BMJ Open

Exercise Response in Parkinson's Disease – A cross-sectional comparison of people with Parkinson's with sedentary controls, combined with a secondary per protocol analysis of the exercise response from a randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017194
Article Type:	Research
Date Submitted by the Author:	31-May-2017
Complete List of Authors:	Mavrommati, Foteini; Oxford Brookes University, Movement Science Group, OxINARH; Oxford University Hospitals NHS Foundation Trust, Research and Development Collett, Johnny; Oxford Brookes University, Movement Science Group, OxINARH Franssen, Marloes; University of Oxford , Nuffield Department of Primary Care Health Sciences ; Oxford Brookes University, Movement Science Group Meaney, Andy; Oxford Brookes University, Movement Science Group, OxINARH Sexton, Claire; University of Oxford, Nuffield Department of Clinical Neurosciences, FMRIB Centre Dennis- West, Andrea; University of Oxford, Nuffield Department of Clinical Neurosciences Izadi, Hooshang; Oxford Brookes University, Department of Mechanical Engineering and Mathematical Sciences; Oxford Brookes University, Movement Science Group, OxINARH Bogdanovic, Marko; Royal Berkshire Hospital, Department of Neurology Tims, Martin; Oxford Brookes University, Movement Science Group, OxINARH Farmer, Andrew; University of Oxford, Nuffield Department of Primary Care Health Sciences Dawes, Helen; Oxford Brookes University, Movement Science Group, OxINARH; University of Oxford, Department of Clinical Neurology
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine, Rehabilitation medicine, Neurology
Keywords:	Exercise, Parkinson-s disease < NEUROLOGY, Rehabilitation medicine < INTERNAL MEDICINE, metabolism, cardiovascular

Exercise Response in Parkinson's Disease – A cross-sectional comparison of people with Parkinson's with sedentary controls, combined with a secondary per protocol analysis of the exercise response from a randomised controlled trial

Foteini Mavrommati, Johnny Collett, Marloes Franssen, Andy Meaney, Claire Sexton, Andrea Dennis- West, Andrew Farmer, Martin Tims, Hooshang Izadi, Marko Bogdanovic, Helen Dawes

Author:
Foteini Mavrommati (MSc), Oxford University Hospitals NHS Foundation Trust- Research and Development, Oxford Brookes University- Movement Science group.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, UK
foteini.mavrommati@brookes.ac.uk & p0084589@brookes.ac.uk , phone number: 01865488212

Co- authors:
1. Johnny Collett (PhD), Oxford Brookes University.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
Jcollett@brookes.ac.uk , phone number: 01865 483630

2. Marloes Franssen (PhD), University of Oxford, Oxford Brookes University.
Postal address: Nuffield Department of Primary Care Health Sciences, Primary Care Clinical Trials Unit, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Rd, OX2 6GG, Oxford, UK
marloes.franssen@phc.ox.ac.uk , Phone number: 01865 617845

3. Andy Meaney (PhD), Oxford Brookes University.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
ameaney@brookes.ac.uk , phone number: 01865 484293

4. Claire Sexton (DPhil), University of Oxford.
Postal address: FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU
claire.sexton@ndcn.ox.ac.uk , phone number: 01865 222736

5. Andrea Dennis-West (PhD), University of Oxford
Postal address: Nuffield Department of Clinical Neurosciences, University of Oxford, OX3 9DU, Oxford, UK.
andrea.dennis@ndcn.ox.ac.uk , phone number: 01865 231511

6. Hooshang Izadi (PhD), Oxford Brookes University
Postal address: Department of Mechanical Engineering and Mathematical Sciences, Oxford Brookes University, Wheatley Campus, Wheatley, OX33 1HX, Oxford, UK
hizadi@brookes.ac.uk , phone number: 01865 741111

7. Marko Bogdanovic (PhD), Royal Berkshire NHS Foundation Trust
Postal address: Department of Neurology, Royal Berkshire Hospital, RG1 5AN, Reading, UK
Marko.Bogdanovic@royalberkshire.nhs.uk , Phone number: 01189 553434

8. Martin Tims, Oxford Brookes University
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
martintims1@btinternet.com , phone number: 01865 483630

9. Andrew Farmer (PhD), University of Oxford
Postal Address: Nuffield Department of Primary Care Health Sciences, University of Oxford, OX26GG, Oxford, UK
andrew.farmer@phc.ox.ac.uk , phone number: 01865 617942

10. Professor Helen Dawes, Oxford Brookes University, University of Oxford: Department of Clinical Neurology
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
hdawes@brookes.ac.uk , 01865 483293

Corresponding Author: Correspondence to Miss Foteini Mavrommati
Postgraduate Research Assistant at Oxford Institute of Nursing, Midwifery and Allied Health Research
Postal address: Oxford Brookes University, Oxford Institute of Nursing, Midwifery and Allied Health Research, Gipsy Lane, Oxford, OX3 0BP
foteini.mavrommati@brookes.ac.uk & p0084589@brookes.ac.uk , phone number: 01865488212

Keywords: Exercise, Parkinson's disease, Rehabilitation medicine, metabolism, cardiovascular

Word count: 3.325 words (excluding title page, references, figures and tables)

Objectives: An investigation of acute and adaptation cardiovascular and metabolic training responses in people with Parkinson's (pwP).

Setting: Community leisure facilities in Oxfordshire and Berkshire.

Participants: pwP (n=83) & sedentary controls (n=55)

Interventions: This research consists of two studies: 1) A cross sectional study of exercise response of pwP compared to sedentary controls and 2) an interventional study of exercise training in pwP. 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 six-month weekly exercise programme (n=37). The intervention (study (2) was a prescribed exercise program consisting of sessions lasting 60 minutes, twice a week over a period of six months. The control group followed the same protocol which derived the same cardio respiratory parameters, except the they were instructed to aim for a cadence of ~60rpm and the unloaded phase lasted 3minutes with an initial step of 25watts.

Results: Study (1) showed higher maximum values for heart rate, VO2l.min-1, VCO2l.min-1 and Ventilationl.min-1 for the control group; Respiratory Exchange Ratio (RER), perceived exertion and O2 Pulse (VO2l.min-1/ HR) did not differ between groups. In study (2), for pwP who adhered to the exercise programme (n=37), RER increased significantly and although there was no significant change in the aerobic capacity or heart rate response, reduced blood pressure was found.

Conclusions: An abnormal cardiovascular response to an exercise program observed at baseline, whereas metabolic deficiencies remained. These observations support an underling metabolic contribution to Parkinson's disease and add to the pathogenic understanding of the condition.

Trial registration: This is not a registered clinical trial; however, the data for pwP was obtained from an RCT registered with ClinicalTrials.Gov (NCT01439022).

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 PwP using a six month exercise intervention in a relatively large sample.

• Our findings support previous works 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 Parkinson's (pwP) and as such is an important research area [2]. There is strong evidence supporting beneficial effects of exercise programs, both in normal aging and specifically in PD [3]. However, whilst there is compelling data that exercise benefits motor symptoms [4], functioning and quality of life [5], it is not clear what exercise type or dose is optimal. It is not clear as to what extent reduced risk of PD, associated with higher physical activity levels [6], and improvements observed in motor symptoms after exercise interventions, can be attributed to metabolic or motor mechanisms[4, 7]. 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 [5, 8]. However, less is known about cardiovascular and metabolic training responses [1]. Previous studies investigating peak responses during cardiopulmonary exercise tests in pwP have contradictory results [1]. Furthermore, whilst studies have consistently found exercise capacity is reduced we do not know the extent to which this is attributable to deconditioning, blunted cardiovascular responses relating to impaired autonomic functioning [1],or to reduced aerobic metabolic responses, from mitochondrial dysfunction in PD [1, 9, 10]. Careful comparisons of the cardiovascular and metabolic exercise response and adaption to training with healthy individuals of similar activity levels, has 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 six-month combined strength and cardiovascular training program for pwP.

Methods

Design

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

Data for pwP was 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[7]. The cross sectional study (1) included all participants at from the RCT 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 was obtained from people recruited by the Oxford Cognitive Therapy Centre (https://www.octc.co.uk)

Setting

Parkinson's assessments were carried out at the Movement Science Laboratory, Oxford Brookes University, Oxford, UK and the intervention took place at community leisure facilities in Oxfordshire and Berkshire. Healthy control assessments were carried out at the Cardiovascular Clinical Research Facility, John Radcliffe Hospital, Oxford.

Participants

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

Inclusion criteria for pwP were: (i) diagnosis of idiopathic PD (as defined by the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [11]); (ii) able to walk ≥100 meters. Exclusion criteria were: (i) dementia; (ii) history of additional prior neurological condition; (iii) severe depression or psychosis or a mental state that would preclude consistent active involvement with the study over its duration; (iv) cardiac precautions that would prevent the subject from participating in the intervention; (v) any known contraindication to exercise; (vi) reduced cognitive function of any cause (Minimental state examination < 23); (vii) 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: (i) self-reported participation in fewer than 60 minutes per week of physical activity sufficient to raise their heart rate (ii) had no known contraindications to MRI scanning or fitness testing (assessed using the physical activity readiness questionnaire, physical activityR-Q. Exclusion criteria were: (i) a history of major vasculature problems or receiving heart rate-controlling medication, (ii) self-reported history or current investigation of a neurological disorder or symptoms or treatment for a psychiatric illness within the past year, (ii) and ability to commit to the requirements of study.

Intervention

The intervention for pwP was a prescribed exercise program consisting of sessions lasting 60 minutes, twice a week over a period of six months; a detailed description can be found[7].

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 program was monitored by session workbooks.

The exercise programme totalled 48 sessions over a 24 week period (2x a week). The 60minute session consisted of the following: At the start of each session, the participants performed 30 minutes of aerobic training (55-85% age predicted heart rate 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 minutes, participants were instructed to exercise so that heart rate was maintained in an aerobic training zone (medication affecting heart rate was considered) for 20 minutes. Participants recorded the type of equipment used and actual duration, as well as the rating of perceived exertion and heart rate in their training diaries. The aerobic exercise was followed by 30 minutes of resistance training. The resistance training schedule consisted of leg press, leg extensions, sit to stands, 2 arm pull down, 'wood chop' [i.e. 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 the participants achieved 55-85 percentage age predicted maximal heart rate [13]. For the duration of the aerobic training, participants were then taught to manipulate speed or resistance in order to maintain the exercise intensity. Initial resistance was selected so ten repetitions could be performed. The exercise professional or physiotherapist instructed the participants that when two full sets of ten could be performed at a given resistance, within two minutes, to increase resistance. 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 program were included in the training response analysis. For these participants' data is reported for exercise tests carried out at baseline (assessment 1), three 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, reported here are age, weight, and blood pressure. 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. 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 three hours prior to the assessment.

For pwP test the exercise test was conducted on an electronically braked cycle ergometer (Excalibur Sport, Lode, Netherlands), integrated with a cardio pulmonary monitoring system (Metalyzer 3B, Cortex, Germany), that controlled the work rate protocol on the ergometer and recorded breath-by-breath measurements of oxygen consumption, carbon dioxide production, ventilation and heart rate (via Polar Heart Rate Monitor (Polar, Finland)) throughout the test. The work rate protocol consisted of two minutes steps starting with unloaded cycling, then increasing to 50 Watts, and there after by 25 Watts. Whilst the ergometer maintained a constant work load, independent of cadence, participants were instructed to aim for cadence of ~50rpm. At the end of each step participants were asked to rate their level of exertion (RPE) using the 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 cardio pulmonary monitoring system power output watts (W), VO_2 ($l.min^{-1}$), VCO_2 ($l.min^{-1}$), ventilation ($VEl.min^{-1}$), respiratory exchange ratio (RER =VO_2 consumed / VCO_2 produced), heart rate, O_2pulse (VO_2 /HR). Oxygen Uptake Efficiency Slope (OUES) was calculated as: VO_2 = a log VE + b, where a = OUES, VO_2in ($l.min^{-1}$) and total ventilation ($VEl.min^{-1}$).

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

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 seven days following an assessment. GENEActiv, is a triaxial acceleration sensor which is lightweight and waterproof. It sampled at 100Hz for seven days. The participants sent the monitor back in a pre-stamped, addressed envelope.

The data was downloaded from the device onto the computer and transformed into a 60-second epoch excel file. An Excel Macro was designed by GENEActiv[14] which generated minutes per day spent sedentary, performing light, moderate or vigorous activities [15]. 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-Witney 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 seconds of the test was used to calculate maximum values of measures. For exercise size response data, a Linear Mixed Models (LMM) 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 (Collett et al, 2016). 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). 37 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 the control group for study 1. All participants provided written informed consent.

Table 1 shows demographic data for participants, including the sub-set of pwP in study 2. The groups were similar in age, weight, and resting blood pressure, however, a great proportion of pwP group were male. Medications taken by pwP are reported in table 04.

Figure 1. Study flowchart

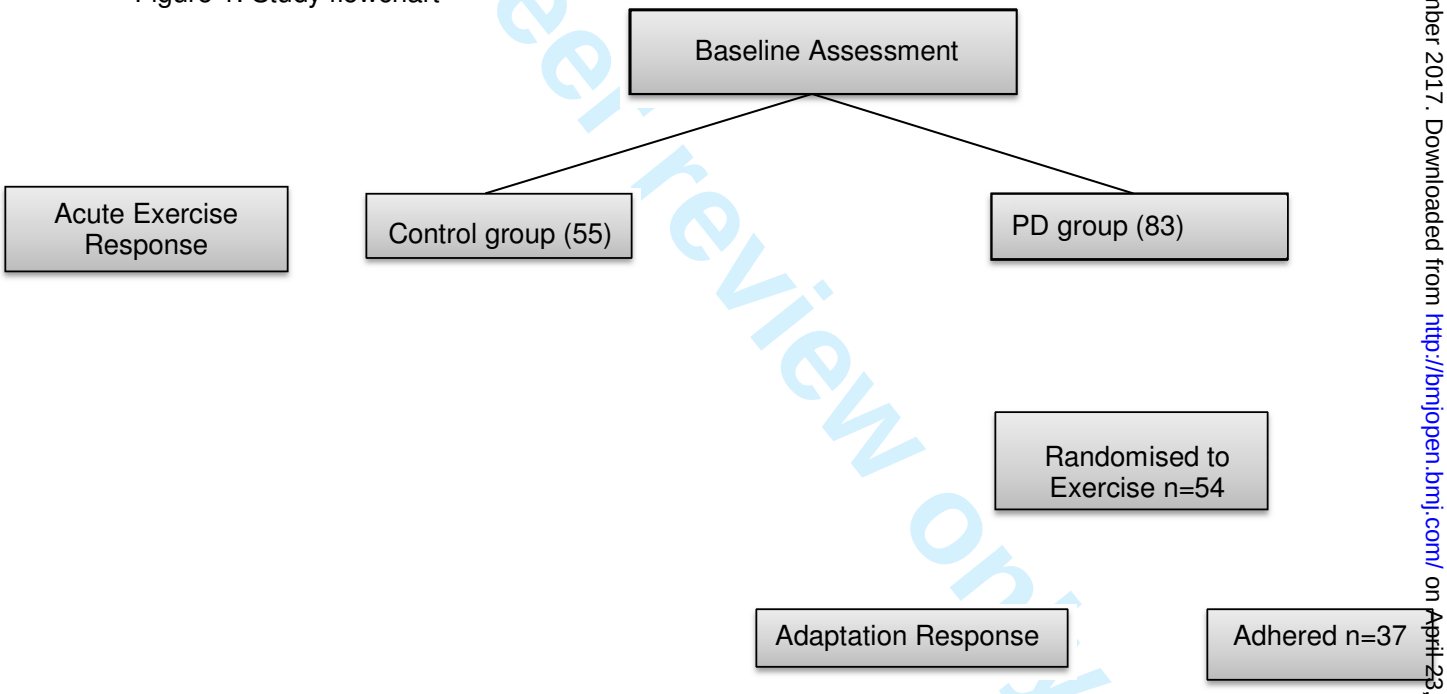


Table 1: Baseline Descriptives

	PD (study1: n=83)	Control (n=55)	PD (study2: 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 (mmHg)	82±13 (53-138)	73±8 (57-89)	82±10 (57-102)
Sys BP (mmHg)	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)

mean±SD (range), DiaBP= Diastolic blood pressure, Sys BP =Systolic Diastolic blood pressure

Study 1

A comparison of the acute response to exercise between pwP and the control group is shown in table 1. The control group obtained higher maximum values for heart rate, VO_2l.min^{-1}, VCO_2l.min^{-1} and Ventilationl.min^{-1}. However, respiratory exchange ratio, perceived exertion and O_2 Pulse (VO_2l.min^{-1}/ HR) did not differ between groups. Though exercise response parameters (slopes) differed between groups, except for OUEs, with heart rate and VO_2l.min^{-1} increasing at a greater rate against work rate in the control group.

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

	PD	Control	p	u	t
HR_{max} (b.min^{-1})	136 (114)	152 (108)	<0.001	1067	
VO_{2max} (l.min^{-1})	1.46 (2.35)	1.69 (2.57)	0.008	1909	
VCO_{2max} (l.min^{-1})	1.74 (2.98)	1.98 (2.67)	0.013	1745	
VE_{max}(l.min^{-1})	48.46 (99.12)	63.45 (106.3)	<0.001	1405	
O_2Pulse_{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	

Median (range), HR =Heart Rate, VE = ventilation, O_2 Pulse = VO_2/ HR, RER= Respiratory exchange ratio, RPE=Rating of perceive exertion (CR-10), OUES

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) minutes per 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 02. 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 highest at the three month assessment (half way through the intervention).

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

	Baseline	3months	6months	P
$Time_{end}$(sec)	682 ± 40	722 ± 39	703 ± 40	0.031
HR_{max} ($b.min^{-1}$)	138 ± 3	140 ± 4	138 ± 3	0.725
VO_{2max} ($l.min^{-1}$)	1.71 ± 0.11	1.66 ± 0.11	1.66 ± 0.09	0.648
VCO_{2max} ($l.min^{-1}$)	2.00 ± 0.13	2.02 ± 0.13	1.96 ± 0.11	0.683
VE_{max}($l.min^{-1}$)	55.01 ± 4.33	55.67 ± 3.71	52.58 ± 4.31	0.724
O_2Pulse_{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_2Pulse_{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 (mmHg)	82 ± 10	75 ± 11	73 ± 13	>0.001
Sys BP (mmHg)	133 ± 20	128 ± 19	126 ± 16	0.014
MAP (mmHg)	99 ± 12	93 ± 12	91 ± 13	>0.001

Mean±SD, HR =Heart Rate, VE = ventilation, O_2 Pulse = VO_2/ HR, RER= Respiratory exchange ratio, RPE=Rating of perceive exertion (CR-10), DiaBP= Diastolic blood pressure, Sys BP =Systolic Diastolic blood pressure, MAP = mean arterial pressure

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

DA= Dopamine Agonists, AChE= Anti- cholinergic drugs, MAOI= Mono- amine Oxidase drug, Anti- Dep= Antidepressant drugs (all), MiTr= Minor Tranquiliser, betab= Beta Blockers, antiBP= Other anti-hypertensive, CVS= Other drugs affecting heart, Other= All other drugs

Discussion

Our study highlighted 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 heart rate 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 over perception of effort or leg fatigue, as found in multiple sclerosis[16], 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[17]. Instead we found that whilst 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 differed to our hypotheses; there was no significant change in the aerobic capacity or HR response. However, our findings agree with the results of a pilot study, by Skidmore et al[18] in which the five enrolled participants showed improvement in peak walking workload capacity and there was no change in [VO.sub.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 O2 supply during exercise [1]. Moreover, lower cardiovascular and metabolic responses could be due to autonomic dysfunction [19, 20]. 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 [21].

Interestingly, there was a trend to reduce heart rate in response to training, suggesting an improved efficiency of cardiovascular system. We found higher diastolic and systolic blood pressure at rest in pwP despite this group being relatively active compared to the low active control group and achieving over 150 minutes of activity a week. This is in contrast to other studies that have found no difference in BP between Parkinson's disease patients and otherwise healthy people (American College of Sports Medicine 2009, Hughes 1992).

Nevertheless we found, in this per protocol analysis, weekly sixty minutes combined cardiovascular and strength exercise, had a positive effect on reducing blood pressure after three and after six months. This is in agreement with the results of a previous study which included a health benefit improvement in terms of reducing blood pressure [23] and further adds to our findings that cardio vascular changes normal whereas respiratory not. Furthermore it supports our general findings of cardiovascular adaption to exercise 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. 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.

Our findings are extremely important taken in the context that pwP improve their movement in response to exercise[22] as they suggest that pwP have a reduced aerobic response during exercise relying on anaerobic metabolism for their capacity gains that at a group level does not change with training whereas their movement does [7]. We utilised a combined training approach and gained benefits to movement behaviour which are reported elsewhere [7].

Implications for research

For pwP who followed the per protocol training, there was a change in cardiovascular symptoms associated to BP, but no change in metabolic symptoms. Moreover, our main trial findings show improvement in motor symptoms. There is an identified need for studies with focus on PD, especially big RCTs, which will explore cardiovascular, metabolic and motor symptoms responses in more detail. In addition, individualised responses to exercise should be further investigated.

Acknowledgements: We would like to thank all the people who volunteered for the studies. For their expertise and direction during the Parkinson's exercise trial we thank Maria Breen, Helen Collins and Jeremy Appleton and for delivering the intervention James Bateman, Lorreta Davis and Michael Challis and the staff at participating leisure centres (Bracknell, Bicester, Chalfont, Fleet, Hart (Fleet), Loddon Valley, Maidenhead, Newbury Leisure Centres, David Lloyd Leisure, CLEAR Unit at Oxford Brookes University and Weights and Measures, Gt Missenden). We would like to thank Oxford Primary Care Clinical Trials Unit, DeNDRoN, PCRN participating hospital clinics (John Radcliffe, Royal Berkshire and Heatherwood and Wexham Park), Parkinson's UK local groups (Oxford, Newbery, Bracknell, Wokingham, Reading, Hazlemere and High Wycombe) and Parkinson's UK and Michael J Fox foundation websites for their support. We would also like to thank Adam Thomas, D.Phil for his assistance and expertise with the control data.

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

Funding: This research was supported by the National Institute for Health Research (NIHR) research for patient benefit programme (PB-PG-0110-20250), Oxford Biomedical Research Centre (BRC) (UK) and the Oxford Health BRC. HD is supported by the Elizabeth Casson Trust; AF is a NIHR Senior Investigator. HD and AF receive support from the NIHR Oxford Biomedical Research Centre. HD and JC are both supported by Higher Education England Thames Valley.

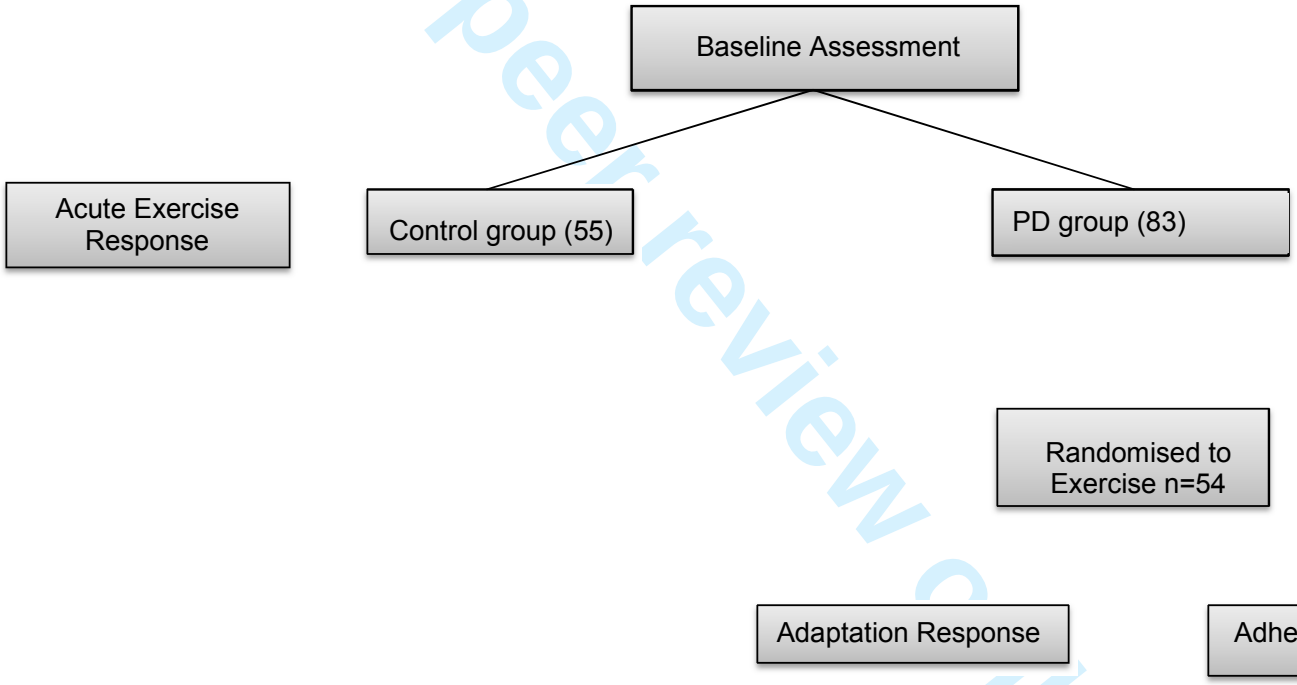
Competing interests: None declared.

Data sharing: No additional data available

References

1. Kanegusuku, H., et al., *Blunted Maximal and Submaximal Responses to Cardiopulmonary Exercise Tests in Patients With Parkinson Disease.* Arch Phys Med Rehabil, 2016. **97**(5): p. 720-5.
2. National, et al., *Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care*. 2006, London: Royal College of Physicians.
3. Petzinger, G.M., et al., *Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease.* Lancet Neurol, 2013. **12**(7): p. 716-26.
4. Duchesne, C., et al., *Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals.* Neuroimage Clin, 2016. **12**: p. 559-569.
5. Schenkman, M., et al., *Exercise for people in early- or mid-stage Parkinson disease: a 16-month randomized controlled trial.* Phys Ther, 2012. **92**(11): p. 1395-410.
6. Thacker, E.L., et al., *Recreational physical activity and risk of Parkinson's disease.* Mov Disord, 2008. **23**(1): p. 69-74.
7. Collett, J., 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, 2016.
8. Ivey, F.M., 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**(8): p. 1269-76.
9. Katzel, L.I., et al., *Repeatability of aerobic capacity measurements in Parkinson disease.* Med Sci Sports Exerc, 2011. **43**(12): p. 2381-7.
10. Scheele, C., 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**: p. 74.
11. Goetz, C.G., 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**(15): p. 2129-70.
12. Balcer, L.J., *Clinical outcome measures for research in multiple sclerosis.* J Neuroophthalmol, 2001. **21**(4): p. 296-301.
13. Peppe, A., et al., *Global Mobility Task: index for evaluating motor impairment and motor rehabilitation programs in Parkinson's disease patients.* Acta Neurol Scand, 2007. **116**(3): p. 182-9.
14. GENEActiv. 2014; Available from: http://www.geneactiv.org/.
15. Welch, W.A., et al., *Cross-validation of waist-worn GENEA accelerometer cut-points.* Med Sci Sports Exerc, 2014. **46**(9): p. 1825-30.
16. Dawes, H., et al., *Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis.* Neurorehabil Neural Repair, 2014. **28**(2): p. 139-48.
17. Cooper, C. and T. Storer, *Exercise testing and interpretation: A practical approach*. 2001, Cambridge: Cambridge University Press
18. Skidmore, F.M., et al., *Pilot safety and feasibility study of treadmill aerobic exercise in Parkinson disease with gait impairment.* J Rehabil Res Dev, 2008. **45**(1): p. 117-24.
19. Jankovic, J., *Parkinson's disease: clinical features and diagnosis.* J Neurol Neurosurg Psychiatry, 2008. **79**(4): p. 368-76.
20. Martinez-Martin, P., et al., *The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease.* Mov Disord, 2011. **26**(3): p. 399-406.
21. Asahina, M., et al., *Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology.* J Neurol Neurosurg Psychiatry, 2013. **84**(6): p. 674-80.
22. Zhang, P. and B. Tian, *Metabolic syndrome: an important risk factor for Parkinson's disease.* Oxid Med Cell Longev, 2014. **2014**: p. 729194.

23. Ridgel, A., et al., Enhanced Exercise Therapy in Pakinson's disease: *A comparative effectiveness trial*. Journal of Science and Medicine in Sport, 2016. **19:** p. 12–17.



BMJ Open

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.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017194.R1
Article Type:	Research
Date Submitted by the Author:	06-Sep-2017

Complete List of Authors:	Mavrommati, Foteini; Oxford Brookes University, Movement Science Group, OxINARH; Oxford University Hospitals NHS Foundation Trust, Research and Development Collett, Johnny; Oxford Brookes University, Movement Science Group, OxINARH Franssen, Marloes; University of Oxford , Nuffield Department of Primary Care Health Sciences ; Oxford Brookes University, Movement Science Group Meaney, Andy; Oxford Brookes University, Movement Science Group, OxINARH Sexton, Claire; University of Oxford, Nuffield Department of Clinical Neurosciences, FMRIB Centre Dennis- West, Andrea; University of Oxford, Nuffield Department of Clinical Neurosciences Izadi, Hooshang; Oxford Brookes University, Department of Mechanical Engineering and Mathematical Sciences; Oxford Brookes University, Movement Science Group, OxINARH Bogdanovic, Marko; Royal Berkshire Hospital, Department of Neurology Tims, Martin; Oxford Brookes University, Movement Science Group, OxINARH Farmer, Andrew; University of Oxford, Nuffield Department of Primary Care Health Sciences Betts, Jill; University of Oxford Nuffield Department of Clinical Neurosciences, FMRIB Centre Dawes, Helen; Oxford Brookes University, Movement Science Group, OxINARH; University of Oxford, Department of Clinical Neurology
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine, Rehabilitation medicine, Neurology
Keywords:	Exercise, Parkinson-s disease < NEUROLOGY, Rehabilitation medicine < INTERNAL MEDICINE, metabolism, cardiovascular

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.

Foteini Mavrommati, Johnny Collett, Marloes Franssen, Andy Meaney, Claire Sexton, Andrea Dennis- West, Andrew Farmer, Martin Tims, Hooshang Izadi, Marko Bogdanovic, Jill F. Betts, Helen Dawes

Author:
Foteini Mavrommati (MSc), Oxford University Hospitals NHS Foundation Trust- Research and Development, Oxford Brookes University- Movement Science group.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, UK
foteini.mavrommati@brookes.ac.uk & p0084589@brookes.ac.uk , phone number: 01865488212

Co- authors:
1. Johnny Collett (PhD), Oxford Brookes University.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
Jcollett@brookes.ac.uk , phone number: 01865 483630

2. Marloes Franssen (PhD), University of Oxford, Oxford Brookes University.
Postal address: Nuffield Department of Primary Care Health Sciences, Primary Care Clinical Trials Unit, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Rd, OX2 6GG, Oxford, UK
marloes.franssen@phc.ox.ac.uk , Phone number: 01865 617845

3. Andy Meaney (PhD), Oxford Brookes University.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
ameaney@brookes.ac.uk , phone number: 01865 484293

4. Claire Sexton (DPhil), University of Oxford.
Postal address: FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU
claire.sexton@ndcn.ox.ac.uk , phone number: 01865 222736

5. Andrea Dennis-West (PhD), University of Oxford
Postal address: Nuffield Department of Clinical Neurosciences, University of Oxford, OX3 9DU, Oxford, UK.
andrea.dennis@ndcn.ox.ac.uk , phone number: 01865 231511

6. Hooshang Izadi (PhD), Oxford Brookes University
Postal address: Department of Mechanical Engineering and Mathematical Sciences, Oxford Brookes University, Wheatley Campus, Wheatley, OX33 1HX, Oxford, UK
hizadi@brookes.ac.uk , phone number: 01865 7411117. Marko Bogdanovic (PhD), Royal Berkshire NHS Foundation Trust
Postal address: Department of Neurology, Royal Berkshire Hospital, RG1 5AN, Reading, UK
Marko.Bogdanovic@royalberkshire.nhs.uk , Phone number: 01189 553434

8. Martin Tims, Oxford Brookes University
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
martintims1@btinternet.com , phone number: 01865 483630

9. Andrew Farmer (PhD), University of Oxford
Postal Address: Nuffield Department of Primary Care Health Sciences, University of Oxford, OX26GG, Oxford, UK
andrew.farmer@phc.ox.ac.uk , phone number: 01865 617942

10. Jill F. Betts (PhD), University of Oxford.
Postal address: FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU
jill.f.betts@gmail.com , phone number: 01865 222780

11. Professor Helen Dawes, Oxford Brookes University, University of Oxford: Department of Clinical Neurology
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
hdawes@brookes.ac.uk , 01865 483293

Keywords: Exercise, Parkinson's disease, Rehabilitation medicine, metabolism, cardiovascular

Word count: 3.300 words (excluding title page, references, figures and tables)

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

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

Setting: Community leisure facilities.

Participants: pwP (n=83) & 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 six-month weekly exercise programme (n=37). The intervention (study (2) was a prescribed exercise program consisting of sessions lasting 60 minutes, twice a week over a period of six months. The control group followed the same protocol which derived the same cardio respiratory parameters, except the they were instructed to aim for a cadence of ~60rpm and the unloaded phase lasted 3minutes with an initial step of 25watts.

Primary and secondary outcome measures: Stepwise incremental exercise test to volitional exhaustion.

Results: Study (1) showed higher maximum values for heart rate, VO_2l.min^{-1}, VCO_2l.min^{-1} and Ventilationl.min^{-1} for the control group; Respiratory Exchange Ratio (RER), perceived exertion and O_2 Pulse (VO_2l.min^{-1}/ HR) did not differ between groups. In study (2), for pwP who adhered to the exercise programme (n=37), RER increased significantly and although there was no significant change in the aerobic capacity or heart rate response, reduced blood pressure was found.

Conclusions: An abnormal cardiovascular response to an exercise program observed in pwP compared to controls. After the exercise programme, metabolic deficiencies remained for pwP despite per-protocol analysis. These observations support an underling metabolic contribution to Parkinson's disease and add to the pathogenic understanding of the condition.

Trial registration: ClinicalTrials.Gov (NCT01439022).

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 PwP using a six month exercise intervention in a relatively large sample.
- Our findings support previous works 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 Parkinson's (pwP) and as such is an important research area [2]. There is strong evidence supporting beneficial effects of exercise programs, both in normal aging and specifically 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, whilst there is compelling data that exercise benefits motor symptoms [6], functioning, quality of life and cognition [7,4], the optimal exercise type and dose is yet to be identified. It is also not clear as to what extent reduced risk of PD associated with higher physical activity levels [8], and improvements observed in motor symptoms after exercise interventions, can both 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]. However, less is known about cardiovascular and metabolic training responses [1]. Previous studies investigating peak responses during cardiopulmonary exercise tests in pwP have contradictory results [1]. Furthermore, whilst 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, 11, 12]. Careful comparisons of the cardiovascular and metabolic exercise response and adaption to training with healthy individuals of similar activity levels, has 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 six-month combined strength and cardiovascular training program for pwP.

Methods

Design

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

Data for pwP was 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 was 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 SOPs and guidance; bio-calibrations have been performed between sites to ensure consistency.

Participants

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

Inclusion criteria for pwP were: (i) diagnosis of idiopathic PD (as defined by the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [13]); (ii) able to walk ≥100 meters. Exclusion criteria were: (i) dementia; (ii) history of additional prior neurological condition; (iii) severe depression or psychosis or a mental state that would preclude

consistent active involvement with the study over its duration; (iv) cardiac precautions that would prevent the subject from participating in the intervention; (v) any known contraindication to exercise; (vi) reduced cognitive function of any cause (Minimental state examination < 23); (vii) 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: (i) self-reported participation in fewer than 60 minutes per week of physical activity sufficient to raise their heart rate (ii) had no known contraindications to MRI scanning or fitness testing (assessed using the physical activity readiness questionnaire, physical activityR-Q. Exclusion criteria were: (i) a history of major vasculature problems or receiving heart rate-controlling medication, (ii) self-reported history or current investigation of a neurological disorder or symptoms or treatment for a psychiatric illness within the past year, (ii) and ability to commit to the requirements of study.

Intervention

The intervention for pwP was a prescribed exercise program consisting of sessions lasting 60 minutes, twice a week over a period of six 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 program was monitored by session workbooks.

The exercise programme totalled 48 sessions over a 24 week period (2x a week) and each session, which lasted 60 minutes, consisted of the following: At the start of each session, the participants performed 30 minutes of aerobic training (plus an initial 10- minute warm up) (55-85% age predicted heart rate 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 minutes, participants were instructed to aim for 30 minutes of aerobic training and exercise so that heart rate was maintained in an aerobic training zone (medication affecting heart rate was considered). Participants recorded the type of equipment used and actual duration, as well as the rating of perceived exertion and heart rate in their training diaries. The aerobic exercise was followed by 30 minutes of resistance training. The resistance training schedule consisted of leg press, leg extensions, sit to stands, 2 arm pull down, 'wood chop' [i.e. 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 the participants achieved 55-85 percentage age predicted maximal heart rate [14,15]. For the duration of the aerobic training, participants were then taught to manipulate speed or resistance in order to maintain the exercise intensity. During the strength training, Initial resistance was selected so ten repetitions could be performed. The exercise professional or physiotherapist instructed the participants that when two full sets of ten could be performed at a given resistance, within two minutes, to increase resistance. 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 program were included in the training response analysis. For these participants' data is reported for exercise tests carried out at baseline (assessment 1), three 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 three hours prior to the assessment.

For pwP test the exercise test was conducted on an electronically braked cycle ergometer (Excalibur Sport, Lode, Netherlands), integrated with a cardio pulmonary monitoring system (Metalyzer 3B, Cortex, Germany), that controlled the work rate protocol on the ergometer and recorded breath-by-breath measurements of oxygen consumption, carbon dioxide production, ventilation and heart rate (via Polar Heart Rate Monitor (Polar, Finland)) throughout the test. The work rate protocol consisted of two minutes steps starting with unloaded cycling, then increasing to 50 Watts, and there after by 25 Watts. Whilst the ergometer maintained a constant work load, independent of cadence, participants were instructed to aim for cadence of ~50rpm. At the end of each step participants were asked to rate their level of exertion (RPE) using the 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 cardio pulmonary monitoring system power output watts (W), VO_2 ($l.min^{-1}$), VCO_2 ($l.min^{-1}$), ventilation ($VEl.min^{-1}$), respiratory exchange ratio (RER =VO_2 consumed / VCO_2 produced), heart rate, O_2pulse (VO_2 /HR). Oxygen Uptake Efficiency Slope (OUES) was calculated as: VO_2 = a log VE + b, where a = OUES, VO_2in ($l.min^{-1}$) and total ventilation ($VEl.min^{-1}$).

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

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 seven days following an assessment. GENEActiv, is a triaxial acceleration sensor which is lightweight and waterproof. It sampled at 100Hz for seven days. The participants sent the monitor back in a pre-stamped, addressed envelope.

The data was downloaded from the device onto the computer and transformed into a 60-second epoch excel file. An Excel Macro was designed by GENEActiv[16] which generated minutes per day spent sedentary, performing light, moderate or vigorous activities [17]. 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-Witney 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 seconds of the test was used to calculate maximum values of measures. For exercise size response data, a Linear Mixed Models (LMM) 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 (Collett et al, 2016). 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 the control group for study 1. All participants provided written informed consent.

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

Figure 1. Study flowchart

Table 1: Baseline Descriptives

	PD (study1: n=83)	Control (n=55)	PD (study2: 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 (mmHg)	82±13 (53-138)	73±8 (57-89)	82±10 (57-102)
Sys BP (mmHg)	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)

mean±SD (range), DiaBP= Diastolic blood pressure, Sys BP =Systolic Diastolic blood pressure

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 heart rate, VO_2l.min^{-1}, VCO_2l.min^{-1} and Ventilationl.min^{-1}. However, respiratory exchange ratio, perceived exertion and O_2 Pulse (VO_2l.min^{-1}/ HR) did not differ between groups. Though exercise response parameters (slopes) differed between groups, except for OUEs, heart rate and VO_2l.min^{-1} increased at a greater rate against work rate in the control group.

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

	PD	Control	p	u	t
HR_{max} (b.min^{-1})	136 (114)	152 (108)	<0.001	1067	
VO_{2max} (l.min^{-1})	1.46 (2.35)	1.69 (2.57)	0.008	1909	
VCO_{2max} (l.min^{-1})	1.74 (2.98)	1.98 (2.67)	0.013	1745	
VE_{max}(l.min^{-1})	48.46 (99.12)	63.45 (106.3)	<0.001	1405	
O_2Pulse_{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	

Median (range), HR =Heart Rate, VE = ventilation, O_2 Pulse = VO_2/ HR, RER= Respiratory exchange ratio, RPE=Rating of perceive exertion (CR-10), OUES

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) minutes per 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 highest at the three month assessment (half way through the intervention).

Medications taken by pwP are reported in table 4.

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

	Baseline	3months	6months	P
$Time_{end}$(sec)	682 ± 40	722 ± 39	703 ± 40	0.031
HR_{max} ($b.min^{-1}$)	138 ± 3	140 ± 4	138 ± 3	0.725
VO_{2max} ($l.min^{-1}$)	1.71 ± 0.11	1.66 ± 0.11	1.66 ± 0.09	0.648
VCO_{2max} ($l.min^{-1}$)	2.00 ± 0.13	2.02 ± 0.13	1.96 ± 0.11	0.683
VE_{max}($l.min^{-1}$)	55.01 ± 4.33	55.67 ± 3.71	52.58 ± 4.31	0.724
O_2Pulse_{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_2Pulse_{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 (mmHg)	82 ± 10	75 ± 11	73 ± 13	>0.001
Sys BP (mmHg)	133 ± 20	128 ± 19	126 ± 16	0.014
MAP (mmHg)	99 ± 12	93 ± 12	91 ± 13	>0.001

Mean±SD, HR =Heart Rate, VE = ventilation, O_2 Pulse = VO_2/ HR, RER= Respiratory exchange ratio, RPE=Rating of perceive exertion (CR-10), DiaBP= Diastolic blood pressure, Sys BP =Systolic Diastolic blood pressure, MAP = mean arterial pressure

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

DA= Dopamine Agonists, AChE= Anti- cholinergic drugs, MAOI= Mono- amine Oxidase drug, Anti- Dep= Antidepressant drugs (all), MiTr= Minor Tranquiliser, betab= Beta Blockers, antiBP= Other anti-hypertensive, CVS= Other drugs affecting heart, Other= All other drugs

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 heart rate 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 over perception of effort or leg fatigue, as found in multiple sclerosis[18], 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[19]. Instead we found that whilst 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 differed to our hypotheses; there was no significant change in the aerobic capacity or HR response. However, our findings agree with the results of a pilot study, by Skidmore et al [20] in which the five enrolled participants showed improvement in peak walking workload capacity and there was no change in [VO.sub.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 O2 supply during exercise [1]. Moreover, lower cardiovascular and metabolic responses could be due to autonomic dysfunction [21, 22]. 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 [23].

Interestingly, there was a trend to reduce heart rate in response to training, suggesting an improved efficiency of cardiovascular system. We found higher diastolic and systolic blood pressure at rest in pwP despite this group being relatively active compared to the low active control group and achieving over 150 minutes of activity a week. This is in contrast to other studies that have found no difference in BP between Parkinson's disease patients and otherwise healthy people (American College of Sports Medicine 2009, Hughes 1992).

Nevertheless we found, in this per protocol analysis, weekly sixty minutes combined cardiovascular and strength exercise, had a positive effect on reducing blood pressure after three and after six months. This is in agreement with the results of a previous study which included a health benefit improvement in terms of reducing blood pressure [24] and further adds to our findings that cardio vascular changes normal whereas respiratory not. Furthermore it supports our general findings of cardiovascular adaption to exercise 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. 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 VO2 kinetics have shown that a training response would be expected in this age group [25, 26].

Our findings are extremely important taken in the context that pwP improve their movement in response to exercise[27] as they suggest that pwP have a reduced aerobic response during exercise relying 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 utilised 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 with focus on PD, especially substantive RCTs, which will explore cardiovascular, metabolic and motor symptoms responses in more detail. In addition, individualised responses to exercise should be further investigated.

Acknowledgements: We would like to thank all the people who volunteered for the studies. For their expertise and direction during the Parkinson's exercise trial we thank Maria Breen, Helen Collins and Jeremy Appleton and for delivering the intervention James Bateman, Lorreta Davis and Michael Challis and the staff at participating leisure centres (Bracknell, Bicester, Chalfont, Fleet, Hart (Fleet), Loddon Valley, Maidenhead, Newbury Leisure Centres, David Lloyd Leisure, CLEAR Unit at Oxford Brookes University and Weights and Measures, Gt Missenden). We would like to thank Oxford Primary Care Clinical Trials Unit, DeNDRoN, PCRN participating hospital clinics (John Radcliffe, Royal Berkshire and Heatherwood and Wexham Park), Parkinson's UK local groups (Oxford, Newbery, Bracknell, Wokingham, Reading, Hazlemere and High Wycombe) and Parkinson's UK and Michael J Fox foundation websites for their support. We would also like to thank Adam Thomas, D.Phil for his assistance and expertise with the control data.

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

Funding: This research was supported by the National Institute for Health Research (NIHR) research for patient benefit programme (PB-PG-0110-20250), Oxford Biomedical Research Centre (BRC) (UK) and the Oxford Health BRC. HD is supported by the Elizabeth Casson Trust; AF is a NIHR Senior Investigator. HD and AF receive support from the NIHR Oxford Biomedical Research Centre. HD and JC are both supported by Higher Education England Thames Valley.

Competing interests: None declared.

Data sharing: No additional data available

Correspondence to Miss Foteini Mavrommati, Postgraduate Research Assistant, Oxford Institute of Nursing, Midwifery and Allied Health Research, Oxford Brookes University, Gipsy Lane, Oxford, OX3 0BP
Email: foteini.mavrommati@brookes.ac.uk

Figure 1. Study Flowchart:

Fig.1. shows the participant flow. For study 1(Acute Exercise Response), 83 pwP and 55 controls were included for cross-sectional comparison. For study 2 (Adaptation to exercise) 37 pwP, who were randomised to exercise in an RCT (reported elsewhere) and adhered to the exercise programme was included.

References

1. Kanegusuku, H., et al., Blunted Maximal and Submaximal Responses to Cardiopulmonary Exercise Tests in Patients With Parkinson Disease. Arch Phys Med Rehabil, 2016. 97(5): p. 720-5.

2.National, et al., Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. 2006, London: Royal College of Physicians.

3.Petzinger, G.M., et al., Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol, 2013. 12(7): p. 716-26.

4. Caciula , M.C. et al., Exercise Frequency and Physical Function in Parkinson's Disease. Sciences of Human Kinetics, 2016. Vol.9(58) No2.

5. Caciula , M.C. et al., The effects of exercise frequency on executive function in individuals with Parkinson's disease. Mental Health and Physical Activity, 2016. 10: p.18-24.

6. Duchesne, C., et al., Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals. Neuroimage Clin, 2016. 12: p. 559-569.

7.Schenkman, M., et al., Exercise for people in early- or mid-stage Parkinson disease: a 16-month randomized controlled trial. Phys Ther, 2012. 92(11): p. 1395-410.

8.Thacker, E.L., et al., Recreational physical activity and risk of Parkinson's disease. Mov Disord, 2008. 23(1): p. 69-74.

9.Collett, J., 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, 2016.

10.Ivey, F.M., 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(8): p. 1269-76.

11.Katzel, L.I., et al., Repeatability of aerobic capacity measurements in Parkinson disease. Med Sci Sports Exerc, 2011. 43(12): p. 2381-7.

12. Scheele, C., 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: p. 74.

13. Goetz, C.G., 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(15): p. 2129-70.

14. Balcer, L.J., Clinical outcome measures for research in multiple sclerosis. J Neuroophthalmol, 2001. 21(4): p. 296-301.

15. Peppe, A., et al., Global Mobility Task: index for evaluating motor impairment and motor rehabilitation programs in Parkinson's disease patients. Acta Neurol Scand, 2007. 116(3): p. 182-9.

16. GENEActiv. 2014; Available from: http://www.geneactiv.org/.

17. Welch, W.A., et al., Cross-validation of waist-worn GENEA accelerometer cut-points. Med Sci Sports Exerc, 2014. 46(9): p. 1825-30.

18. Dawes, H., et al., Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis. Neurorehabil Neural Repair, 2014. 28(2): p. 139-48.

19. Cooper, C. and T. Storer, Exercise testing and interpretation: A practical approach. 2001, Cambridge: Cambridge University Press

20. Skidmore, F.M., et al., Pilot safety and feasibility study of treadmill aerobic exercise in Parkinson disease with gait impairment. J Rehabil Res Dev, 2008. 45(1): p. 117-24.

21. Jankovic, J., Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry, 2008. 79(4): p. 368-76.

22. Martinez-Martin, P., et al., The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord, 2011. 26(3): p. 399-406.

23. Asahina, M., et al., Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology. J Neurol Neurosurg Psychiatry, 2013. 84(6): p. 674-80.

24. Ridgel, A., et al., Enhanced Exercise Therapy in Pakinson's disease: A comparative effectiveness trial. Journal of Science and Medicine in Sport, 2016. 19: p. 12–17.

25. Buzza, G 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. 10(11).

26. Grey, T.M. et al., Effects of age and long-term endurance training on VO2 kinetics. Med Sci Sports Exerc. ,2015. 47(2): p.289-98.

27. Zhang, P. and B. Tian, Metabolic syndrome: an important risk factor for Parkinson's disease. Oxid Med Cell Longev, 2014. 2014: p. 729.

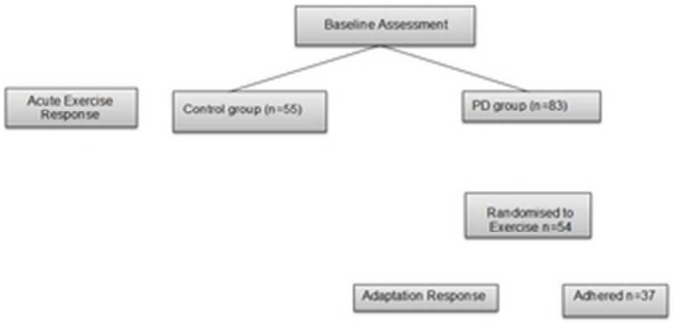


Fig.1. shows the participant flow. For study 1(Acute Exercise Response), 83 pwP and 55 controls were included for cross-sectional comparison. For study 2 (Adaptation to exercise) 37 pwP, who were randomised to exercise in an RCT (reported elsewhere) and adhered to the exercise programme was included.

29x15mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies			
	Item No	**Recommendation**	**Paper: 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**
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract	Within the title page and Design section in the abstract
		Provide in the abstract an informative and balanced summary of what was done and what was found	See Interventions and Results sections in the abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Included in the introduction- p.5
	3	State specific objectives, including any prespecified hypotheses	Included in the introduction- p.5- See last sentence
Methods			
Study Design	4	Present key elements of study design early in the paper	See Methods section- beginning- page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up and data collection	Included in Methods- different sections (p. 6-10)
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	See Methods: Participants section (p.6-7)
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed	

		Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria if applicable	See Methods: Intervention, Exercise test and Activity sections (p.7- 9)
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	See Methods: Intervention, Exercise test and Activity sections (p.7- 9)
Bias	9	Describe any efforts to address potential sources of bias	n/a to this research- It is mentioned in the trial paper for the RCT which is referenced many timed in this paper
Study Size	10	Explain how the study size was arrived at	study sample numbers explained in Methods- Participants section (p.6-7)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	See Methods: Analysis section (p.10)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	See Methods: Analysis section (p.10)
		(b) Describe any methods used to examine subgroups and interactions	See Methods: Analysis section (p.10)
		(c) Explain how missing data were addressed	See Methods: Analysis section (p.10)
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	N/A
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up and	See Results: Participants section (p.11)

		analysed	
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Included within Results (p.11)
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	See Results- Table 1 (p.12)
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Cohort study—Summarise follow-up time (e.g., average and total amount)	N/A
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence why they were included interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	See Results: Table 2 and table 3 (p12- 14)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Within Discussion (p.15-16)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	(p.16)

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Within Implications for research (p.16)
Generalisability	21	Discuss the generalisability (external validity) of the study results	Within Implications for research (p.16)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Within acknowledgements

BMJ Open

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.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017194.R2
Article Type:	Research
Date Submitted by the Author:	19-Oct-2017
Complete List of Authors:	Mavrommati, Foteini; Oxford Brookes University, Movement Science Group, OxINARH; Oxford University Hospitals NHS Foundation Trust, Research and Development Collett, Johnny; Oxford Brookes University, Movement Science Group, OxINARH Franssen, Marloes; University of Oxford , Nuffield Department of Primary Care Health Sciences ; Oxford Brookes University, Movement Science Group Meaney, Andy; Oxford Brookes University, Movement Science Group, OxINARH Sexton, Claire; University of Oxford, Nuffield Department of Clinical Neurosciences, FMRIB Centre Dennis- West, Andrea; University of Oxford, Nuffield Department of Clinical Neurosciences Izadi, Hooshang; Oxford Brookes University, Department of Mechanical Engineering and Mathematical Sciences; Oxford Brookes University, Movement Science Group, OxINARH Bogdanovic, Marko; Royal Berkshire Hospital, Department of Neurology Tims, Martin; Oxford Brookes University, Movement Science Group, OxINARH Farmer, Andrew; University of Oxford, Nuffield Department of Primary Care Health Sciences Betts, Jill; University of Oxford Nuffield Department of Clinical Neurosciences, FMRIB Centre Dawes, Helen; Oxford Brookes University, Movement Science Group, OxINARH; University of Oxford, Department of Clinical Neurology
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine, Rehabilitation medicine, Neurology
Keywords:	Exercise, Parkinson-s disease < NEUROLOGY, Rehabilitation medicine < INTERNAL MEDICINE, metabolism, cardiovascular

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.

Foteini Mavrommati, Johnny Collett, Marloes Franssen, Andy Meaney, Claire Sexton, Andrea Dennis- West, Andrew Farmer, Martin Tims, Hooshang Izadi, Marko Bogdanovic, Jill F. Betts, Helen Dawes

Author:
Foteini Mavrommati (MSc), Oxford University Hospitals NHS Foundation Trust- Research and Development, Oxford Brookes University- Movement Science group.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, UK
foteini.mavrommati@brookes.ac.uk & p0084589@brookes.ac.uk , phone number: 01865488212

Co- authors:
1. Johnny Collett (PhD), Oxford Brookes University.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
Jcollett@brookes.ac.uk , phone number: 01865 483630

2. Marloes Franssen (PhD), University of Oxford, Oxford Brookes University.
Postal address: Nuffield Department of Primary Care Health Sciences, Primary Care Clinical Trials Unit, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Rd, OX2 6GG, Oxford, UK
marloes.franssen@phc.ox.ac.uk , Phone number: 01865 617845

3. Andy Meaney (PhD), Oxford Brookes University.
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
ameaney@brookes.ac.uk , phone number: 01865 484293

4. Claire Sexton (DPhil), University of Oxford.
Postal address: FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU
claire.sexton@ndcn.ox.ac.uk , phone number: 01865 222736

5. Andrea Dennis-West (PhD), University of Oxford
Postal address: Nuffield Department of Clinical Neurosciences, University of Oxford, OX3 9DU, Oxford, UK.
andrea.dennis@ndcn.ox.ac.uk , phone number: 01865 231511

6. Hooshang Izadi (PhD), Oxford Brookes University
Postal address: Department of Mechanical Engineering and Mathematical Sciences, Oxford Brookes University, Wheatley Campus, Wheatley, OX33 1HX, Oxford, UK
hizadi@brookes.ac.uk , phone number: 01865 7411117. Marko Bogdanovic (PhD), Royal Berkshire NHS Foundation Trust
Postal address: Department of Neurology, Royal Berkshire Hospital, RG1 5AN, Reading, UK
Marko.Bogdanovic@royalberkshire.nhs.uk , Phone number: 01189 553434

8. Martin Tims, Oxford Brookes University
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
martintims1@btinternet.com , phone number: 01865 483630

9. Andrew Farmer (PhD), University of Oxford
Postal Address: Nuffield Department of Primary Care Health Sciences, University of Oxford, OX26GG, Oxford, UK
andrew.farmer@phc.ox.ac.uk , phone number: 01865 617942

10. Jill F. Betts (PhD), University of Oxford.
Postal address: FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU
jill.f.betts@gmail.com , phone number: 01865 222780

11. Professor Helen Dawes, Oxford Brookes University, University of Oxford: Department of Clinical Neurology
Postal address: Oxford Institute of Nursing, Midwifery and Allied Health Research- Oxford Brookes University- Gipsy Lane, OX3 0BP, Oxford, UK
hdawes@brookes.ac.uk , 01865 483293

Keywords: Exercise, Parkinson's disease, Rehabilitation medicine, metabolism, cardiovascular

Word count: 3.418 words (excluding title page, references, figures and tables)

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

Design: 1) A cross sectional study of exercise response of pwP compared to sedentary controls,2) an interventional study of exercise training in pwP.

Setting: Community leisure facilities.

Participants: pwP (n=83) & 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 six-month weekly exercise programme (n=37). The intervention (study (2) was a prescribed exercise program consisting of sessions lasting 60 minutes, twice a week over a six-month period. The control group followed the same protocol which derived the same cardio respiratory parameters, except the they were instructed to aim for a cadence of ~60rpm and the unloaded phase lasted 3minutes with an initial step of 25watts.

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, VO_2l.min^{-1}, VCO_2l.min^{-1} and Ventilation l.min^{-1} for the control group; Respiratory Exchange Ratio (RER), perceived exertion and O_2 Pulse (VO_2l.min^{-1}/ 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 heart rate 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

Trial registration: ClinicalTrials.Gov (NCT01439022).

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 PwP using a six 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 Parkinson's (pwP); as such this is an important research area [2]. There is strong evidence supporting beneficial effects of exercise programs both in normal aging 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, whilst there is compelling data that exercise benefits motor symptoms [6], functioning, quality of life and cognition [7,4], 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, whilst 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, has 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 six-month combined strength and cardiovascular training program for pwP. Methods

Design

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

Data for pwP was 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 was 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 SOPs and guidance; bio-calibrations have been performed between sites to ensure consistency.

Participants

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

Inclusion criteria for pwP were: (i) diagnosis of idiopathic PD (as defined by the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [14); (ii) able to walk ≥100 meters. Exclusion criteria were: (i) dementia; (ii) history of additional prior neurological condition; (iii) severe depression or psychosis or a mental state that would preclude consistent active involvement with the study over its duration; (iv) cardiac precautions that would prevent the subject from participating in the intervention; (v) any known contraindication to exercise; (vi) reduced cognitive function of any cause (Minimental state

examination < 23); (vii) 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: (i) self-reported participation in fewer than 60 minutes per week of physical activity sufficient to raise their heart rate (ii) had no known contraindications to MRI scanning or fitness testing (assessed using the physical activity readiness questionnaire, physical activityR-Q. Exclusion criteria were: (i) a history of major vasculature problems or receiving heart rate-controlling medication, (ii) self-reported history or current investigation of a neurological disorder or symptoms or treatment for a psychiatric illness within the past year, (ii) and ability to commit to the requirements of study.

Intervention

The intervention for pwP was a prescribed exercise program consisting of sessions lasting 60 minutes, twice a week over a period of six 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 program was monitored by session workbooks.

The exercise programme totalled 48 sessions over a 24 week period (2x a week) and each session, which lasted 60 minutes, consisted of the following: At the start of each session, the participants performed 30 minutes of aerobic training (plus an initial 10- minute warm up) (55-85% age predicted heart rate 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 minutes, participants were instructed to aim for 30 minutes of aerobic training and exercise so that heart rate was maintained in an aerobic training zone (medication affecting heart rate was considered). Participants recorded the

type of equipment used and actual duration, as well as the rating of perceived exertion and heart rate in their training diaries. The aerobic exercise was followed by 30 minutes of resistance training. The resistance training schedule consisted of leg presses, leg extensions, sit to stands, 2 arm pull down, 'wood chop' [i.e. 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 percentage age predicted maximal heart rate [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 ten repetitions could be performed. The exercise professional or physiotherapist instructed the participants to increase resistance when two full sets of ten could be performed at a given resistance, within two minutes. 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 program were included in the training response analysis. For these participants' data is reported for exercise tests carried out at baseline (assessment 1), three 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 three hours prior to the assessment.

For pwP test the exercise test was conducted on an electronically braked cycle ergometer (Excalibur Sport, Lode, Netherlands), integrated with a cardio pulmonary monitoring system (Metalyzer 3B, Cortex, Germany), that controlled the work rate protocol on the ergometer and recorded breath-by-breath measurements of oxygen consumption, carbon dioxide production, ventilation and heart rate (via Polar Heart Rate Monitor (Polar, Finland)) throughout the test. The work rate protocol consisted of two minutes steps starting with unloaded cycling, then increasing to 50 Watts, and there after by 25 Watts. Whilst the ergometer maintained a constant work load, independent of cadence, participants were instructed to aim for cadence of ~50rpm. At the end of each step participants were asked to rate their level of exertion (RPE) using the 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 cardio pulmonary monitoring system power output watts (W), VO_2 ($l.min^{-1}$), VCO_2 ($l.min^{-1}$), ventilation ($VEl.min^{-1}$), respiratory exchange ratio (RER =VO_2 consumed / VCO_2 produced), heart rate, O_2pulse (VO_2 /HR). Oxygen Uptake Efficiency Slope (OUES) was calculated as: VO_2 = a log VE + b, where a = OUES, VO_2in ($l.min^{-1}$) and total ventilation ($VEl.min^{-1}$).

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

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 seven days following an assessment. GENEActiv, is a triaxial acceleration sensor which is lightweight and waterproof. It sampled at 100Hz for seven days. The participants sent the monitor back in a pre-stamped, addressed envelope.

The data was downloaded from the device onto the computer and transformed into a 60-second 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-Witney 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 seconds of the test was used to calculate maximum values of measures. For exercise size response data, a Linear Mixed Models (LMM) 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 (Collett et al, 2016). 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 the control group for study 1. All participants provided written informed consent.

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

Figure 1. Study flowchart

Table 1: Baseline Descriptives

	PD (study1: n=83)	Control (n=55)	PD (study2: 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 (mmHg)	82±13 (53-138)	73±8 (57-89)	82±10 (57-102)
Sys BP (mmHg)	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)

mean±SD (range), DiaBP= Diastolic blood pressure, Sys BP =Systolic Diastolic blood pressure

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 heart rate, VO_2l.min^{-1}, VCO_2l.min^{-1} and Ventilationl.min^{-1}. However, respiratory exchange ratio, perceived exertion and O_2 Pulse (VO_2l.min^{-1}/ HR) did not differ between groups. Though exercise response parameters (slopes) differed between groups, except for OUEs, heart rate and VO_2l.min^{-1} increased at a greater rate against work rate in the control group.

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

	PD	Control	p	u	t
HR_{max} (b.min^{-1})	136 (114)	152 (108)	<0.001	1067	
VO_{2max} (l.min^{-1})	1.46 (2.35)	1.69 (2.57)	0.008	1909	
VCO_{2max} (l.min^{-1})	1.74 (2.98)	1.98 (2.67)	0.013	1745	
VE_{max}(l.min^{-1})	48.46 (99.12)	63.45 (106.3)	<0.001	1405	
O_2Pulse_{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	

Median (range), HR =Heart Rate, VE = ventilation, O_2 Pulse = VO_2/ HR, RER= Respiratory exchange ratio, RPE=Rating of perceive exertion (CR-10), OUES

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) minutes per 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 highest at the three month assessment (half way through the intervention).

Medications taken by pwP are reported in table 4.

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

	Baseline	3months	6months	P
$Time_{end}$(sec)	682 ± 40	722 ± 39	703 ± 40	0.031
HR_{max} ($b.min^{-1}$)	138 ± 3	140 ± 4	138 ± 3	0.725
VO_{2max} ($l.min^{-1}$)	1.71 ± 0.11	1.66 ± 0.11	1.66 ± 0.09	0.648
VCO_{2max} ($l.min^{-1}$)	2.00 ± 0.13	2.02 ± 0.13	1.96 ± 0.11	0.683
VE_{max}($l.min^{-1}$)	55.01 ± 4.33	55.67 ± 3.71	52.58 ± 4.31	0.724
O_2Pulse_{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_2Pulse_{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 (mmHg)	82 ± 10	75 ± 11	73 ± 13	>0.001
Sys BP (mmHg)	133 ± 20	128 ± 19	126 ± 16	0.014
MAP (mmHg)	99 ± 12	93 ± 12	91 ± 13	>0.001

Mean±SD, HR =Heart Rate, VE = ventilation, O_2 Pulse = VO_2/ HR, RER= Respiratory exchange ratio, RPE=Rating of perceive exertion (CR-10), DiaBP= Diastolic blood pressure, Sys BP =Systolic Diastolic blood pressure, MAP = mean arterial pressure

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

DA= Dopamine Agonists, AChE= Anti- cholinergic drugs, MAOI= Mono- amine Oxidase drug, Anti- Dep= Antidepressant drugs (all), MiTr= Minor Tranquiliser, betab= Beta Blockers, antiBP= Other anti-hypertensive, CVS= Other drugs affecting heart, Other= All other drugs

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 heart rate 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 over perception 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 whilst 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 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.sub.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 O2 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 heart rate in response to training, suggesting an improved efficiency of cardiovascular system. We found higher diastolic and systolic blood pressure at rest in pwP despite this group being relatively active compared to the low active control group and achieving over 150 minutes of activity a week. This is in contrast to other studies that have found no difference in BP between Parkinson's disease patients and otherwise healthy people (American College of Sports Medicine 2009, Hughes 1992).

Nevertheless we found, in this per protocol analysis, weekly sixty minutes of combined cardiovascular and strength exercise, had a positive effect on reducing blood pressure after three and after six months. This is in agreement with the results of a previous study which reported a health benefit of reduced blood pressure [25] 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. 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 VO2 kinetics have shown that a training response would be expected in this age group [26, 27].

PwP present improved movement in response to exercise [28]. 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 utilised 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.

Acknowledgements: We would like to thank all the people who volunteered for the studies. For their expertise and direction during the Parkinson's exercise trial we thank Maria Breen, Helen Collins and Jeremy Appleton and for delivering the intervention James Bateman, Lorreta Davis and Michael Challis and the staff at participating leisure centres (Bracknell, Bicester, Chalfont, Fleet, Hart (Fleet), Loddon Valley, Maidenhead, Newbury Leisure Centres, David Lloyd Leisure, CLEAR Unit at Oxford Brookes University and Weights and Measures, Gt Missenden). We would like to thank Oxford Primary Care Clinical Trials Unit, DeNDRoN, PCRN participating hospital clinics (John Radcliffe, Royal Berkshire and Heatherwood and Wexham Park), Parkinson's UK local groups (Oxford, Newbery, Bracknell, Wokingham, Reading, Hazlemere and High Wycombe) and Parkinson's UK and Michael J Fox foundation websites for their support. We would also like to thank Adam Thomas, D.Phil for his assistance and expertise with the control data.

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

Funding: This research was supported by the National Institute for Health Research (NIHR) research for patient benefit programme (PB-PG-0110-20250), Oxford Biomedical Research Centre (BRC) (UK) and the Oxford Health BRC. HD is supported by the Elizabeth Casson Trust; AF is a NIHR Senior Investigator. HD and AF receive support from the NIHR Oxford Biomedical Research Centre. HD and JC are both supported by Higher Education England Thames Valley.

Competing interests: None declared.

Data sharing: No additional data available

Correspondence to Miss Foteini Mavrommati, Postgraduate Research Assistant, Oxford Institute of Nursing, Midwifery and Allied Health Research, Oxford Brookes University, Gipsy Lane, Oxford, OX3 0BP
Email: foteini.mavrommati@brookes.ac.uk

Figure 1. Study Flowchart:

Fig.1. shows the participant flow. For study 1(Acute Exercise Response), 83 pwP and 55 controls were included for cross-sectional comparison. For study 2 (Adaptation to exercise) 37 pwP, who were randomised to exercise in an RCT (reported elsewhere) and adhered to the exercise programme was included.

References

1. Kanegusuku, H., et al., Blunted Maximal and Submaximal Responses to Cardiopulmonary Exercise Tests in Patients with Parkinson Disease. Arch Phys Med Rehabil, 2016. 97(5): p. 720-5.

2.National, et al., Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. 2006, London: Royal College of Physicians.

3.Petzinger, G.M., et al., Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol, 2013. 12(7): p. 716-26.

4. Caciula , M.C. et al., Exercise Frequency and Physical Function in Parkinson's Disease. Sciences of Human Kinetics, 2016. Vol.9(58) No2.

5. Caciula , M.C. et al., The effects of exercise frequency on executive function in individuals with Parkinson's disease. Mental Health and Physical Activity, 2016. 10: p.18-24.

6. Duchesne, C., et al., Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals. Neuroimage Clin, 2016. 12: p. 559-569.

7.Schenkman, M., et al., Exercise for people in early- or mid-stage Parkinson disease: a 16-month randomized controlled trial. Phys Ther, 2012. 92(11): p. 1395-410.

8.Thacker, E.L., et al., Recreational physical activity and risk of Parkinson's disease. Mov Disord, 2008. 23(1): p. 69-74.

9.Collett, J., 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, 2016.

10.Ivey, F.M., 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(8): p. 1269-76.

11.Kanegusuku, H., 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.

12.Katzel, L.I., et al., Repeatability of aerobic capacity measurements in Parkinson disease. Med Sci Sports Exerc, 2011. 43(12): p. 2381-7.

13. Scheele, C., 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: p. 74.

14. Goetz, C.G., 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(15): p. 2129-70.

15. Balcer, L.J., Clinical outcome measures for research in multiple sclerosis. J Neuroophthalmol, 2001. 21(4): p. 296-301.

16. Peppe, A., et al., Global Mobility Task: index for evaluating motor impairment and motor rehabilitation programs in Parkinson's disease patients. Acta Neurol Scand, 2007. 116(3): p. 182-9.

17. GENEActiv. 2014; Available from: http://www.geneactiv.org/.

18. Welch, W.A., et al., Cross-validation of waist-worn GENEA accelerometer cut-points. Med Sci Sports Exerc, 2014. 46(9): p. 1825-30.

19. Dawes, H., et al., Delayed recovery of leg fatigue symptoms following a maximal exercise session in people with multiple sclerosis. Neurorehabil Neural Repair, 2014. 28(2): p. 139-48.

20. Cooper, C. and T. Storer, Exercise testing and interpretation: A practical approach. 2001, Cambridge: Cambridge University Press

21. Skidmore, F.M., et al., Pilot safety and feasibility study of treadmill aerobic exercise in Parkinson disease with gait impairment. J Rehabil Res Dev, 2008. 45(1): p. 117-24.

22. Jankovic, J., Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry, 2008. 79(4): p. 368-76.

23. Martinez-Martin, P., et al., The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord, 2011. 26(3): p. 399-406.

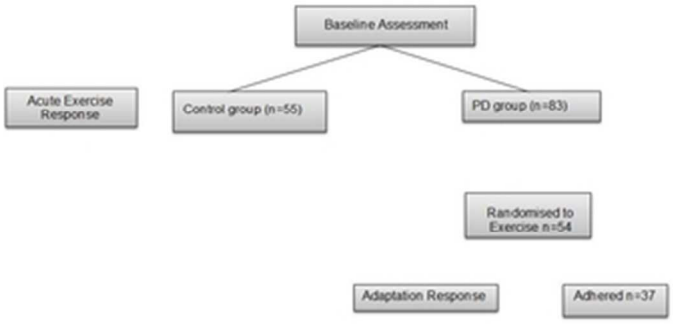
24. Asahina, M., et al., Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology. J Neurol Neurosurg Psychiatry, 2013. 84(6): p. 674-80.

25. Ridgel, A., et al., Enhanced Exercise Therapy in Pakinson's disease: A comparative effectiveness trial. Journal of Science and Medicine in Sport, 2016. 19: p. 12–17.

26. Buzza, G 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. 10(11).

27. Grey, T.M. et al., Effects of age and long-term endurance training on VO2 kinetics. Med Sci Sports Exerc. ,2015. 47(2): p.289-98.

28. Zhang, P. and B. Tian, Metabolic syndrome: an important risk factor for Parkinson's disease. Oxid Med Cell Longev, 2014. 2014: p. 729.



29x15mm (300 x 300 DPI)