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Exercise response in Parkinson's disease: insights from a cross-sectional comparison with sedentary controls and a per-protocol analysis of a randomised controlled trial

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ABSTRACT

Objectives To investigate the acute and adaptation cardiovascular and metabolic training responses in people with Parkinson's disease (pwP).

Design (1) A cross-sectional study of exercise response of pwP compared with sedentary controls and (2) an interventional study of exercise training in pwP.

Setting Community leisure facilities.

Participants pwP (n=83) and sedentary controls (n=55).

Interventions Study 1 included participants from a two-arm-parallel single-blind phase II randomised controlled trial (RCT), that undertook a baseline maximal incremental exercise test and study 2 included those randomised to the exercise group in the RCT, who completed a 6-month weekly exercise programme (n=37). The intervention study 2 was a prescribed exercise program consisting of sessions lasting 60 min, two times a week over a 6-month period. The control group followed the same protocol which derived the same cardiorespiratory parameters, except that they were instructed to aim for a cadence of ~60 revolutions per minute and the unloaded phase lasted 3 min with an initial step of 25 W.

Primary and secondary outcome measures Stepwise incremental exercise test to volitional exhaustion was the primary outcome measure.

Results Study 1 showed higher maximum values for heart rate (HR), VO_2 L/min, VCO_2 L/min and ventilation L/min for the control group; respiratory exchange ratio (RER), perceived exertion and O_2 pulse (VO_2 L/min/HR) did not differ between groups. In study 2, for pwP who adhered to training (n=37), RER increased significantly and although there was no significant change in aerobic capacity or HR response, reduced blood pressure was found.

Conclusions An abnormal cardiovascular response to exercise was observed in pwP compared to controls. After the exercise programme, metabolic deficiencies remained for pwP. These observations add to the pathogenic understanding of PD, acknowledge an underling metabolic contribution and support that certain cardiovascular symptoms may improve as a result of this type of exercise.

Strengths and limitations of this study

- ► Our study explores for the first time the extent and nature of previously suggested altered cardiovascular and metabolic responses in people with Parkinson's disease using a 6-month exercise intervention in a relatively large sample.
- ► Our findings support previous work that indicate Parkinson's is also a disorder of metabolic and energy-producing systems which would explain fatigue symptoms and provide a more targeted approach for exercise therapies for fatigue and open avenues for drug therapies.
- ► This project was a secondary analysis of a pragmatic trial, with a small number of participants on medications that may have impacted on the exercise response.
- ► There was no direct measurement of mitochondria and autonomic dysfunction for the purpose of this study.

INTRODUCTION

Parkinson's disease (PD) is a progressive disorder primarily associated with motor symptoms resulting from abnormal activity in basal ganglia motor circuits, and also presenting with dysfunctions of the autonomic, metabolic and cardiovascular systems.[1] Pharmaceutical interventions are the primary treatment option, but exercise has been formally recognised as a disease-management option for people with PD (pwP); as such this is an important research area.[2] There is strong evidence supporting beneficial effects of exercise programme both in normal ageing and in PD.[3] In addition, according to research evidence, there is a connection between the frequency of weekly exercise and physical

function in PD.[4] Walking speed, balance and executive function—specifically cognitive flexibility and working memory—of pwP can improve following adherence to a high-frequency exercise programme.[4 5] However, while there is compelling data that exercise benefits motor symptoms,[6] functioning, quality of life and cognition,[4 7] the optimal exercise type and dose is yet to be identified. It is also not clear as to what extent reduced risk of PD is associated with higher physical activity levels,[8] and improvements observed in motor symptoms after exercise interventions can be attributed to metabolic or motor mechanisms.[6 9] Gaining a better understanding of the mechanisms underpinning the exercise effect is important, as it will lead to more targeted and optimal physical activity interventions. Exercise training that involves repetitive movement has been shown to activate neuromuscular systems and improve motor functioning.[7 10] Furthermore, progressive resistance training programme has been found to have a positive effect on cardiovascular autonomic regulation in PD and improve systolic blood pressure response to orthostatic stress.[11] However, less is known about cardiovascular and metabolic responses to exercise training.[1] Previous studies investigating peak responses during cardiopulmonary exercise tests in pwP have contradictory results.[1] Furthermore, while studies have consistently found that exercise capacity is reduced, we do not know the extent to which this is attributable to deconditioning and blunted cardiovascular responses relating to impaired autonomic functioning,[1] or to reduced aerobic metabolic responses because of mitochondrial dysfunction in PD.[1 12 13] Careful comparisons of the cardiovascular and metabolic exercise response and adaption to training with healthy individuals of similar activity levels have yet to be performed.

The aim of this research was to explore the acute cardiovascular and metabolic response to exercise and the extent of their adaptation in response to a 6-month combined strength and cardiovascular training programme for pwP.

METHODS

Design

This research is formed from two studies: (1) a cross-sectional study of exercise response of pwP compared with a sedentary healthy control group and (2) an interventional study of exercise training in pwP.

Data for pwP were obtained from a two-arm-parallel single-blind phase II randomised controlled trial (RCT) (registered with ClinicalTrials.Gov (NCT01439022) of community-delivered exercise for pwP).[9] The cross-sectional study 1 included all participants from the RCT (all participants before randomisation to exercise and handwriting group) that undertook a baseline maximal incremental exercise test and the interventional study 2 included those randomised to the exercise group in the RCT.

Data for the healthy control group for the cross-sectional study of exercise response were obtained from people recruited by the Oxford Cognitive Therapy Centre (https://www.octc.co.uk).

Setting

For the above registered RCT,[9] Parkinson's assessments were carried out at the Movement Science Laboratory, Oxford Brookes University, Oxford, UK. The exercise group's intervention took place at community leisure facilities in Oxfordshire and Berkshire and the control intervention was handwriting practice at participants home. The healthy controls, whose data were used for the baseline comparison (study 1), underwent assessment at the Cardiovascular Clinical Research Facility, John Radcliffe Hospital, Oxford. Both testing centres collaborate on a regular basis and work under similar standard operating procedures (SOPs) and guidance; biocalibrations have been performed between sites to ensure consistency.

Participants

People with idiopathic PD were recruited from neurology clinics and general practitioner practices in the Thames Valley, UK, and though local Parkinson's UK group meetings.

Inclusion criteria for pwP were: (1) diagnosis of idiopathic PD (as defined by the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [14]; (2) able to walk ≥100 m. Exclusion criteria were: (1) dementia; (2) history of additional prior neurological condition; (3) severe depression or psychosis or a mental state that would preclude consistent active involvement with the study over its duration; (4) cardiac precautions that would prevent the subject from participating in the intervention; (5) any known contraindication to exercise; (6) reduced cognitive function of any cause (Mini-Mental State Examination <23) and (7) an orthopaedic condition that limited independent walking. Participants' medication was continued as normal and was recorded.

The control group were recruited from the local via media and poster advertisement. The study received National Health Service ethical approval (NRES Committee South Central—Oxford B Ref: 10/H0605/48). Inclusion criteria for controls were: (1) self-reported participation in fewer than 60 min/week of physical activity sufficient to raise their heart rate (HR), (2) had no known contraindications to MRI scanning or fitness testing (assessed using the Physical Activity Readiness Questionnaire (physical activity R-Q). Exclusion criteria were: (1) a history of major vasculature problems or receiving HR-controlling medication, (2) self-reported history or current investigation of a neurological disorder or symptoms or treatment for a psychiatric illness within the past year and (3) ability to commit to the requirements of study.

Intervention

The intervention for pwP was a prescribed exercise programme consisting of sessions lasting 60 min, two times a week over a period of 6 months. Participants

self-managed their exercise scheduling in relation to their medication; a detailed description can be found.[9] Process data from the RCT would suggest the individuals who underwent the exercise intervention were able to manage their exercise scheduling effectively.

The exercise sessions took place at leisure facilities in Oxfordshire and Berkshire, UK. Participants were able to choose participating facilities nearby their home to minimise travel burden. Exercise was supported by either a specialist exercise professional (registry of exercise professional's level 4 qualification in exercise for long-term neurological conditions) or a physiotherapist. Members of the leisure facility staff working in the gym were fully informed about the study and that the participants were following a prescribed exercise programme. Adherence to prescribed exercise programme was monitored by session workbooks.

The exercise programme totalled 48 sessions over a 24-week period (2× a week) and each session, which lasted 60 min, consisted of the following: At the start of each session, the participants performed 30 min of aerobic training (plus an initial 10 min warm-up) (55%–85% age-predicted HR_{max} (220—age)) and were able to choose from on a treadmill, bicycle ergometer, cross-trainer or rowing ergometer, depending on equipment was availability. After an initial warm-up of 10 min, participants were instructed to aim for 30 min of aerobic training and exercise so that HR was maintained in an aerobic training zone (medication affecting HR was considered). Participants recorded the type of equipment used and actual duration, as well as the rating of perceived exertion and HR in their training diaries. The aerobic exercise was followed by 30 min of resistance training. The resistance training schedule consisted of leg presses, leg extensions, sit to stands, two-arm pull down, 'wood chop' (ie, exercise which includes rotation of the trunk, shoulder flexion and shoulder adduction—the arm is moving in a diagonal direction) and arm raises.

The intervention was personalised and progressed according to the following protocols. At the initial session, the exercise professional or physiotherapist set the exercise intensity so that each participant achieved 55%–85% age-predicted maximal HR.[15 16] For the duration of the aerobic training, participants were taught to manipulate speed or resistance in order to maintain the exercise intensity. During the strength training, Initial resistance was selected so 10 repetitions could be performed. The exercise professional or physiotherapist instructed the participants to increase resistance when two full sets of 10 could be performed at a given resistance, within 2 min. This would lead to a resultant decrease in repetitions and then the protocol repeated. At the monthly support session, exercise intensities and progression was monitored.

Only pwP who adhered (did not discontinue intervention) to the exercise programme were included in the training response analysis. For these participants' data are reported for exercise tests carried out at baseline (assessment 1), 3 months (assessment 2—midway thought intervention) and 12 months (assessment 3—end of intervention).

Demographic information for pwP and the control group was recorded at baseline; age, weight and blood pressure are reported here. Medical history relating to Parkinson's, including current medication use and score on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III are also reported.

Exercise test

For pwP, the exercise test was carried out during ON state with participants asked to follow their usual Parkinson's medication regime. PwP experience ON and OFF states and the time OFF state occurs since taking medication varies considerable between individuals. As such, no time of taking medication was directed and people were able to take their medication as required. However, assessments were scheduled to fit with individuals' medication regimen and details of ON and OFF states and time since medication was recorded via the MDS-UPDRS. Both pwP and controls were asked to refrain from the consumption of alcohol, cigarettes, food and caffeine and to avoid exercise for a period of 3 hours prior to the assessment.

For pwP test, the exercise test was conducted on an electronically braked cycle ergometer (Excalibur Sport, Lode, The Netherlands), integrated with a cardiopulmonary-monitoring system (Metalyzer 3B, Cortex, Germany), that controlled the work rate protocol on the ergometer and recorded breath-by-breath measurements of VO_2, VCO_2, ventilation and HR (via Polar Heart Rate Monitor; Polar, Finland) throughout the test. The work rate protocol consisted of 2 min steps starting with unloaded cycling, then increasing to 50 W, and there after by 25 W. While the ergometer maintained a constant work load, independent of cadence, participants were instructed to aim for cadence of ~50 revolutions per minute (rpm). At the end of each step, participants were asked to rate their level of exertion (rating of perceive exertion) using the borg rating of perceived exertion 10 point category ratio scale (BORG CR10 scale, 0–10). Participants were verbally encouraged to carry on for as long as they could and the test was terminated when the participant reached volitional exhaustion. The following exercise response measures were obtained from the cardiopulmonary-monitoring system power output watts (Watt), VO_2 (litre per minute), VCO_2 (litre per minute), ventilation (VE litre per minute), respiratory exchange ratio (RER =VO_2 consumed/VCO_2 produced), HR, O_2 pulse (VO_2/HR). Oxygen uptake efficiency slope (OUES) was calculated as: VO_2=a log VE +b, where a=OUES, VO_2(litre per minute) and total ventilation (VE litre per minute).

The control group followed the same protocol which derived the same cardiorespiratory parameters, except the they were instructed to aim for a cadence of ~60 rpm and the unloaded phase lasted 3 min with an initial step of 25 W.

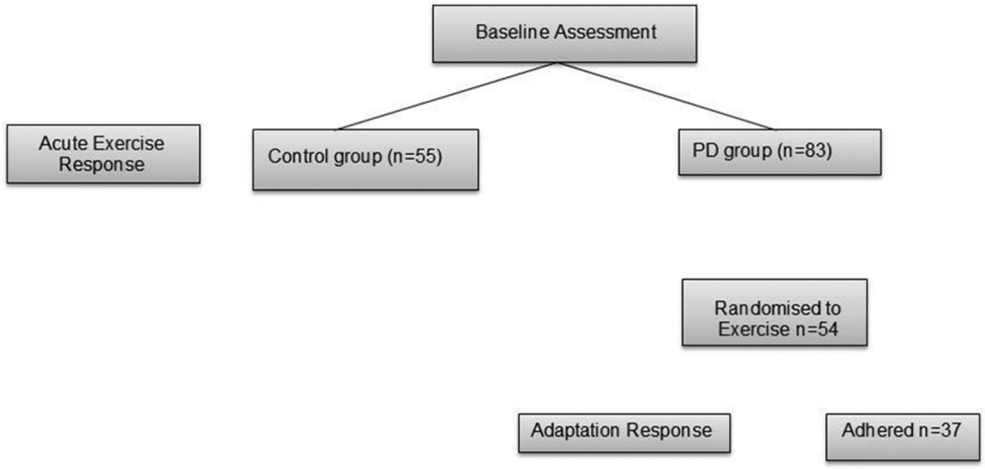

Figure 1 Study flowchart. The participant flow. For study 1(acute exercise response), 83 pwP and 55 controls were included for cross-sectional comparison. For study 2 (Aadaptation to exercise), 37 pwP, who were randomised to exercise in an RCTrandomised controlled trial (reported elsewhere) and adhered to the exercise programme, wasere included. PD, Parkinson's disease; pwP, people with PD.

Activity

Physical activity in pwP was measured using the wrist-worn activity monitor: GENEActiv. The GENEActiv was worn by the participants around the wrist for 7 days following an assessment. GENEActiv is a triaxial acceleration sensor which is lightweight and waterproof. It sampled at 100 Hz for 7 days. The participants sent the monitor back in a prestamped, addressed envelope.

The data were downloaded from the device onto the computer and transformed into a 60 s epoch excel file. An Excel Macro was designed by GENEActiv[17] which generated minutes per day spent sedentary, performing light, moderate or vigorous activities.[18] The file that was collected from the participants was run through this Macro to calculate a total weekly activity count. Finally, one outcome was calculated by averaging the data across the days.

Analysis

Descriptive statistics were calculated for demographic characteristics and session and activity adherence. Independent samples t-test, or Mann-Whitney U test was used to assess differences between the two groups (pwP and controls) at baseline.

Regression analysis was used to determine slopes and intercepts for exercise response measures. The average the last 30 s of the test was used to calculate maximum values of measures. For exercise size response data, a linear mixed models procedure of SPSS was used to determine the changes in measures, as response variables, according to three repeated measurements. Alpha was set at 0.05.

RESULTS

Participants

Participant flow for the pwP recruited to the RCT can be found elsewhere.[9] A flow diagram for the current report can be found in figure 1. Eighty-three pwP took part in the exercise test and were included in study 1. Thirty-seven people randomised to the exercise group that were deemed to adhere to the intervention were included in study 2. Fifty-five people were recruited to

Table 1 Baseline descriptives

	PD (study 1: N=83)	Control (N=55)	PD (study 2: N=37)
Gender	Male: 61/Female: 22	Male: 26/Female: 29	Male: 21/Female: 16
Age (years)	67±8 (39–86)	67±5 (60–80)	65±7 (43–77)
Weight (kg)	77±15 (42–108)	78±11 (61–103)	80±17 (52–108)
Dia BP (mm Hg)	82±13 (53–138)	73±8 (57–89)	82±10 (57–102)
Sys BP (mm Hg)	137±22 (75–201)	130±14 (103–175)	134±21 (98–178)
MDS-UPDRS III	17±9 (0–43)	NA	16±10 (0–43)
GA light to moderate activity	183±111 (21–526) (n=70)	NA	186±125 (31–527) (n=31)

The values are expressed in mean±SD (range).
Dia BP, diastolic blood pressure; GA, GENEActiv; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; NA, not applicable; PD, Parkinson's disease; Sys BP, systolic diastolic blood pressure.

Table 2 Comparison of acute response to exercise between pwP and control groups

	PD	Control	P	u	t
HR_{max} (beats/min)	136 (114)	152 (108)	<0.001	1067	
VO_{2max} (L/min)	1.46 (2.35)	1.69 (2.57)	0.008	1909	
VCO_{2max} (L/min)	1.74 (2.98)	1.98 (2.67)	0.013	1745	
VE_{max}(L/min)	48.46 (99.12)	63.45 (106.3)	<0.001	1405	
O_2 $pulse_{max}$	0.01 (0.02)	0.01 (0.02)	0.850	1756	
RER_{max}	1.19 (0.52)	1.16 (0.45)	0.998		0.003
$RPE_{end\ test}$	7 (8)	7 (9)	0.012	1635	
$HR/Watts_{slope}$	0.37 (0.89)	0.52 (0.75)	<0.001		7.363
$VO_2/Watts_{slope}$	0.01 (0.0080) (0.02)	0.01 (0.0095) (0.01)	<0.001	1150	
$OUES_{slope}$	1.7 (2.43)	1.84 (2.45)	0.198	20224	
$VO_2/Watts_{intercept}$	0.42 (1.01)	0.33 (0.53)	<0.001	1222	

The values are expressed in median (range).
HR, heart rate; O_2pulse = V_{O2}/HR; OUES, oxygen uptake efficiency slope; PD, Parkinson's disease; pwP, people with PD; RER, respiratory exchange ratio; RPE, rating of perceive exertion (CR-10); VE, ventilation.

the control group for study 1. All participants provided written informed consent.

Table 1 shows demographic data for participants, including the subset of pwP in study 2. The groups were similar in age, weight and resting blood pressure; however, a great proportion of pwP group were men.

STUDY 1

A comparison of the acute response to exercise between pwP and the control group is shown in table 2. The control group obtained higher maximum values for HR, VO_2L/min, VCO_2L/min and VE L/min. However, respiratory exchange ratio, perceived exertion and O_2 pulse (VO_2L/min/HR) did not differ between groups. Though exercise response parameters (slopes) differed between groups, except for OUES, HR and VO_2L/min increased at a greater rate against work rate in the control group.

STUDY 2

The median number of sessions attended by the pwP that did not discontinue the RCT intervention was 40 out of the 48 prescribed sessions and most (n=32) attended one or more sessions a week on average. In 99% of these sessions, the aerobic component was performed with a mean (SD) time spent on the aerobic component of 30.2 (±3.6) min/session. 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. Adaption to exercise is displayed in table 3. Individuals went further on the exercise test ($Time_{end}$); however, no significant change was observed in any other parameter, except for a higher respiratory exchange ratio. Exercise test time and respiratory exchange ratio were the highest at the 3-month assessment (halfway through the intervention).

Medications taken by pwP are reported in table 4.

DISCUSSION

This paper highlights key exercise responses for the first time; this could lead to a change in the approach to exercise prescription for pwP. As expected, we observed a blunted exercise capacity in pwP, with reduced workload achieved in exercise testing. In addition, cardiovascular and metabolic responses during exercise, as reflected by lower oxygen utilisation and HR responses, did not change significantly over the course of the interventional study. Importantly, both groups achieved a maximal level of exercise at the end of the test, as indicated by RER values above one, suggesting an anaerobic contribution. PwP did not rate effort any higher than the control group, which indicates that an overperception of effort or leg fatigue, as found in multiple sclerosis,[19] was not a factor affecting their test termination. In summary, we observed both reduced aerobic and cardiovascular responses to exercise in pwP who were physically active and were pushing themselves hard. When we explored the impact of training on both cardiovascular and metabolic systems in the Parkinson's group, we expected to see a typical training effect on exercise capacity and cardiovascular and metabolic responses.[20] Instead, we found that while their exercise capacity increased there were no significant changes in metabolic measures; rather, any increase in exercise performance was likely to be achieved by tolerating a higher anaerobic contribution increasing the duration of the test.

With regard to the exercise adaptation response, our results were different to our hypotheses; there was no significant change in the aerobic capacity or HR response. However, our findings agree with the results

Table 3 Long-term response to exercise for the pwP who adhered to training

	Baseline	3 months	6 months	P
$Time_{end}$ (s)	682±40	722±39	703±40	0.031
HR_{max} (beats/min)	138±3	140±4	138±3	0.725
VO_{2max} (L/min)	1.71±0.11	1.66±0.11	1.66±0.09	0.648
VCO_{2max} (L/min)	2.00±0.13	2.02±0.13	1.96±0.11	0.683
VE_{max}(L/min)	55.01±4.33	55.67±3.71	52.58±4.31	0.724
O_2 $Pulse_{max}$	0.012±0.001	0.012±0.001	0.012±0.001	0.949
RER_{max}	1.16±0.02	1.26±0.02	1.18±0.02	0.035
$RPE_{end\ test}$	6±0	7±0	7±0	0.300
$HR/Watts_{slope}$	0.38±0.02	0.37±0.02	0.36±0.02	0.118
$VO_2/Watts_{slope}$	0.008±0.000	0.008±0.000	0.008±0.000	0.578
$OUES_{slope}$	1.85±0.10	1.80±0.09	1.90±0.08	0.279
O_2 $Pulse_{slope}$	1.124±0.86	1.022±0.071	1.008±0.060	0.190
$VO_2/Watts_{intercept}$	0.41±0.03	0.40±0.02	0.43±0.02	0.486
Dia BP (mm Hg)	82±10	75±11	73±13	>0.001
Sys BP (mm Hg)	133±20	128±19	126±16	0.014
MAP (mm Hg)	99±12	93±12	91±13	>0.001

The values are expressed in mean ±SD.
Dia BP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; O_2 Pulse = VO_2/HR; OUES , oxygen uptake efficiency slope; pwP, people with Parkinson's disease; RER, respiratory exchange ratio; RPE, rating of perceive exertion (CR-10); Sys BP, systolic diastolic blood pressure; VE, ventilation.

of a pilot study, by Skidmore *et al*[21] in which the five enrolled participants showed improvement in peak walking workload capacity and there was no change in VO_2 peak, which was measured with open-circuit spirometry. This antithesis could be explained by either of our two hypothesises: (1) 'impaired autonomic function' and (2) 'mitochondrial dysfunction in PD'. Mitochondrial dysfunction in PD might alternate O_2 supply during exercise.[1] Moreover, lower cardiovascular and metabolic responses could be due to autonomic dysfunction.[22 23] PwP present lower elevations in HR and BP during exercise; these non-motor features are being defined across literature by a dysfunctional autonomic nervous system.[24]

Interestingly, there was a trend to reduce HR in response to training, suggesting an improved efficiency of the cardiovascular system. We found higher diastolic and systolic blood pressure at rest in pwP despite this group being relatively active compared with the low active control group and achieving over 150 min of activity a week. This is in contrast to other studies that have found no difference in BP between patients with PD and otherwise healthy people.[25 26]

Nevertheless, we found in this per-protocol analysis, weekly 60 min of combined cardiovascular and strength exercise, had a positive effect on reducing blood pressure after 3 and after 6 months. This is in agreement with the results of a previous study which reported a health benefit of reduced blood pressure[27] and a recent study that[11] found progressive resistance training had a positive effect on cardiovascular autonomic regulation in PD. This supports our findings that cardiovascular changes are normal whereas respiratory changes are not, indicating cardiovascular adaption to exercise occurs in the absence of effects on metabolic systems.

STUDY LIMITATIONS

This project was a secondary analysis of a pragmatic trial with a small number of participants included on medications that may have impacted on the exercise response.

Table 4 pwP group medication

	DA	AChE	MAOI	AntiDep	MiTr	betab	antiBP	CVS	Other
Baseline (n=83)	74	15	16	6	1	6	8	0	34
Baseline (n=37)	34	5	1	4	1	3	2	0	14

AChE, anticholinergic drugs; antiBP, other antihypertensive; AntiDep, antidepressant drugs (all); betab, beta blockers; CVS, other drugs affecting heart; DA, dopamine agonists; MAOI, mono amine oxidase drug; MiTr, minor tranquiliser; other, all other drugs; pwP, people with Parkinson's disease.

In addition, there was no direct measurement of mitochondria and autonomic dysfunction. Considering the complex aetiology with genotype and phenotype presentation, there is now a need to explore individual responses in more detail in order to consider more optimal prescription to benefit movement. In addition, we did not have intervention data for the control in order to compare exercise response. However, studies that examined the effect of exercise endurance training on VO_2 kinetics have shown that a training response would be expected in this age group.[28 29]

PwP present improved movement in response to exercise.[30] Our findings suggest that pwP have a reduced aerobic response during exercise and rely on anaerobic metabolism for their capacity gains; at a group level, this does not change with training, whereas their movement does.[9] In order to inform optimal intervention, this needs to be investigated further. In study 2, we used a combined training approach and gained benefits to movement behaviour which are reported elsewhere.[9]

IMPLICATIONS FOR RESEARCH

PwP had a blunted exercise capacity and in those who followed an exercise intervention according to protocol, there was a change in cardiovascular parameters associated to BP, but no change in metabolic parameters. Moreover, our main trial findings show improvement in motor symptoms.

There is an identified need for studies that will focus on metabolic and cardiovascular changes in PD; especially substantive RCTs, which will explore cardiovascular, metabolic, cognitive and motor symptoms responses to different types of structured exercise training in more detail. In addition, individualised responses to exercise should be further investigated.

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Contributors All authors were involved in drafting or critically revising the manuscript for important intellectual content. JC, MT, HD, AF, MB, FM and MF were involved in the conception and design of the work. JC, MF, AM, CS, JB, AD-W and HD were involved in the acquisition of the data. FM, JC, MF, CS, JB, AD-W, HD and HI were involved in analysis and interpretation of data. FM, JC, MF, AM, CS, JB, AD-W, AF, MD, HI, HD and MT were involved in drafting and critically revising the manuscript. All authors have approved this manuscript.

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Competing interests None declared.

Ethics approval The study received National Health Service ethical approval (NRES Committee South Central—Southampton A: 11/SC/0267) and was conducted in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional unpublished data from the study are available to anyone at the moment.

REFERENCES

1. Kanegusuku H, Silva-Batista C, Peçanha T, *et al*. Blunted maximal and submaximal responses to cardiopulmonary exercise tests in patients with parkinson disease. *Arch Phys Med Rehabil* 2016;97:720–5.
2. National. *Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care*. London: Royal College of Physicians, 2006.
3. Petzinger GM, Fisher BE, McEwen S, *et al*. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol* 2013;12:716–26.
4. Caciula MC, Horvat M, Nocera J, *et al*. Exercise frequency and physical function in Parkinson's disease. *Sciences of Human Kinetics* 2016;9:2.
5. Caciula MC, Horvat M, Tomporowski PD, *et al*. The effects of exercise frequency on executive function in individuals with Parkinson's disease. *Ment Health Phys Act* 2016;10:18–24.
6. Duchesne C, Gheysen F, Bore A, *et al*. Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals. *Neuroimage Clin* 2016;12:559–69.
7. Schenkman M, Hall DA, Barón AE, *et al*. Exercise for people in early- or mid-stage Parkinson disease: a 16-month randomized controlled trial. *Phys Ther* 2012;92:1395–410.
8. Thacker EL, Chen H, Patel AV, *et al*. Recreational physical activity and risk of Parkinson's disease. *Mov Disord* 2008;23:69–74.
9. Collett J, Franssen M, Meaney A, *et al*. Phase II randomised controlled trial of a 6-month self-managed community exercise programme for people with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2017;88.
10. Ivey FM, Katzel LI, Sorkin JD, *et al*. The unified Parkinson's disease rating scale as a predictor of peak aerobic capacity and ambulatory function. *J Rehabil Res Dev* 2012;49:1269–76.

11. Kanegusuku H, Silva-Batista C, Peçanha T, *et al*. Effects of progressive resistance training on cardiovascular autonomic regulation in patients with parkinson disease: a randomized controlled trial. *Arch Phys Med Rehabil* 2017;98:2134–41.
12. Katzel LI, Sorkin JD, Macko RF, *et al*. Repeatability of aerobic capacity measurements in Parkinson disease. *Med Sci Sports Exerc* 2011;43:2381–7.
13. Scheele C, Petrovic N, Faghihi MA, *et al*. The human PINK1 locus is regulated in vivo by a non-coding natural antisense RNA during modulation of mitochondrial function. *BMC Genomics* 2007;8:74.
14. 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.
15. Balcer LJ. Clinical outcome measures for research in multiple sclerosis. *J Neuroophthalmol* 2001;21:296–301.
16. Peppe A, Ranaldi A, Chiavalon C, *et al*. Global mobility task: index for evaluating motor impairment and motor rehabilitation programs in Parkinson's disease patients. *Acta Neurol Scand* 2007;116:182–9.
17. GENEActiv. Professional wearables. 2014 http://www.geneactiv.org/.
18. Welch WA, Bassett DR, Freedson PS, *et al*. Cross-validation of waist-worn GENEA accelerometer cut-points. *Med Sci Sports Exerc* 2014;46:1825–30.
19. Dawes H, Collett J, Meaney A, *et al*. Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis. *Neurorehabil Neural Repair* 2014;28:139–48.
20. Cooper C, Storer T. *Exercise testing and interpretation: a practical approach*. Cambridge: Cambridge University Press, 2001.
21. Skidmore FM, Patterson SL, Shulman LM, *et al*. Pilot safety and feasibility study of treadmill aerobic exercise in Parkinson disease with gait impairment. *J Rehabil Res Dev* 2008;45:117–24.
22. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79:368–76.
23. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, *et al*. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord* 2011;26:399–406.
24. Asahina M, Vichayanrat E, Low DA, *et al*. Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology. *J Neurol Neurosurg Psychiatry* 2013;84:674–80.
25. Hughes AJ, Ben-Shlomo Y, Daniel SE, *et al*. What features improve the accuracy of clinical diagnosis in Parkinson's disease: A clinicopathologic study. *Neurology* 1992;42:1142.
26. 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. *Circulation* 2007;116:1094–105.
27. Ridgel AL, Walter BL, Tatsuoka C, *et al*. ENhanced exercise therapy in Parkinson's disease: a comparative effectiveness trial. *J Sci Med Sport* 2016;19:12–17.
28. Buzza G, Lovell GP, Askew CD, *et al*. The effect of short and long term endurance training on systemic, and muscle and prefrontal cortex tissue oxygen utilisation in 40 - 60 year old women. *PLoS One* 2016;11:e0165433.
29. Grey TM, Spencer MD, Belfry GR, *et al*. Effects of age and long-term endurance training on VO2 kinetics. *Med Sci Sports Exerc* 2015;47:289–98.
30. Zhang P, Tian B. Metabolic syndrome: an important risk factor for Parkinson's disease. *Oxid Med Cell Longev* 2014;2014:1–7.

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