Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial

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Summary

Background High-intensity aerobic exercise might attenuate the symptoms of Parkinson's disease, but high-quality evidence is scarce. Moreover, long-term adherence remains challenging. We aimed to evaluate the effectiveness of aerobic exercise—gamified and delivered at home, to promote adherence—on relieving motor symptoms in patients with Parkinson's disease with mild disease severity who were on common treatment regimes.

Methods In this single-centre, double-blind, randomised controlled trial (Park-in-Shape), we recruited sedentary patients with Parkinson's disease from the outpatient clinic at Radboudumc, Nijmegen, Netherlands. Patients were made aware of the study either by their treating neurologist or via information in the waiting room. Patients could also contact the study team via social media. We included patients aged 30–75 years with a Hoehn and Yahr stage of 2 or lower, who were on stable dopaminergic medication. Patients were randomly assigned (in a 1:1 ratio) to either aerobic exercise done on a stationary home-trainer (aerobic intervention group) or stretching (active control group) by means of a web-based system with minimisation for sex and medication status (treated or untreated) and permuted blocks of varying sizes of more than two (unknown to study personnel). Patients were only aware of the content of their assigned programme. Assessors were unaware of group assignments. Both interventions were home based, requiring 30–45 min training three times per week for 6 months. Both groups received a motivational app and remote supervision. Home trainers were enhanced with virtual reality software and real-life videos providing a so-called exergaming experience (ie, exercise enhanced by gamified elements). The primary outcome was the between-group difference in the Movement Disorders Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor section at 6 months, tested during the off state (≥12 h after last dopaminergic medication). The analysis was done on an intention-to-treat basis in patients who completed the follow-up assessment, regardless of whether they completed the assigned intervention. Patients reported adverse events directly to their coach and also after the 6-month visit retrospectively. A between-group difference of 3·5 points or more was deemed a-priori clinically relevant. The study is concluded and registered with the Dutch Trial Registry, NTR4743.

Findings Between Feb 2, 2015, and Oct 27, 2017, 139 patients were assessed for eligibility in person, of whom 130 were randomly assigned to either the aerobic intervention group (n=65) or the active control group (n=65). Data from 125 (96%) patients were available for the primary analysis; five patients were lost to follow-up (four in the intervention group; one in the control group). 20 patients (ten in each group) did not complete their assigned programme. The off-state MDS-UPDRS motor score revealed a between-group difference of 4·2 points (95% CI 1·6–6·9, p=0·0020) in favour of aerobic exercise (mean 1·3 points [SE 1·8] in the intervention group and 5·6 points [SE 1·9] for the control group). 11 patients had potentially related adverse events (seven [11%] in the intervention group, four [6%] in the control group) and seven had unrelated serious adverse events (three in the intervention group [vestibilar disorder, vasovagal collapse, knee injury during gardening that required surgery; 6%], four in the control group [supraventricular tachycardia, hip fracture, fall related injury, severe dyskinesias after suprathreshold dose levodopa in a patient with deep brain stimulation; 7%]).

Interpretation Aerobic exercise can be done at home by patients with Parkinson's disease with mild disease severity and it attenuates off-state motor signs. Future studies should establish long-term effectiveness and possible disease-modifying effects.

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Introduction

Parkinson's disease is a progressive neurodegenerative disorder.[1] Pharmacotherapy alleviates symptoms but is limited by response fluctuations with disease progression.[2] Non-pharmacological approaches might offer additional symptomatic relief. High-intensity aerobic exercise appears to be promising with beneficial effects on several functional outcomes (that were often specifically trained

Research in Context

Evidence before this study

We searched for randomised controlled studies on aerobic exercise and Parkinson's disease published in MEDLINE up to Mar 21, 2019, using comprehensive electronic search strategies combining terms "aerobic exercise", "exercise", "physical therapy", "physiotherapy", "endurance training", "cardiovascular training", "walking", "cycling", "bicycling", "treadmill", "ergometry", "Parkinson disease", Parkinson's disease", without language restrictions. We included studies evaluating exercise interventions that lasted at least 4 weeks, that were primarily or solely aerobic in nature (as indicated by either target heart rates) and that compared aerobic exercise with non-aerobic exercise or no exercise.

Evidence from animal studies indicates that high-intensity exercise might offer relief of Parkinson motor symptoms through adaptive neuroplasticity. We identified 16 studies in Parkinson's disease patients evaluating the clinical effects of aerobic exercise; almost half of these were published in the past 2 years. The Movement Disorders Society—Unified Parkinson's Disease Rating Scale, a validated score for Parkinson's disease severity, was used as primary or secondary outcome in ten of these studies. So far, the evidence is inconclusive because of conflicting results. Also, previous studies had methodological shortcomings such as small sample sizes, lack of masking, and improper randomisation methods. Two feasibility trials (both published in 2018) were of higher quality, reporting similar beneficial effects on attenuation of motor signs, but these findings need further confirmation. A major challenge remains how the possible beneficial effects of aerobic exercise can be implemented in the patients' own home environment. Only one previous study evaluated a home-based aerobic exercise programme in a randomised controlled trial. Compliance in most earlier studies depended on intensive supervision rates, limiting a wider implementation.

Added value of the study

To our knowledge, this is one of the largest high-quality aerobic exercise studies in Parkinson's disease. The results add to previous work because of the new setting (fully home-based *vs* highly supervised fitness facility in earlier work), the double-blind design, and the unique motivational programme, with only minimal and almost exclusively remote supervision, versus a more intense and direct supervision scheme in earlier work. This multifaceted home-based approach has good potential for a wider implementation with good long-term adherence.

Implications of all available evidence

Aerobic exercise, even when done at home, is a valuable non-pharmacological treatment for patients with Parkinson's disease with mild disease severity.

with the intervention) and physical fitness.[3–8] However, these studies showed no effect on specific Parkinson's disease signs or Parkinson's disease severity.[9,10] A dose-finding treadmill study (SPARX trial),[11] which was specifically powered to find an effect on Parkinson's disease severity, showed that high-intensity aerobic exercise attenuated Parkinson's disease motor signs in de-novo unmedicated patients. Whether these results can also be reached with different types of exercise, in a more pragmatic home-based setting that is easier to implement and within a broader patient population entailing somewhat more severely affected patients on medication, remains to be shown.

It is challenging for patients with Parkinson's disease to adhere to exercise programmes for extended periods. Providing supervision and making exercise more engaging and accessible could improve adherence. We designed the Park-in-Shape intervention, which incorporates gaming elements (to engage patients) and allows patients to exercise at home (cycling on a stationary home-trainer), with remote supervision by professional trainers and social support from near coaches.[12] We report the outcome of a randomised controlled, assessor-blinded and patient-blinded, single-centre study comparing this intervention with a non-aerobic active control intervention. Our primary aim was to evaluate the effect of home-based high-intensity aerobic exercise on motor signs of Parkinson's disease (tested off dopaminergic medication) in patients with mild disease severity who were on common treatment regimens. The aim of this analysis was to confirm and extend the results of the previously published SPARX trial to a broader patient population, a different type of exercise, and a more pragmatic setting.

See Online for appendix

Methods

Study design and participants

The Park-in-Shape trial is a single-centre, double-blind, home-based, randomised controlled trial comparing aerobic exercise with a non-aerobic intervention. Both groups received coaching and a specifically designed motivational app to enhance engagement and increase compliance.[12] The trial protocol was approved by the medical ethical committee Arnhem-Nijmegen. Assessments were done at the Radboudumc Department of Neurology Center of Expertise for Parkinson and Movement Disorders, Nijmegen. The intervention in both groups was delivered in the patients' homes, with remote supervision by a coach (physical therapists or research assistant).

The full protocol, including detailed descriptions of the intervention and statistical analysis plan, has been published previously.[12] The trial protocol is available in the appendix (pp 1–86).

Patients with mild Parkinson's disease (Hoehn and Yahr stage ≤2) were eligible for inclusion if, in everyday life, they did less than the recommended aerobic exercise for older adults (ie, vigorous exercise done <3 times per week,

20 min per session; or moderate exercise done <5 times per week, 30 min per session),[13] were aged 30–75 years, and were on stable dopaminergic pharmacotherapy (stable dose for at least 1 month) or were still without treatment and expected not to start treatment within the next month. We excluded patients on beta-blocking agents or antipsychotics; patients with neurological, orthopaedic, or cardiac comorbidities that make them unfit to do aerobic or stretching exercises; patients with psychiatric diseases diagnosed in the past year by a psychiatrist; patients with dementia; patients who were unable to complete questionnaires after dementia (Mini-Mental State Examination score <24) or perform a computer task; patients without internet access at home; and patients who were unavailable for more than 10% of the study period. Changes in medication and deep brain stimulation settings during participation were discouraged but allowed at the discretion of the treating physician, creating a realistic real-life clinical setting. All patients provided written informed consent.

Patients who visited the outpatient clinic of the Radboudumc were made aware of the study either by their treating neurologist or via information in the waiting room. Patients could also contact the study team via social media. Eligibility was established through telephone screening followed by in-person assessments. During telephone screening, a trained research nurse interviewed the patients regarding their physical activity (aerobic sports activities were assessed with the sports activities section of the Longitudinal Aging Study Amsterdam physical activity questionnaire), comorbidity, medication use, ability to complete questionnaires or perform computer tasks, and facilities at home and availability. If there was no reason for exclusion at this stage, participants were invited to the study site for an additional face-to-face screening. The face-to-face screening was combined with the baseline assessment to minimise the number of study visits. At the beginning of the day, patients were tested in a standardised off state (12 h since last dopaminergic medication and, if applicable, deep brain stimulation switched off during measurements). At this timepoint, they were screened for dementia (Mini-Mental State Examination score <24) and Parkinson's disease severity. When this was unremarkable, the additional outcomes as outlined below were assessed in the off state. 1 h after ingestion of a suprathreshold dose of levodopa (125% of their morning levodopa equivalent dose), we did assessments in the on state including a graded maximal aerobic exercise test supervised by a cardiologist or sports medicine physician (to exclude contraindications for aerobic exercise).

All patients provided written informed consent at the beginning of the face-to-face test day (eg, before screening tests).

Randomisation and masking

Eligible patients were randomly assigned (in a 1:1 ratio) to either aerobic exercise (aerobic intervention group) or stretching (active control group) by means of a web-based system with minimisation for sex and medication status (treated or untreated) and permuted blocks of varying sizes of more than two (unknown to study personnel). The system was created by an independent statistician and randomisation was done by a study personnel member who was not involved in patient recruitment or assessment or data analysis. Patients were unaware of the content of either treatment group before participation. After randomisation, they were only informed about the content of their allocated programme by their coach, remaining unaware of the intervention in the other group). Patient information stated that the study purpose was to evaluate the effects of exercise on Parkinson's disease symptoms by comparing two home-based exercise programmes, without specifying that one of the programmes was considered a control intervention. Information about the details of both programmes was not provided except for similarities across both groups (coaching, motivational app, home-based exercise three times per week). Both programmes were personalised to the patient's abilities to ensure all eligible patients could complete the programme. Researchers who assessed outcomes or did data analyses were masked to group allocation. Patients were instructed not to talk about the content of their exercise programme during the post-intervention visit and could contact their coach in case of any problems during trial participation.

Procedures

The aerobic exercise group was instructed to cycle on a stationary home-trainer for 30–45 min (30 min aerobic and 15 min warming up and cooling down) at least three times per week, within a predetermined heart rate zone on the basis of their heart rate reserve (HRR; difference between resting heart rate and maximal heart rate).[14] We opted for cycling because this type of exercise is typically well preserved in patients with Parkinson's disease, even in those with severe walking difficulties,[15,16] and has a low risk of falling when patients exercise at home without physical supervision. The home-trainer was enhanced with virtual reality software and real-life videos, creating an exergaming experience. Patients were instructed to cycle at a target heart rate zone, which was gradually increased for goal setting as patients became fitter. Before starting the trial, we decided to use a slightly lower intensity than specified in our trial protocol at the start of the intervention to allow the patients to get used to the equipment as well as the intensity. This change was specified explicitly in the publication of our study design.[11] The lower boundary of the target heart rate zone was set between 50% and 70% of HRR and was gradually increased as patients became fitter during the trial; the upper boundary was set at 80% of HRR. Training heart rate was registered with a chest-bound heart rate monitor and visualised to patients on the connected computer screen for direct feedback.

The active control group was instructed to do stretching, flexibility, and relaxation exercises (strength, balance, aerobic, and functional components were excluded) three times per week for 30 min per session. These exercises were selected from several physiotherapy programmes designed for patients with Parkinson's disease.

Patients in both groups received a customised tablet-based motivational app and coaching (one home visit and additional remote supervision by telephone). The motivational apps were designed specifically for both groups to maintain masking, providing similar items such as training instructions, tips for optimal training effect, support from loved ones via messages, and the opportunity to monitor their progress. The coaching was done according to a standardised manual in both groups and entailed a home visit to instruct the patients on how to use the provided equipment, as well as regular phone calls (every fortnight) to evaluate whether the intervention required adjustments on the basis of both the patient's experience and the objective training data. There were three coaches who supervised both groups. The interventions lasted 6 months.

All exercise activities (including training heart rates) were saved on the bike's computer. Controls registered their completed exercises in the app by ticking boxes of the exercises done. These results were automatically uploaded to a secured website that connected with the motivational app, allowing patients to view their own progress (number of weekly sessions and cumulative number of sessions were displayed for both groups, and additionally time within heart rate zone and average training heart rate for the aerobic exercise group). Coaches could also track exercise performance on the website.

Outcomes were assessed at baseline (T0) and after the 6 months, when the programme was completed (T1). Three trained and certified raters assessed all outcomes for a single patient in real time. Most patients were assessed at both timepoints by the same rater (17 were assessed by a different rater at T0 and T1). Patients were instructed to report adverse events directly to their coach. At the end of the T1 visit, adverse events were also reported retrospectively. Adverse events occurring during the training sessions and any event that could be in any way related to the exercise done were considered possibly related.

Outcomes

The primary outcome was the between-group difference of the motor section score of the sponsored revision of the Movement Disorders Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[17] at T1, measured in a standardised off state (as defined above). The MDS-UDPRS is the most widely used, well validated clinical rating scale for Parkinson's disease. Also, we assessed the MDS-UPDRS motor section at T1 in the subjectively best on state and MDS-UPDRS part IV at T1 as secondary outcomes. Neither of the other sections of the UPDRS (part I: non-motor experiences in daily living and part II: motor experiences in daily living) were assessed. Other prespecified secondary outcomes[12] were the scores at T1 on several motor scales (Mini-Balance Evaluation Systems test, Timed Up and Go, Six-minute-walk test, pegboard and fingertapping, fall frequency) and non-motor scales (Hamilton Anxiety and Depression Scale, sleep section of Scales for Outcomes in Parkinson's disease [SCOPA], Fatigue Severity Scale, gastrointestinal section of the SCOPA Autonomic scale, Montreal Cognitive Assessment, Trial Making Test, Test of Attentional Performance), quality of life (Parkinson's Disease Questionnaire-39), cardiovascular fitness (VO_2 max with graded maximal exercise testing), and adherence to the prescribed intervention (appendix pp 87–89). All tests, except for the graded maximal exercise test, which was used to measure cardiovascular fitness, were done in a standardised off state.

Statistical analysis

The power calculation is detailed elsewhere.[12] Our study was powered to show an effect of aerobic exercise on MDS-UPDRS motor scores after 6 months. The minimal clinically important difference on the MDS-UPDRS motor score was not yet defined at the time of the power calculation (in 2015, a within-group change of 4·63 was suggested to indicate a relevant worsening and a 3·25 difference a relevant improvement);[18] instead, we used data from the UPDRS motor score that indicated 2·5 as a minimal difference, 5·2 as a moderate, and 10·8 as a large clinically important difference for patients with Parkinson's disease with moderate disease severity.[19,20] Combining this with unpublished data from our previous feasibility study in patients with early Parkinson's disease where a between-group difference of 5 points was observed at our site (note that the published data reflected the combined data from our centre with a second site),[21] a difference of 3·5 points between intervention and active controls on the MDS-UPDRS motor score (tested off) was deemed clinically relevant. The SD from our feasibility study (9 points) was used and our power calculation considered our planned analysis method, by means of an analysis of covariance (ANCOVA) in which baseline measurements served as a covariates, reducing the needed sample size.[22] Taken together, a sample size of 65 patients per group was needed to obtain a power of 80% and to accommodate an attrition rate of 18–20%.

The primary and secondary outcomes were analysed with ANCOVA, with group allocation, sex, and treatment status as fixed factors and baseline values of the dependent variables, age at baseline, Hoehn and Yahr stage at baseline, and disease duration as covariates. Analyses were done on an intention-to-treat basis in patients who completed the follow-up assessment, regardless of whether they completed the assigned intervention. Missing data for the primary outcome were imputed by

means of multiple imputation techniques (five imputed datasets, missing at random for reasons unrelated to the data). Additionally, a second imputation analysis was done in which the scenario of missing data not at random was tested and delta-adjustment was done assuming a progression of MDS-UPDRS motor score for patients who dropped out. Natural progression over 6 months is estimated at 2–3 points;[23] therefore, 3 points were added to the imputed dataset for patients who dropped out. Multiple imputations done in an ANCOVA model are solely based on data from similar patients in the database and not on baseline values of the imputed variable. Therefore, we additionally did a linear mixed-model analysis with the same covariates as in the ANCOVA analysis. Sensitivity analyses were also done to assess the influence of inter-rater variability and unmasking of patients. Analyses were done with a two-tailed α of 0·05 in IBM SPSS statistics version 25.0.

To ascertain the optimal effect of aerobic exercise, an additional per-protocol analysis was done including all patients who completed the programme. Adherence to the programme was analysed according to intention to treat. Adherence to the prescribed intensity (heart rate zone) was analysed per protocol. This study is registered with the Dutch Trial Registry, NTR4743.

The role of the funding source

The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or in the preparation and submission of the manuscript. The first author and the corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Inclusion occurred between Feb 2, 2015, and Oct 27, 2017. We screened 429 potential participants by telephone, which led to an additional face-to-face screening in 139 patients. Four individuals declined to participate and five met one or more exclusion criteria (figure). In total, 130 patients were included and randomly assigned to either aerobic exercise (n=65) or active control (n=65; figure). Five patients were lost to follow-up and therefore had no available data for the primary outcome analysis (figure). The technical challenges most frequently encountered in the intervention group that led to discontinuation of the intervention included failure of the Bluetooth connection between the heart rate monitor and the bike computer and failure of the software on the bikes due to incompatibility with updated operating systems owing to the long duration of the trial. 20 patients (ten in each group) did not complete their allocated exercise programme but attended the post-intervention visit after 6 months and were therefore included in the data analysis (figure). This resulted in a total attrition rate of 19%: 22% for aerobic exercise and 17% for active controls (not significant). After study completion, 112 (93%) of 120 patients were still unaware of the intervention content of the other group.

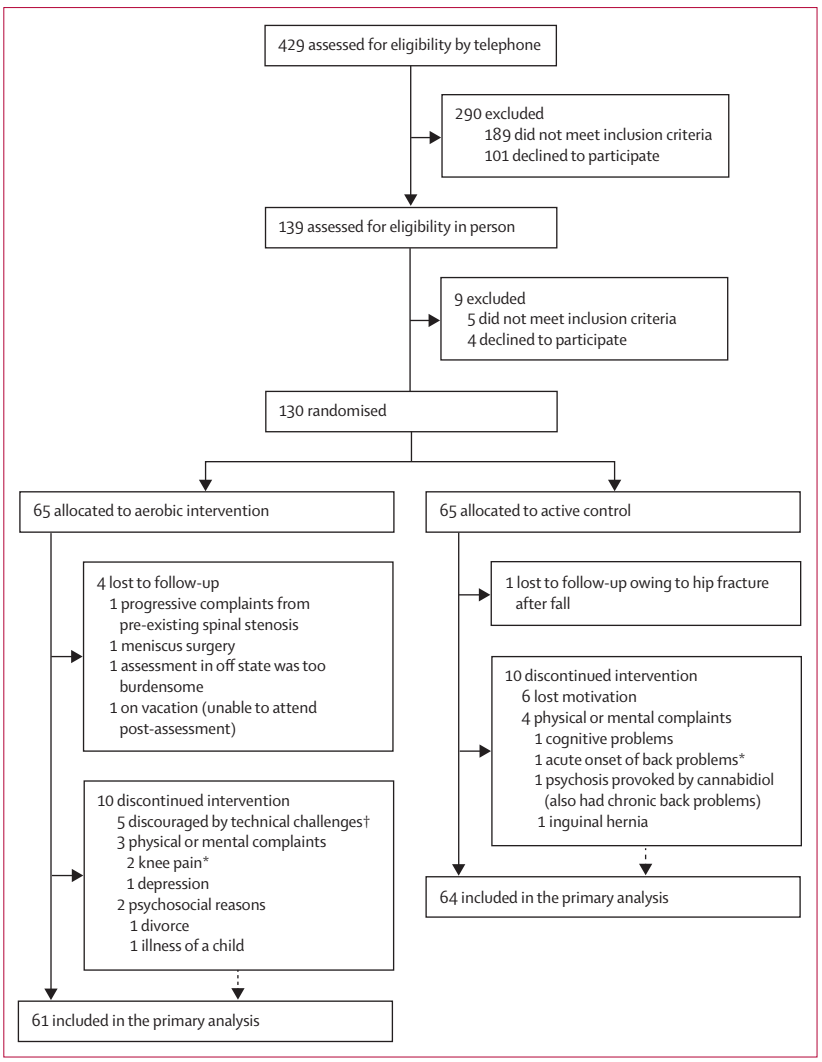

***Figure*: Trial profile**

The primary analysis was done with an intention-to-treat principle, however for the five drop-outs no outcome scores were available. The analysis was done in patients who completed the follow-up assessment, regardless of whether they completed the assigned intervention. *The acute back problems and the knee pain were deemed adverse events that could possibly be related to the exercise programme. †See appendix p 90 for details.

Baseline characteristics were similar across both groups (table 1). The increase in MDS-UPDRS motor score tested in the off state between baseline and 6 months was significantly smaller in the aerobic exercise group (1·3 points) compared with controls (5·6 points), resulting in a between-group adjusted mean difference of 4·2 points (95% CI 1·6–6·9; p=0·0020) in favour of aerobic exercise.

Exercise frequency, duration, and intensity are shown in table 2. During the 6 months, aerobic exercise was done during a mean of 54 sessions (SD 29) and stretching during a mean of 60 sessions (SD 28)—corresponding to 75% and 83% of the expected 72 sessions for each group, respectively. Physical fitness improved in the aerobic exercise group (within-group change in VO_2 max

	Aerobic intervention group (n=65)	Active control group (n=65)
Mean age, years	59·3 (8·3)	59·4 (9·3)
Sex		
Female	23 (35%)	27 (42%)
Male	42 (65%)	38 (58%)
Body-mass index	25·9 (3·9)	25·6 (4·3)
Years of education	15·1 (4·0)	16·1 (4·5)
Work situation		
Paid work	16 (25%)	23 (35%)
Retired	21 (32%)	28 (43%)
(Partially) unemployed due to medical issues	20 (31%)	14 (22%)
Unemployed due to other reasons	3 (5%)	0
Marital status		
Married or cohabiting	55 (85%)	53 (82%)
Single	10 (15%)	12 (18%)
Disease duration, months since diagnosis	41 (16–87)	38 (19–81)
Hoehn and Yahr stage in off state		
1	4 (6%)	3 (5%)
2	61 (94%)	62 (95%)
Movement Disorders Society-Unified Parkinson's Disease Rating Scale-III score in off state*	29·5 (15·7)	27·2 (14·8)
Patients on dopaminergic therapy	61 (94%)	63 (97%)
Levodopa equivalent dose, mg	600 (375–890)	532 (300–838)
Patients with advanced therapies†	4 (6%)	2 (3%)
Montreal Cognitive Assessment score‡	26·3 (2·2)	26·3 (2·5)
VO_2 max , mL/kg per min§	26·4 (6·6)	26·0 (6·3)
Good cardiovascular fitness¶	13 (20%)	17 (26%)

Data are n (%), median (IQR), or mean (SD). *The MDS-UPDRSIII is a composite score of 33 items on a 5-point Likert scale scored 0–4 indicating the severity of Parkinson's disease motor symptoms. Higher scores reflect more Parkinson's disease motor symptoms. †All patients with advanced therapy had deep brain stimulation. ‡The Montreal Cognitive Assessment is an education-adjusted scale of global cognitive functioning with a maximum total score of 30. §The VO_2 max is the maximal aerobic power in mL oxygen consumed per kg of bodyweight per min. ¶Good cardiovascular fitness is based on VO_2 max reference scores adjusted for age and sex.

Table 1: **Characteristics of patients at baseline**

	Aerobic intervention group (n=65)	Active control group (n=65)
Frequency		
Number of participants at different exercise frequencies		
≥3 times per week	16 (25%)	24 (37%)
2–3 times per week	35 (54%)	34 (52%)
<2 times per week	14 (22%)	7 (11%)
Median number of sessions per week	2·6 (2·0–2·9)	2·8 (2·4–3·1)
Duration		
Median number of weeks exercised	22 (16–25)	23 (19–25)
Median time per session, h:min:s	0:33:34 (0:31:28–0:36:38)	NA
Intensity		
Median time per session within prescribed heart rate zone, h:min:s	0:29:11 (0:27:47–0:30:08)	NA
Mean training heart rate as a percentage of heart rate max	76·4% (8·2)	NA
Mean training heart rate as a percentage of heart rate reserve	57·0 % (9·6)	NA

Data are n (%), median (IQR), or mean (SD). Heart rate reserve=difference between resting heart rate and maximal heart rate. Results are calculated over the weeks that the patients actually did the exercise (ie, excluding weeks in which they were unable to exercise because of vacation or illness). Frequency and duration analyses include all patients (n=130); intensity is analysed per-protocol and includes only patients who completed the aerobic intervention (n=51). NA=not available.

Table 2: **Adherence outcomes**

2·0 mL/kg per min), whereas it decreased in controls (–0·4 mL/kg per min), resulting in a between-group adjusted mean difference of 2·4 mL/kg per min (95% CI 1·1–3·7). All other secondary outcomes showed no between-group differences (table 3). Medication changes were made in both groups without a significant difference between the groups (table 3).

27 adverse events occurred in 23 patients in the aerobic exercise group and 29 adverse events occurred in 21 patients in the active control group. Although most events were unrelated to the exercise, a potential relationship could not be excluded in seven (11%) patients in the aerobic exercise group and four (6%) in the active control group. These potentially related events included arthralgia or back pain (n=2 [3%] in the aerobic group and n=4 [6%] in the control group) or palpitations (n=4 [6%] in the aerobic group) and mostly concerned a worsening or reoccurrence of a pre-existing condition. For three patients, these adverse events were reason to discontinue their intervention. There were seven serious adverse events (three for aerobic exercise [vestibilar disorder, vasovagal collapse, knee injury during gardening that required surgery] and four among active controls [supraventricular tachycardia, hip fracture, fall related injury, severe dyskinesias after suprathreshold dose levodopa in a patient with deep brain stimulation]); all were unrelated to the exercise program (table 4; appendix pp 90–91). Two serious adverse events resulted in loss to follow-up and discontinuation of the intervention (hip fracture after a fall in the garden and a knee injury sustained during gardening which required surgery). Results from sensitivity analyses are detailed in the appendix (p 90).

Discussion

This double-blind, randomised controlled trial involving patients with Parkinson's disease with mild disease severity shows that a multifaceted aerobic exercise

	Baseline		6 months		Within-group change from baseline after 6 months		Between-group difference in change from baseline	
	Aerobic intervention group (n=65)	Active control group (n=65)	Aerobic intervention group (n=65)	Active control goup (n=65)	Aerobic intervention group (n=65)	Active control group (n=65)	Available data	p value
Primary outcome								
MDS-UPDRS III, motor score in the off state*	29·5 (2·7)	27·2 (2·7)	29·0 (2·5)	31·4 (2·5)	1·3 (1·8)	5·6 (1·9)	−4·2 (1·3; −6·9 to −1·6)	0·0020
Secondary outcomes								
Physical fitness								
VO_2 max, mL/kg per min†	26·6 (1·1)	26·3 (1·1)	28·1 (1·2)	25·8 (1·2)	2·0 (0·9)	−0·4 (0·9)	2·4 (0·7; 1·1 to 3·7)	<0·0001
Motor symptoms								
MDS-UPDRS III, motor score in the on state*	19·4 (1·8)	17·4 (1·8)	21·2 (2·0)	20·3 (2·0)	1·5 (0·8)	2·8 (0·8)	−1·2 (1·1; −3·4 to 0·9)	0·26
MDS-UPDRS IV, motor complications score*	2·7 (0·6)	3·1 (0·6)	3·3 (0·9)	3·6 (0·9)	−0·4 (0·7)	−0·4 (0·7)	−0·04 (0·5; −1·0 to 0·9)	0·94
Number of falls	4·3 (0·9)	3·0 (0·9)	2·3 (0·9)	4·5 (0·9)	−2·1 (3·7)	−0·7 (1·8)	−1·3 (4·1; −12·8 to 0·1)	0·76
6-min walk test, m	499·4 (18·2)	486·4 (18·2)	510·6 (17·7)	492·8 (17·7)	−11·3 (11·8)	−15·6 (12·2)	4·3 (8·8; −13·0 to 21·6)	0·62
Timed Up and Go test, s	8·3 (0·5)	8·7 (0·5)	8·2 (0·5)	8·6 (0·5)	0·5 (0·4)	0·7 (0·4)	−0·2 (0·3; −0·7 to 0·3)	0·49
Mini-Balance Evaluation Systems Test‡	24·3 (0·6)	24·2 (0·6)	24·4 (0·6)	24·5 (0·6)	0·5 (0·5)	0·5 (0·5)	−0·03 (0·4; −0·7 to 0·7)	0·94
Pegboard test for the most affected side, s§	19·5 (0·9)	19·6 (0·9)	18·8 (0·7)	19·4 (0·7)	−0·4 (0·7)	−0·04 (0·7)	−0·4 (0·5; −1·4 to 0·6)	0·44
Finger Tapping Test for the most affected side, number of cycles§	65·8 (6·4)	72·6 (6·4)	65·7 (6·4)	73·3 (6·4)	−4·9 (7·2)	−1·6 (7·4)	−3·3 (5·3; −13·7 to 7·2)	0·54
Quality of life								
Parkinson's Disease Questionnaire 39 summary index score¶	24·9 (2·2)	24·0 (2·2)	26·0 (2·3)	26·3 (2·3)	−0·2 (1·9)	0·0 (1·9)	−0·2 (1·5;−3·2 to 2·8)	0·91
Non-motor symptoms								
Hospital Anxiety and Depression Scale depression score‖	4·2 (0·5)	3·6 (0·5)	4·5 (0·6)	4·2 (0·6)	0·5 (0·6)	0·7 (0·6)	−0·3 (0·6; −1·2 to 0·6)	0·55
Hospital Anxiety and Depression Scale anxiety score‖	4·2 (0·6)	5·2 (0·6)	4·1 (0·5)	4·2 (0·5)	0·05 (0·5)	0·2 (0·5)	−0·1 (0·4; −1·0 to 0·7)	0·74
Scales for Outcomes in Parkinson's Disease—sleep, day**	3·2 (0·6)	4·1 (0·6)	3·5 (0·6)	3·9 (0·6)	0·1 (0·5)	−0·5 (0·5)	0·6 (0·4; −0·3 to 1·4)	0·20
Scales for Outcomes in Parkinson's Disease—sleep, night**	4·4 (0·6)	4·6 (0·6)	4·6 (0·6)	4·6 (0·6)	−0·1 (0·7)	−0·2 (0·7)	0·1 (0·5; −0·9 to 1·1)	0·85
Fatigue Severity Scale scale††	3·7 (0·2)	3·9 (0·2)	3·7 (0·2)	3·7 (0·2)	0·5 (0·3)	0·4 (0·3)	0·1 (0·2; −0·3 to 0·5)	0·52
Scales for Outcomes in Parkinson's Disease—autonomic dysfunction, constipation questions‡‡	1·6 (0·3)	1·6 (0·3)	1·6 (0·3)	1·5 (0·3)	0·03 (0·3)	−0·1 (0·3)	0·1 (0·2; −0·3 to 0·5)	0·50
Trail Making Test—Part A, s§§	39·1 (2·9)	40·3 (2·9)	35·5 (2·6)	37·9 (2·6)	−5·9 (2·5)	−4·0 (2·6)	−2·0 (1·8; −5·6 to 1·7)	0·29
Trail Making Test—Part B, s§§	95·0 (9·3)	92·2 (9·3)	83·8 (9·1)	90·6 (9·1)	−13·8 (9·3)	−4·0 (9·5)	−9·8 (6·7; −23·0 to 3·5)	0·15
Test of Attentional Performance Flexibility—baseline conditions, median reaction time, s¶¶	590·6 (35·0)	586·6 (35·0)	645·5 (25·4)	656·8 (25·4)	63·3 (31·4)	77·0 (32·9)	−13·6 (23·7; −60·7 to 33·4)	0·57
Test of Attentional Performance Flexibility—alternating conditions, total performance index¶¶	−3·5 (2·2)	−4·4 (2·2)	−3·6 (1·9)	−5·6 (1·9)	0·1 (1·9)	−0·5 (2·0)	0·5 (1·5; −2·4 to 3·4)	0·71
Cognitive domain score—Flexibility‖‖	0·004 (0·2)	−0·03 (0·2)	0·01 (0·1)	−0·06 (0·1)	0·03 (0·08)	-0·05 (0·08)	0·08 (0·06; −0·03 to 0·2)	0·17
Cognitive domain score—Psychomotor speed‖‖	−0·01 (0·1)	−0·003 (0·1)	0·3 (0·1)	0·2 (0·1)	0·4 (0·1)	0·4 (0·1)	0·04 (−0·1; −0·1 to 0·2)	0·64
Montreal Cognitive Assessment	26·3 (0·4)	26·3 (0·4)	25·7 (0·5)	25·9 (0·5)	−0·3 (0·6)	−0·1 (0·6)	−0·2 (0·4; −1·0 to 0·7)	0·70
Explanatory variable***								
Levodopa equivalent dose, mg	653·7 (75·7)	644·1 (75·7)	696·9 (81·7)	714·7 (81·7)	47·8 (34·7)	71·1 (35·3)	−23·3 (24·2; −71·2 to 24·7)	0·34

Data are mean (SE) or mean (SE; 95% CI). p values and 95% CIs for secondary outcomes are not adjusted for multiple comparisons and cannot be used for hypothesis testing or inference. Post-hoc adjustment for multiple comparisons of secondary outcomes by means of the Bonferroni method requires a significance level of p<0·002. The displayed mean baseline SEs are the uncorrected values for both groups. MDS-UPDRS=Movement Disorders Society—Unified Parkinson's Disease Rating Scale. *Higher scores reflect greater severity of Parkinson's disease signs or more complications. †The VO_2 max measures maximal aerobic power and higher scores reflect better cardiovascular fitness. ‡Higher scores reflect better balance. §Both outcomes are shown for the side that is most affected by their Parkinson's disease. ¶Higher scores correspond with a poorer health-related quality of life. ‖Higher scores reflect more symptoms of anxiety and depression. **Higher scores reflect more severe sleep problems and sleepiness. ††Higher scores reflect more complaints of fatigue. ‡‡Higher scores reflect more constipation. §§Higher scores reflect poorer performance on executive functioning. ¶¶Higher scores reflect fewer errors and shorter reaction times. ‖‖Higher scores reflect better cognitive performance. ***Data included to suggest a reason for the difference in MDS-UPDRS motor score.

Table 3: **Primary and secondary outcomes (by intention to treat)**

	Aerobic intervention (n=65)	Active control (n=65)
Adverse events	23 (35%)	21 (32%)
Possibly related to exercise	7 (11%)	4 (6%)
Possibly related to exercise, severity greater than mild	1 (2%)	1 (2%)
Most common events		
Arthralgia and back pain	4 (6%)	3 (4%)
Vasovagal reaction during first visit	2 (3%)	2 (3%)
Fall (related injury)	2 (3%)	2 (3%)
Palpitations	4 (6%)	0
Arrhythmias	0	2 (3%)
Organ systems affected in >5% of participants in a single group		
Musculoskeletal and connective tissue disorders	7 (11%)	8 (12%)
Musculoskeletal and connective tissue disorders, severity greater than mild	4 (6%)	2 (3%)
Cardiac disorders	4 (6%)	2 (3%)
Cardiac disorders, severity greater than mild	0	1 (1%)
Nervous system disorders	2 (3%)	5 (8%)
Nervous system disorders, severity greater than mild	2 (3%)	4 (6%)
Serious adverse events		
Musculoskeletal	1 (2%)	0
Cardiac disorders	0	1 (2%)*
Nervous system disorders	1 (2%)	0
Injury, poisoning and procedural complications	0	3 (5%)
Ear and labyrinth disorders	1 (2%)	0

Data are n (%). *One patient had two events.

Table 4: **Number of patients with adverse events and serious adverse events**

programme done at home attenuates MDS-UPDRS motor scores compared with stretching, flexibility, and relaxation exercises. Specifically, the off-state MDS-UPDRS motor score showed a between-group difference of 4·2 points in favour of aerobic exercise. This difference is similar to previous studies that tested institution-based aerobic exercise programmes but that required fairly intensive supervision.[11,21] For example, in an institution-based aerobic exercise trial (SPARX), newly diagnosed and unmedicated patients with Parkinson's disease received full supervision during the first 2 weeks and were thereafter supervised at least twice a month.[11] By contrast, the effect in this trial was achieved by means of a home-based exercise programme with minimal remote supervision. Nevertheless, adherence to the home-based intervention was good. Aerobic exercise frequency was comparable with two previous home-based aerobic exercise trials.[24,25] Attrition rates were comparable with previous laboratory-based exercise trials[7,8,11] and a (partly) home-based trial.[25] Importantly, our high exercise intensity[10] was similar to laboratory-based trials[7,8,11] and higher compared with a previous (partly) home-based trial,[25] underlining the feasibility of our multifaceted approach. Active controls showed a similarly good compliance as the aerobic exercise group, thus reducing the risk of off-protocol exercises among patients assigned to the control group.[26] Being able to exercise at home might be an important facilitator for prolonged adherence to exercise programmes and to achieve sustained improvements in patient functioning. Besides the home-based setting, we added several components to our intervention to increase adherence (remote supervision by sports coaches, a motivational app, and gamification of the intervention itself). Informed by our successful pilot study,[27] the entire package was introduced to promote compliance but this itself was not the object of study. The specific added value of this multifaceted approach over simple home-based exercise without motivation and the relative influence of its individual components must be established in future studies.

Our results strengthen previous evidence on the beneficial effects of aerobic exercise on Parkinson's disease symptoms. Without valid and reliable biomarkers of disease progression, the MDS-UPDRS motor section is often used as a proxy. The downside is that this score might be contaminated by medication effects,[26] especially when tested while in the on state. We therefore used a standardised off state to score motor signs to better clarify how the intervention affected the disease itself and to minimise medication confounding. The time between last medication intake and testing was similar in each group and similar for both assessments. Changes in medication throughout the trial (expressed as levodopa equivalent dose) were similar across both groups, so this is an improbable explanation for the observed between-group difference in MDS-UPDRS motor score tested in the off state. The attenuated worsening in motor performance after aerobic exercise is considered clinically relevant[18,28] and within the range of symptomatic pharmacological treatment effects. For example, the effect of levodopa initiated in early Parkinson's disease ranges between 3·8 and 6·6 points depending on the prescribed dose.[29]

The present study confirms and extends the results of the SPARX study[11] to people who are medicated and have had deep brain stimulation. This is an important finding with high clinical relevance. Increases over time in UPDRS motor scores in people with mild disease severity are less steep than in de-novo patients with Parkinson's disease,[30] making it more difficult to achieve similar effects. Whether even more advanced patients will equally benefit from our intervention should be investigated further. Additionally, compared with the single-blind design with a wait-list control group in the SPARX trial, we used a double-blind design with a rigorously monitored non-aerobic control group, and this adds to the robustness of the observed beneficial effect in our trial. The present study also extends the findings from a treadmill to a cycle, which is again important. Also, our findings suggest that the exercise effects are robust to how target heart rate is calculated—by means of HRR in this study versus

percentage of measured maximal heart rate in the SPARX study. Finally, the present study confirms and extends the results from a highly supervised health-club setting to a home-based setting with minimal remote supervision, thus increasing external validity. Taken together, there are now two studies with sample sizes of greater than 40 participants, thus building a strong body of evidence for the benefits of endurance exercise.

By contrast with the large differences in off scores, there was no significant effect in MDS-UPDRS motor scores in the on state in favour of aerobic exercise. Specifically, exercise afforded only a small attenuation of motor symptoms in the on state (a difference of 1·2 points on the MDS-UPDRS) and this difference is not clinically relevant. This could be interpreted as a limitation of the clinical relevance of exercise, since ideally an effect would be observed over and above optimal medication.[31] However, clear effects in the off state are certainly relevant from a patient perspective because, with disease progression, most patients on dopaminergic medication will have fluctuations in UPDRS motor scores due to the wearing off phenomenon, unpredictable off periods, dose failures, and nocturnal off periods (when patients regularly have to walk to the bathroom because of nycturia). We are uncertain why exercise exerted a relatively greater effect on symptoms seen during the off phase compared with the on phase. A possible explanation is that the symptomatic effects of exercise are mediated primarily by restoration of dopaminergic transmission,[32] which would be best visible during the off phase. Levodopa presumably has a relatively stronger effect on dopaminergic transmission, and this would then override the smaller dopaminergic effects of exercise in the on phase.

Other motor and non-motor symptoms tested in our study showed no between-group differences, perhaps because baseline values were relatively good (creating a possible ceiling effect) or because aerobic exercise alone is not able to improve these symptoms. As previously suggested, a combination of task-specific exercise, cognitive engagement, and aerobic exercise might be required for an effect on functional mobility, as measured with tests such as the Timed Up and Go test and Mini-Balance Evaluation System Test.[33] Previous studies that used task-specific aerobic training (ie, gait-based exercise) did show improvements on these outcomes.[4,8] Our intervention involved a generic aerobic exercise without specific gait or balance training, possibly explaining the lack of effect on the secondary motor outcomes. However, two earlier cycling studies did show an improvement on the 6-min walking test (as measured in the on state),[5,34] which is probably a reflection of improved physical fitness. The discrepancy with our findings might be attributed to the fact that their baseline and follow-up scores were considerably worse compared with ours, suggesting the possibility of a ceiling effect in our relatively mildly affected study population.

The absence of effect on several non-motor domains is most probably explained by the relatively short duration of the intervention tested here, in combination with the good baseline values set against the slowly progressive nature of Parkinson's disease. More prolonged interventions and larger sample sizes might be required to achieve tangible improvements in non-motor domains such as cognition. We would also expect that a sustained improvement in non-motor domains—which affect quality of life considerably—might be needed to achieve a tangible improvement in quality of life. Another explanation for the absence of change in secondary outcomes is that the observed effect on MDS-UPDRS motor score in the off state was a coincidental finding, rather than a true effect. However, we consider this improbable, given the positive results of the SPARX trial (which found a dose-dependent effect of aerobic exercise on UPDRS motor scores) and considering the excellent treatment compliance (and resultant good exercise effort) provided by our participants, as reflected by their significantly improved physical fitness.

We observed a weak but significant correlation between the increase in physical fitness (as measured with the VO_2 max) and the attenuation in MDS-UPDRS motor scores tested in the off state, suggesting a genuine effect of aerobic exercise on motor signs. The underlying mechanisms of exercise-induced brain health benefits are still poorly understood but presumably involve angiogenesis, increased neurotrophic factors, activation of the immune system, and improved mitochondrial function. These circumstances create an optimal environment for neuroplasticity to occur. Parkinson's disease animal studies show enhanced corticostriatal neurotransmission and reduced symptomatology after aerobic exercise.[32]

Masking in non-pharmacological studies is virtually impossible because the intervention is obvious to those who receive it and sham procedures are usually not available. Unequal placebo effects from insufficient or absence of masking can seriously threaten trial validity.[35] By withholding information about the exact content of the interventions and the hypothesis of our trial, we tried to provide the best alternative to a double-blind non-pharmacological intervention study. Only a few exercise trials in Parkinson's disease have pursued this alternative double-blind methodology before, but with qualified success.[25] To diminish the effect of unmasking the assessors, the primary outcome was always the first test done during follow-up. Patients were unaware of the content of the other exercise programme in 93% of cases, providing the best masking of trial hypothesis in Parkinson's disease exercise trials so far. Moreover, excluding unmasked patients from the analysis resulted in even larger between-group differences. It is therefore improbable that placebo effects explain our findings.

There are risks when prescribing exercise for patients with Parkinson's disease, especially when it is home based, strenuous, and with minimal supervision. The

main concerns are musculoskeletal injuries, cardiac events, and falls. In our trial, only two falls occurred, both of which were unrelated to the exercise. However, musculoskeletal complaints occurred frequently in both exercise programmes (11·5%) but were unrelated to the programme in 60% cases and of mild severity in all but one patient. These numbers do not seem to differ from the healthy older population, although data for musculoskeletal complaints from exercise are scarce in this population. The thorough cardiac evaluation before participation reduced the risk of ischaemic cardiac events in our trial; the main cardiac events reported were palpitations and arrhythmias. These are not specific to the Parkinson's disease population and probably reflect an age-related risk. Only one patient had an arrhythmia that required medical treatment. Taken together, our intervention can be considered safe for patients with Parkinson's disease of mild severity, with a small and acceptable risk of exercise-related injuries.

Our trial has several limitations. First, the use of innovative techniques such as motivational apps or exergaming comes with challenges, especially in an older population. We used technological innovations to objectively measure adherence, to motivate patients to exercise, and to improve their performance. Occasional technical failures discouraged some patients, leading to drop-outs (n=5). Second, establishing physical activity levels on the basis of questionnaires remains challenging and is not a good estimate for physical fitness. We included several patients who turned out to have good cardiovascular fitness at baseline, introducing a ceiling effect when trying to improve VO_2 max. Finally, we do not know whether the observed effect on motor symptoms persisted beyond the intervention because no follow-up assessment was done.

In conclusion, the Park-in-Shape trial provides level 1 evidence that aerobic exercise attenuates motor symptoms in Parkinson's disease and improves cardiovascular fitness. The good compliance makes this home-based intervention suitable for further studies with larger sample sizes, longer intervention periods, and several post-intervention visits, aiming to examine possible effects on motor scores while on medication and on non-motor symptoms and to examine the sustainability of the effects. Finally, encouraged by experimental work in rodents, which offered preliminary evidence that exercise could beneficially alter the neurodegenerative process,[32] future studies could use similar home-based programmes to examine possible disease-modifying effects in humans.

Contributors

NMK and BRB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NMK, BRB, and BP were responsible for the concept and design. NMK, NMV, RPCK, HJ, AHZ, BP, and BRB did the acquisition, analysis, and interpretation of the data. The first draft was written by NMK, with input from all authors. Data analysis was done by NMK, with oversight by AHZ. NMK and BRB obtained funding. BRB, BP, and NMV were responsible for supervision.

Declaration of interests

BRB has no conflicts of interests with relevance to the study. His other disclosures are as follows. He serves as Associate Editor for the *Journal of Parkinson's Disease*, serves on the editorial board of *Practical Neurology* and *Digital Biomarkers*, has received honoraria from serving on the scientific advisory board for Abbvie, Biogen, UCB, and Walk with Path, has received fees for speaking at conferences from AbbVie, Zambon, Roche, and Bial, and has received research support from the Netherlands Organization for Scientific Research, the Michael J Fox Foundation, UCB, Abbvie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, and the Parkinson Vereniging. BP receives funding from the Movement Disorders Society, Parkinson Vereniging and the European Commission Fair-Park2 grant N° 633190 of the H2020 programme; NCT02655315. No Honoraria. RPCK has no disclosures or conflicts of interest in relation to this study. He receives support from the Gravitation Grant 024.001.006 of the Language in Interaction Consortium of the Netherlands Organization for Scientific Research. He serves on the editorial board of the *Journal of the International Neuropsychological Society* and *Cognitive Processing*. NMK received a travel grant from the Movement Disorders Society to present the preliminary results of the present article at the International Congress of Parkinson's Disease and Movement Disorders in Hong Kong in October 2018. NMV, HJ and AHZ have no conflicts of interest.

Data sharing statement

De-identified participant data will be made available by the corresponding author to colleagues who propose a reasonable scientific request.

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References

1 Dorsey ER, Bloem BR. The Parkinson pandemic-a call to action. *JAMA Neurol* 2018; **75:** 9–10.

2 Ahlskog JE, Uitti RJ. Rasagiline, Parkinson neuroprotection, and delayed-start trials: still no satisfaction? *Neurology* 2010; **74:** 1143–48.

3 Altmann LJ, Stegemoller E, Hazamy AA, et al. Aerobic exercise improves mood, cognition, and language function in Parkinson's disease: results of a controlled study. *J Int Neuropsychol Soc* 2016; **22:** 878–89.

4 Cugusi L, Solla P, Serpe R, et al. Effects of a Nordic walking program on motor and non-motor symptoms, functional performance and body composition in patients with Parkinson's disease. *NeuroRehabilitation* 2015; **37:** 245–54.

5 Ferraz DD, Trippo KV, Duarte GP, Neto MG, Bernardes Santos KO, Filho JO. The effects of functional training, bicycle exercise, and exergaming on walking capacity of elderly patients with Parkinson disease: a pilot randomized controlled single-blinded trial. *Arch Phys Med Rehab* 2018; **99:** 826–33.

6 Marusiak J, Fisher BE, Jaskolska A, et al. Eight Weeks of Aerobic Interval Training Improves psychomotor function in patients with Parkinson's disease-randomized controlled trial. *Int J Env Res Public Health* 2019; **16**.

7 Schenkman M, Hall DA, Baron AE, Schwartz RS, Mettler P, Kohrt WM. Exercise for people in early- or mid-stage Parkinson disease: a 16-month randomized controlled trial. *Phys Ther* 2012; **92:** 1395–410.

8 Shulman LM, Katzel LI, Ivey FM, et al. Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. *JAMA Neurol* 2013; **70:** 183–90.

9 Uhrbrand A, Stenager E, Pedersen MS, Dalgas U. Parkinson's disease and intensive exercise therapy—a systematic review and meta-analysis of randomized controlled trials. *J Neurol Sci* 2015; **353:** 9–19.

10 Lamotte G, Rafferty MR, Prodoehl J, et al. Effects of endurance exercise training on the motor and non-motor features of Parkinson's disease: a review. *J Parkinsons Dis* 2015; **5:** 21–41.

11 Schenkman M, Moore CG, Kohrt WM, et al. Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo Parkinson disease: a phase 2 randomized clinical trial. *JAMA Neurol* 2018; **75:** 219–26.

12 van der Kolk NM, Overeem S, de Vries NM, et al. Design of the Park-in-Shape study: a phase II double blind randomized controlled trial evaluating the effects of exercise on motor and non-motor symptoms in Parkinson's disease. *BMC Neurol* 2015; **15:** 56.

13 Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007; **39:** 1435–45.

14 Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn* 1957; **35:** 307–15.

15 Snijders AH, Bloem BR. Images in clinical medicine. Cycling for freezing of gait. *N Engl J Med* 2010; **362:** e46.

16 Snijders AH, van Kesteren M, Bloem BR. Cycling is less affected than walking in freezers of gait. *J Neurol Neurosurg Psychiatry* 2012; **83:** 575–76.

17 Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008; **23:** 2129–70.

18 Horvath K, Aschermann Z, Acs P, et al. Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. *Parkinsonism Relat Disord* 2015; **21:** 1421–26.

19 Schrag A, Sampaio C, Counsell N, Poewe W. Minimal clinically important change on the unified Parkinson's disease rating scale. *Mov Disord* 2006; **21:** 1200-7.

20 Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol* 2010; **67:** 64–70.

21 van der Kolk NM, de Vries NM, Penko AL, et al. A remotely supervised home-based aerobic exercise programme is feasible for patients with Parkinson's disease: results of a small randomised feasibility trial. *J Neurol Neurosurg Psychiatry* 2017.

22 Teerenstra S, Eldridge S, Graff M, de Hoop E, Borm GF. A simple sample size formula for analysis of covariance in cluster randomized trials. *Stat Med* 2012; **31:** 2169–78.

23 Poewe W. Clinical measures of progression in Parkinson's disease. *Mov Disord* 2009; **24** (Suppl 2)**:** S671–76.

24 Canning CG, Allen NE, Dean CM, Goh L, Fung VS. Home-based treadmill training for individuals with Parkinson's disease: a randomized controlled pilot trial. *Clin Rehabil* 2012; **26:** 817–26.

25 Uc EY, Doerschug KC, Magnotta V, et al. Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting. *Neurology* 2014; **83:** 413–25.

26 Ahlskog JE. Aerobic exercise: evidence for a direct brain effect to slow Parkinson disease progression. *Mayo Clin Proc* 2018; **93:** 360–72.

27 van der Kolk NM, de Vries NM, Penko AL, et al. A remotely supervised home-based aerobic exercise programme is feasible for patients with Parkinson's disease: results of a small randomised feasibility trial. *J Neurol Neurosurg Psychiatry* 2018; **89:** 1003–05.

28 Holden SK, Finseth T, Sillau SH, Berman BD. Progression of MDS-UPDRS scores over five years in de novo Parkinson disease from the Parkinson's Progression Markers Initiative Cohort. *Mov Disord Clin Pract* 2018; **5:** 47–53.

29 Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004; **351:** 2498–508.

30 Schrag A, Dodel R, Spottke A, Bornschein B, Siebert U, Quinn NP. Rate of clinical progression in Parkinson's disease. A prospective study. *Mov Disord* 2007; **22:** 938–45.

31 Rascol O. Physical exercise in Parkinson disease: moving toward more robust evidence? *Mov Disord* 2013; **28:** 1173–75.

32 Petzinger GM, Holschneider DP, Fisher BE, et al. The effects of exercise on dopamine neurotransmission in Parkinson's disease: targeting neuroplasticity to modulate basal ganglia circuitry. *Brain Plast* 2015; **1:** 29–39.

33 Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol* 2013; **12:** 716–26.

34 Burini D, Farabollini B, Iacucci S, et al. A randomised controlled cross-over trial of aerobic training versus Qigong in advanced Parkinson's disease. *Europa Medicophys* 2006; **42:** 231–38.

35 Lidstone SC, Schulzer M, Dinelle K, et al. Effects of expectation on placebo-induced dopamine release in Parkinson disease. *Arch Gen Psychiatry* 2010; **67:** 857–65.