) which was significantly lower at the primary endpoint (end intervention) in the exercise group ($p<0.005$) indicating an improvement in motor symptoms. 2minute walk distance, the primary outcome measure, produced the second largest effect 0.20 (95%CI -0.44:0.45), in favour of the intervention group, with the largest difference found between groups at 12months ($p<0.063$). Small effects were found for improvement in leg power and aerobic capacity fitness parameters and in perceived health related quality of life health (EQ5D-5L visual analogue scale and SF36 physical subscale). Effects that favoured the control group were found for non-motor symptoms and fatigue. For the above measures the direction of effect was consistent over all 3 assessment points.

DISCUSSION

People with PD will use community leisure facilities to undertake exercise delivered through an exercise booklet supported by a professional with expertise in clinical exercise. Furthermore, our data is encouraging that six month intervention seems to lead to improvements in mobility and motor symptoms that are sustained over a year. Although the exercise program was not fully adhered to by all, most patients became engaged with the exercise program, and these potential long-term benefits were observed with intention-to-treat analysis. There were no serious adverse events related to the exercise and, after investigation, all individuals that had related adverse event were able to continue with the intervention. Essentially most patients, after receiving instructions to initiate the program, were able to largely self-manage their exercise, achieving and progressing the prescribed exercise, with minimal support. As such our study establishes that the use of community exercise facilities is feasible to achieve long-term gains for pwP.

The effects we observed compare favourably to those reported in systematic reviews. A meta-analysis of aerobic training, primarily driven by studies with short interventions and follow-ups (less than 16weeks), found a pooled mean difference in MDS-UPDRS III of -0.57(95%CI –0.95:0.19) in favour of exercise,[1] we found a difference of -3.0±1.5, -4.0±1.4 and -1.5±1.6 at 3, 6 and 12months respectively. Uhrbrand et al[2] found in their review that improvements in the MSD-UPDRS III were more associated with resistance than aerobic exercise modes. Our exercise program incorporated both aerobic and resistance exercise and combining training modalities may be important to optimise benefits.[2] However, whilst individuals progressed, we did not observe the improvements in aerobic and resistance fitness measures that might be expected.[1, 2] It is therefore plausible that the

improvements in motor symptoms observed might be to some extent attributable to exercise-induced neuroplasticity identified in animal models of the disease,[35] rather than just improved physical capacity. This supports the need for studies designed to distinguish improvements in physical capacity from any possible neuroplasticity effects.

These findings should be interpreted considering limitations. It should be recognised that the study was not designed to determine efficacy and the number of patients was not large, reducing the precision of estimating the size of any benefit. We also used a control group that received a handwriting intervention in order to engage people through the study period, participant flow indicates that this was successfully achieved and indicates a desire for interventions to address handwriting problem in this group. However, the engagement of the control group may have diluted the effects found. Overall physical activity levels did not differ between groups and both groups increased physical activity levels from baseline. This may have particularly impacted on health and wellbeing measures that reflect multiple factors, indeed, effects for non-motor symptoms and fatigue favoured the control group. In Multiple Sclerosis the effect of exercise on fatigue has received considerable research attention and whilst individuals may have to balance rest and activity to participate in exercise,[36] exercise is recommended to benefit this symptom.[37] Currently there is insufficient evidence to inform fatigue management in Parkinson's. [6] However, we did observe, albeit small, potential positive effects on quality of life. This is encouraging as systematic reviews have not established improvements in this construct despite the improvements in motor symptoms.[1 2] Certainly, while systematic reviews supports that exercise interventions can benefit PwP and are safe,[1, 2, 7, 38] they also confirm that the longer-term effects have not been established and that pragmatic delivery models are

largely untested.[3-6, 39, 40] We propose that the intervention provides evidence for effectively supporting PwP to engage with an exercise program for six months through standard community resources. The adherence to the program compares favourably to adherence to standard UK exercise referral,[41] with 69% of our participants adhering to the exercise program and 86% of these individuals attending more than 1 session a week on average compared with a pooled rate of 37% (95%CI 20%:54%) for exercise referral. There was also excellent compliance to the exercise program content and there was good evidence demonstrating that individuals progressed through the program, in terms of increasing training volume.

Considering our intervention, individuals participated safely in the community supported exercise program. The eligibility criteria and participant screening and monitoring were effective in selecting people suitable for the intervention. However, this group may present or develop co-existing pathology that can affect their ability to exercise and medical reasons were the predominant reason for discontinue intervention. We found most issues effecting exercise participation could be safely managed either directly by the practitioner supporting the intervention or through advice from or referral to appropriate medical professionals, highlighting the role of appropriately trained professionals to support and guild self-managed community exercise programs. Importantly a National Occupational Standards, for supporting exercise in people with neurological conditions are available for professional education.

It should be considered that, whilst we used a wide range of recruitment routes methods reducing the risk of recruitment bias, participants were recruited from Oxfordshire,

Berkshire and Buckinghamshire, which are affluent areas of the UK. Acknowledging this limitation we nevertheless propose the findings are largely generalizable to relatively healthy PwP. Therefore, the intervention represents a sustainable viable exercise program for supporting PwP in community leisure venues across the UK, which could be implemented through existing exercise referral systems. The fundamental components of the intervention and delivery model could also be applied or adapted to other healthcare systems and conditions. Pwp in England have higher rates of emergency admissions with longer hospital stays, higher costs (£907 million over four years) and in-hospital mortality; with many of the issues secondary to inactivity.[21] Thus, PD is a good model for developing community clinical exercise programs suitable for other neurological/degenerative conditions and, as such, the study has application to another three million individuals. The information gained from this research remain highly relevant and important to the needs of the public health services to adapt both to the ageing demographic and to people living longer with long-term neurological conditions.

In summary at present the evidence indicates that patients can be informed that attending a leisure centre to undertake this program carries minimal risk and may improve or maintain motor symptoms. A substantive evaluation including wider geography, longer follow-up and cost effectiveness is now indicated in order to determine whether this technology should be taken up by the NHS and would significantly add to the scientific knowledge of the cost effectiveness of longer-term exercise for this group. This technology has the potential to be implemented in the UK and worldwide.

Table 1: Baseline characteristic and pre intervention assessment data

	Exercise	Handwriting	Delta (p)
Demographics	n=54	n=51	
Age (years)	66±9	67±7	-2±2 (0.307)
Gender (M:F)	31:23	30:21	X^2 (0.883)
MMSE	29±1	29±1	0±0 (0.882)
Time since diagnosis	4.8±4.1	5.3±4.1	-0.5±0.8 (0.547)
On PD Medication (Y:N)	52:2	47:4	
Levodopa	*n=39*	*n=30*	
Dopamine agonists	*n=25*	*n=29*	
Anticholinergics	*n=2*	*n=3*	
MOA-B inhibitors	*n=14*	*n=14*	
COMT inhibitors	*n=2*	*n=1*	
Motor Symptoms			
2 minute walk test (m)	146.6±23.9	137.7±22.9	8.8±4.6 (0.061)
UPDRS part III	16.7±10.1	19.9±9.9	-2.4±2.0 (0.214)
9 hole peg test (sec)	24.9±5.4	26.8±5.9	-1.9±1.1 (0.089)
TUG (sec)	9.4±2.0	10.1±2.1	-0.7±0.4 (0.069)
Fitness			
VO_2 ($l.min^{-1}$)	1.65±0.64(n=43)	1.49±0.53 (n=40)	0.17±0.13 (0.205)
Leg power (watts)	84±36	76±36	8±7 (0.257)
Grip strength (watts)	31±10	31±10	-0±2 (0.915)
Health and wellbeing			
EQ5D-5L	76±15.4	75±15	0±3 (0.903)
SF36- physical	64±18	61±19	3±4 (0.397)
SF36- metal	71±17	68±17	2±3 (0.470)
N-MSQ	8.4±5.0	8.6±4.2	-0.2±0.9 (0.118)
FSS	3.6±1.4	3.9±1.4	-0.32±0.28 (0.261)
BMI	26.8±5.2	26.7±4.1	0.1±0.9 (0.908)
MAP BP (mmHg)	100±12	94±19	6±3 (0.054)
PASE	66±35	61±35	5±8 (0.519)

Mean±SD, Delta = between group difference (Exercise – Handwriting) ± Standard error of difference reported with p value of independent samples T test, for nominal data p value for X^2 statistic reported. Abbreviations: MMSE = mini-mental State Examination; MOA-B = Monoaomine oxidase type B; COMT = catechol-O-methyl transferase; MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; TUG = Timed up and go test; EQ5D-5L (VAS) index score of the Euro-QOL EQ5D-5L; SF36= Short form (36 item) health survey, physical and mental sub scores; N-MSQ= Parkinson's disease non-motor symptom questionnaire; FSS = fatigue severity scale; BMI = Body mass index (Weight (kg)/ (height(m) ^{2}); MAP BP= mean arterial Blood pressure ((Systolic blood pressure (mm Hg) + 2 x Diastolic blood pressure(mm Hg) / 3)); PASE = Physical Activity Scale for the Elderly.

Table 2: Outcome

	3month			6month			12month			Effect size
	Exercise	Handwriting	Delta	Exercise	Handwriting	Delta	Exercise	Handwriting	Delta	d (95%CI)
Motor Symptoms										
2 minute walk test (m)	145.7±2.4	141.9±2.4	3.8±3.5	146.3±2.4	142.9±2.4	3.4±3.5	144.6±2.5	137.9±2.6	6.7± 3.6	0.20 (-0.44:0.45)
MDS-UPDRS III	14.7±1.1	17.7±1.1	-3.0±1.5	14.1±1.0	18.1±1.0	-4.0±1.4	17.7±1.1	19.2±1.2	-1.5± 1.6	-0.30 (0.07:0.54)
9 hole peg test (sec)	26.4±0.6	26.0±0.6	0.4±0.8	25.6±0.6	25.6±0.6	-0.1±0.8	26.2±0.6	25.7±0.6	0.5±0.8	0.05 (-0.19:0.30)
TUG (sec)	9.8± 0.3	9.8± 0.3	-0.1± 0.4	9.9±0.3	9.8± 0.3	0.1± 0.4	10.1±0.3	10.6± 0.3	-0.5± 0.4	-0.06 (0.00:0.30)
Fitness										
Aerobic (VO_2max: $l.min^{-1}$)	1.59±0.05	1.58±0.05	0.01±0.07	1.63± 0.05	1.55±0.05	0.09±0.07	1.57±0.05	1.53±0.06	0.04±0.08	0.10 (-0.19:0.30)
Leg power (watts)	148±7	136±7	12±10	152±7	137±7	15±10	143±7	128±7	15±10	0.19 (-0.06:0.45)
Grip strength (kg)	29±1	30±1	-1±2	29±1	29±1	-1±2	33±1	30±2	3±2	0.03 (-0.21:0.27)
Health and wellbeing										
EQ5D-5L (VAS)	76±2	75±2	1±3	78±2	74±2	3±3	76±2	74±2	2±3	0.12 (-0.12:0.36)
SF36- physical	64±2	63±2	1±3	62±2	61±2	1±3	62±3	58±3	4±4	0.10 (-0.14:0.34)
SF36- metal	72±2	71± 2	1±3	70±2	68±2	2±3	68±3	66± 3	2± 4	0.08 (-0.16:0.32)
N-MSQ	8.2±0.4	7.7±0.4	0.5± 0.6	8.6± 0.4	8.0± 0.4	0.6± 0.6	8.9± 0.4	8.0± 0.4	0.9±0.6	0.19 (-0.06:0.43)
FSS	3.7±0.1	3.3±0.1	0.4±0.20	3.5±0.1	3.3±0.1	0.1±0.2	3.6±0.1	3.4±0.2	0.1± 0.2	0.18 (-0.07:0.42)
BMI	26.5±0.1	26.4±0.1	0.1±0.2	26.4±0.2	26.2±0.2	0.1±0.2	26.4±0.3	26±0.3	0.2±0.4	0.08 (-0.17:0.32)
MAP BP (mm)Hg)	89±2	93±2	-3±3	91±2	92±2	-1±3	88±3	89±3	-1± 4	-0.09 (0.00:0.33)
PASE	79±7	74±8	5±11	77±6	79±6	-2±9	58±6	62±7	-5±8	-0.01 (0.00:0.74)

Least squares means ± Standard error estimates, delta = between group difference (Exercise – Handwriting), Effect size = Cohen's d based on least squares (marginal) means differences over all assessments with non-central 95% Confidence Intervals. Abbreviations: MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; TUG = Timed up and go test; EQ5D-5L (VAS) index score of the Euro-QOL EQ5D-5L; SF36= Short form (36 item) health survey, physical and mental sub scores; N-MSQ= Parkinson's disease non-motor symptom questionnaire; FSS = fatigue severity scale; BMI = Body mass index (Weight (kg)/ (height(m) ^{2}); MAP BP= mean arterial Blood pressure ((Systolic blood pressure (mm Hg) + 2 x Diastolic blood pressure(mm Hg) / 3)); PASE = Physical Activity Scale for the Elderly

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COMPETING INTERESTS

The authors report no conflict of interest

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