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Factors associated with limited exercise capacity and feasibility of high intensity interval training in people with mild to moderate Parkinson's disease

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Factors associated with limited exercise capacity and feasibility of high intensity interval training in people with mild to moderate Parkinson's disease

Abstract

Background/Aims:

Fitness and function can improve with exercise in people with Parkinson's Disease. Animal models suggest that exercise may also have a neuro-protective effect, with higher intensity exercise being more beneficial than lower intensity exercise. However, in people with Parkinson's disease the factors limiting exercise capacity are not fully understood and it is unclear whether training at very high intensities would be safe, feasible and acceptable.

Methods:

Eighteen people with Parkinson's disease were recruited to explore respiratory and neuromuscular factors that may limit exercise capacity. In a purposive subgroup of 6 participants able to achieve >75% of their predicted maximum heart rate the feasibility of undertaking six high intensity interval training sessions over 3 weeks was tested. Their experience was further explored in a focus group.

Findings:

Lower exercise capacity was associated with lower limb flexor muscle strength (r^2=0.51) but not with disease severity or respiratory function. There were no adverse events or drop-outs in those taking part in the exercise regimen. Improvements were seen in fitness, health related quality of life, activity levels, walking speed, muscle strength and cycle endurance. Participants reported that they enjoyed high intensity, supervised exercise. High intensity interval training may be feasible and safe.

Keywords

Parkinson's disease, exercise, physical fitness

Factors associated with limited exercise capacity and feasibility of high intensity interval training in people with mild to moderate Parkinson's disease

Introduction

Parkinson's Disease (PD) is a neurodegenerative condition with a prevalence of 105-178 per 100,000 (Hobson, Gallacher and Meara, 2005). It leads to motor symptoms such as bradykinesia, rigidity and tremor and non-motor symptoms such as sleep disturbances, autonomic dysfunction, abulia, cognitive deficit, dementia, anxiety and depression (Shulman et al., 2001). Lack of mobility and engagement in regular exercise can lead to reduced aerobic capacity in people with PD with the maximal oxygen consumption (VO_{2max}) being 34% lower than healthy controls (Speelman et al., 2012). Participation in exercise can improve function, quality of life, balance, muscle strength and gait in people with PD (Goodwin et al., 2008; Allen et al., 2012; van der Kolk and King, 2013; Murphy et al., 2012; Murray et al., 2014; Prodoehl et al., 2014). However, significant barriers exist and limit the uptake and maintenance of regular physical activity and development of exercise habits in PD and in neuromuscular conditions more generally (Phillips, Flemming and Tsintzas, 2009; Ellis et al., 2013). These barriers include low expectations of its benefits, fear of falling or worsening of symptoms and a perceived lack of time (Ellis et al., 2011, 2013). Current guidelines advise that people with PD should exercise at least 150 min/week (Durstine and Moore, 2003). This may be increasingly challenging for a person with a deteriorating movement disorder. Therefore, exercising more intensively but at less volume may help to overcome this barrier.

High intensity interval training (HIT) is a specific mode of intensive exercise training that involves high intensity bursts of activity at 75-100% of maximum heart rate, but with low volume duration (Gibala and Little, 2010; Gibala and McGee, 2008). Findings from studies involving healthy young and older participants as well as in individuals with diabetes, hypertension and heart conditions (Adamson et al., 2014; Burgomaster et al., 2008; Gibala et al., 2012; Hood et al., 2011; Wisløff et al., 2007; Ciolac, 2012) have shown that exercising at higher intensities but reduced volume has similar or even better health benefits compared to more traditional endurance type exercise. Exercising more intensively and for shorter periods of time may also be more enjoyable, thus contributing to better exercise adherence outside of the laboratory setting (Bartlett et al., 2011; Jung et al., 2015). Higher intensity exercise has also shown promising results in people with PD in preliminary

studies using strength training (Allen et al., 2012), assisted cycling (Ridgel, Vitek and Alberts, 2009) and treadmill training (Rose et al., 2013) as exercise modes.

In addition to achieving shorter term improvements in function animal models of PD suggest that exercise may also have a longer term neuroprotective effect (Zigmond et al., 2012). This is partly caused by the release of Brain Derived Neurotrophic Factor (BDNF) with exercise. BDNF stimulates several processes that underlie neuroprotection such as long term potentiation, synaptogenesis and neurogenesis. In both animals and humans greater BDNF levels are seen with higher exercise intensity levels (Schmolesky, Webb and Hansen, 2013). Exercise at higher intensities may therefore have additional neuroprotective benefits in people with PD as well as being less time consuming and potentially being associated with greater exercise adherence. However, it is unclear whether symptoms seen in people with PD may limit their ability to exercise at the required high intensity and whether repetitive training at higher intensities is feasible and safe in this population.

Symptom severity is a potentially important factor limiting exercise capacity and the ability to undertake HIT in people with PD. Knee extensor muscle strength limits chair-rise performance whilst a lower walking capacity, as defined by the distance walked in 6 minutes, is associated with greater hypokinesia and lower knee extensor strength (Canning et al., 2006; Pääsuke et al., 2004). Cardiorespiratory factors may also limit exercise capacity on a cycle ergometer stress test. Respiratory muscle weakness has been found to limit the number of stages completed on an exercise stress test (Haas, Trew and Castle, 2004) although Canning et al. (1997) found no relationship with VO_2 peak and measures of respiratory function or symptom severity. In a large observational study (n=546) (Speelman et al., 2012) an inadequate heart rate response was seen during a submaximal, cycle ergometer exercise test. This was felt to be related to autonomic dysfunction and was associated with a higher body weight, lower systolic blood pressure, lower resting heart rate and lower maximal workload.

The aim of this study was therefore to explore the neuromuscular and respiratory factors that were associated with limited exercise capacity in people with PD and, in a purposive sample who could exercise at high intensity, whether repeated training at this level was feasible and safe.

Methods

Methodology: This study was conducted in 2 stages. Stage 1 consisted of a cross sectional observational study design to explore factors limiting exercise capacity in people with PD. Stage 2 was a non-randomised controlled study (before and after design) that aimed to assess the feasibility of HIT training in people with PD. Figure 1 shows the outline of the study design.

Figure 1 approximately here

Setting and Timescales: The study was performed in the Human Movement and Function Laboratory at Plymouth University between October and December 2013.

Participants: Participants were recruited through the advertising and mailing to the local Parkinson's UK group. Participants were included if they had a diagnosis of PD and had a symptom severity defined as Hoehn and Yahr 1-4 (Hoehn and Yahr, 1967). Participants were excluded if they had other neurological conditions in addition to PD or other orthopaedic or cardiovascular conditions which would limit their ability to exercise. We recruited an initial 37 participants, following telephone screening of eligibility criteria and after providing further information, eighteen participants were recruited.

Ethical Approval: This study was approved by the Plymouth University Ethics committee. All people participated with informed written consent in accordance with the Declaration of Helsinki.

Procedure and Interventions:

Stage 1: Factors associated with limited exercise capacity in people with PD

Eighteen individuals were recruited through the local Parkinson's UK group. The sample Size was based on Canning et al 2006 (Canning et al., 2006) who found a correlation between walking capacity and knee extensor strength (r^2=0.30) and hypokinesia while turning (r2=0.38). To detect a r^2 of 0.36 (power=0.8) required a sample size of 18 participants.

The following measures were taken by the same researcher (SC) who followed standardised operating procedures based on guidelines from the Movement Disorders Society (Goetz et al., 2007), previous research and instrument manufacturers as indicated:

1. Unified Parkinson's Disease Rating Scale (UPDRS) scores for tremor, leg agility, rigidity and freezing (Goetz et al., 2007)
2. Inspiratory muscle strength (Maximum Inspiratory Mouth Pressure - MIP); Micro Medical Respiratory Pressure Metre, Micro Medical, Rochester, Kent).
3. Respiratory function (Forced Vital Capacity - FVC) and Forced Expiratory Volume in one second (FEV1) (Micro Medical Micro Lab, Micro Medical Rochester UK)
4. Lower limb isokinetic muscle strength (100º/sec speed) for knee extensors and flexors (Biodex System 3 IPRS, Ipswich UK)
5. Health Related Quality of Life questionnaire (PDQ-39) (Jenkinson et al., 1997)
6. Activity levels over the past week (Phone-FITT questionnaire) (Gill et al., 2008)
7. Walking function using the Timed up and Go test (TUG) (Nordin et al., 2008)

In tests 2-4 three attempts were measured and the best of the three tests assessed.

Exercise capacity was evaluated by measuring maximal oxygen uptake (VO_2max), peak heart rate (HRpeak), rating of perceived exertion (RPE) (Borg, 1998) and exercise endurance (total duration of cycling against load until pedalling could no longer be maintained) during an incremental exercise stress test on a cycle ergometer (Monark 939E, Monark, Vansbro, Sweden), based on a previously used protocol (Haas, Trew and Castle, 2004).Measures of VO_2max have been previously shown to be reliable in people with PD (Katzel et al., 2011).Workloads started at 25W and increased by 25W every 2 minutes up to a maximum of 175W (7 stages), whilst participants maintained a steady pedalling rhythm of 50 revolutions/min. Heart rate was measured with short-distance telemetry (Polar, Kempele, Finland), and oxygen consumption was measured via a face mask linked to a Metamax metabolic test system (Cortex Biophysik, Leipzig, Germany).Verbal encouragement throughout was used to help participants continue cycling until they felt unable to maintain the workload or until the test was completed or terminated for any of the pre-determined reasons following recognised guidelines (American College of Sports Medicine, 2014). The exercise testing was always supervised by two experienced physiotherapists.

The relationship between fitness capacity for HIT (represented in our study by HRpeak and VO_2max) and tests 1-4 were assessed using a linear regression. Data from test 1-4 was normally distributed as assessed using a Shaprio-Wilks test.

Stage 2: Feasibility of HIT in a purposive sample

A purposive sample of six was selected from our original pool of eighteen to take part in six HIT training sessions over three weeks. These were the first six individuals who reached > 75% of their HR_{max} and were also able to commit to six exercise training sessions over the following three weeks.

Training started and finished with a 5 minute low resistance warm up/ down on the ergometer. Training consisted of cycle ergometer sessions using a modified Wingate protocol with 10 one minute bursts at HR_{peak} to HR_{max} interspersed with one minute cycling against zero workload. The training load was the level gained when achieving the HR_{peak} in the exercise stress test and so was individualised to each participant. Participants performed training with one-to-one supervision provided by a physiotherapist (SC) with experience in exercise prescription, supervision and monitoring. Standardised verbal encouragement was provided throughout.

Within three days of the final exercise session measures 1-7 from stage 1 were repeated with these six individuals. Differences between pre and post exercise measurements were assessed using descriptive statistics and effect sizes calculated. Feasibility was assessed in terms of participant drop out, presence of adverse events and participants' subjective view. These views also provided insight into the participants' overall experience of the exercise regimen and helped to develop recommendations for future research. Views were assessed six weeks after the final test in a focus group interview (facilitated by BH) with all the exercising participants from stage 2. The facilitator used semi structured interview questions and was recorded and transcribed verbatim.

The analysis of the transcripts followed guidance by Smith (Smith, 1995); this involved reading the interview transcript a number of times to obtain an overall impression of participants' views and making notes of any potential themes and meaningful statements. Groups of statements were then categorised and themes identified looking for commonalities while not discounting minority view points. The themes were initially clustered around positive and less positive aspects of the exercise experience. The transcript was continually interrogated to assess the extent to which the statements provided consistent as well as divergent viewpoints from all participants and if they provided a reflection of the themes. We also identified recommendations for the provision of any future HIT exercise sessions.

Findings

Stage 1: Factors associated with limited exercise capacity in people with PD

Eighteen people with PD (15 men and 3 women) with a mean age of 65.11 years (±6.2), a mean of 8.5 years since diagnosis (±3.8) and at Hoehn & Yahr stages 1-4 were assessed. Of the eighteen participants twelve (66.7%) reached over 75% of their HRmax at the end of the incremental exercise test. The main reason for terminating the exercise test was leg fatigue, which was reported by sixteen participants. One participant reported knee pain during the fifth increment and the test was terminated at that point. Only one participant completed all seven increments of the exercise test and felt that he could have continued further. As a group (n=18) measured maximal inspiratory muscle strength (MIP) was significantly lower than the predicted values (Wilson et al., 1984) for MIP (measured mean 55.83 cmH2O ±25.1; predicted mean 74.50 cmH2O ±6.3; p=0.006, table 1). This was also the case for the other respiratory function values which were also significantly lower than their predicted values (European Respiratory Society, 1993) (FVC measured mean 3.31 litre ±0.9; predicted mean 4.01 litre ±0.7; p=0.003 ; FEV1 measured mean 2.71 litre ± 0.7; predicted mean 3.14 litre ±0.5; p=0.01,table 1).

Table 1 approx here

Higher knee flexor muscle strength was associated with higher VO_2max (p=0.001; R^2= 0.51). None of the other impairment measurements (tests 1-4) were associated with either HRpeak or VO2max.

Stage 2: Feasibility of HIT in a purposive sample

The six participants who were selected for the exercise intervention did not differ from those who were not selected in any of the measurements ($p > 0.05$) except for having higher knee flexor muscle strength (table 1). This is in keeping with the finding that higher knee strength was associated with higher VO_2max. HR_{peak} was lower ($p < 0.05$) in the group which was not selected for the exercise programme, as it included those who did not reach 75% of their HR_{max}. Importantly the selected group included a wide range of disease severities (Hoehn and Yahr 1-4)

The weekly exercise training commitment was 48 minutes, of which 20 minutes were at high intensity, the remaining 28 minutes were at low intensity cycling against zero workload. There were no drop outs and all participants completed all six exercise training sessions. No adverse effects were noted during training.

Disease severity (Hoehn & Yahr scores and UPDRS scores) did not change following the exercise training. Table 2 shows the outcome measures before and after training and their effect sizes. Improvements were seen in all measurements with cycle endurance time showing the largest increase (effect size= 0.73).

Table 2 approx here

Qualitative focus group themes

The focus group interview lasted approximately an hour and twenty minutes and a number of themes emerged. Below are direct quotes from the participants; all names have been changed.

HIT is enjoyable: All participants reported that they found the HIT exercise enjoyable, contributing to better mood and motivation.

… I could see the improvement I had achieved. Parkinson's doesn't have to stop you exercising. I know it sounds obvious but I never really believed I could improve on something again … (Johnny)

… I was elated. I was euphoric in the end that I had achieved it… (Jack)

HIT is preferred to low intensity exercise: Those who also engaged in other less intensive exercise preferred the high intensity nature of HIT

… I preferred it to the hour on [exercise weekday] really to be honest… (James)

Improved wellbeing: Others spoke of improvements in confidence and receiving compliments from friends about a healthy complexion. All of this contributed to an improved sense of wellbeing. One participant also reported that he slept much better and that this also made him feel better overall.

… at least half a dozen people told me "you don't half look well… (James)

… maybe it's confidence in that you've achieved something and you can do it. It does make you feel more confident… (Ruth)

HIT is perceived to increase muscle strength and activity levels: and that this increase in strength had encouraged them to do more, be more active and exercise more. Some were so pleased with the cycling that they have now purchased their own personal cycle ergometer.

… It encouraged me to walk more; [my wife] used to go and get the paper in the morning and I said I'm gonna go now … (Jack)

… My walking has got better, definitively, no doubt about that … (Penny)

HIT can cause temporary muscle soreness: All participants reported that they had temporary muscle soreness as a consequence of exercising hard and maybe not being used to that initially.

... I really enjoyed it, but after the first session, my legs ached ... (Johnny)

HIT in a group setting would assure motivation: The group experience was seen as positive and being able to exercise together as a group was suggested. The group experience could provide that element of competition and help motivate individuals to exercise intensively and also to commit to attend the exercises.

... you have the small group and if you're committed to that you're more likely to continue ... (Penny)

HIT needs facilitation and staff expertise: An important aspect of the success of HIT exercises would be to have a good facilitator. This person would also provide monitoring for safety. Some thought that being pushed by the facilitators helped them to exercise intensively – and likewise without a facilitator this may not have been the case. The intensive nature of the exercise had been a concern to some and therefore they needed the assurance of careful screening and monitoring during exercise. They would definitively like to see this included in any future arrangement. Some thought that without the presence of monitoring and trained personal in attendance, they would feel less safe and therefore less inclined to push themselves as much.

... I thought [instructor name] was a terrific motivator. There were times when you could see [participant's name] flagging and [instructor name] was really good at keeping her going ... (George)

... it was quite nice to actually push yourself and be measured within a safe environment…it was within restraints and I was being monitored, so I felt happy with that than I would have just getting on a bike at home and pushing ... (Ruth)

Discussion

This study aimed to explore in people with mild to moderate Parkinson's disease the factors associated with limited exercise capacity as measured using a cycle ergometer stress test. Further, in a purposive sample of people with PD who could exercise at high intensity we assessed whether repeated high intensity training was feasible and safe.

Factors associated with limited exercise capacity in people with PD

This study assessed the association between some factors and limited exercise capacity in people with PD. The factors chosen (PD symptoms, leg strength and respiratory function) were based upon previous research exploring this relationship (Haas, Trew and Castle, 2004; Speelman et al., 2012) . The majority of our participants felt subjectively limited by leg strength and terminated the test when they felt they 'could no longer pedal'. Strength of the flexor leg muscles around the knee was significantly associated with VO_2max (r^2=0.51), suggesting that weakness of the hamstrings or ability to activate the hamstrings during a cycling pedal motion is associated with reduced exercise capacity and may limit the ability to take part in HIT on a cycle ergometer. In our experiment the participant's feet were 'strapped' to the ergometer pedal and therefore hamstrings would normally participate in the cycling effort. Our findings may be very specific to cycling activity and not relevant to other forms of exercise, such as running or jogging.

Regression analysis showed that neither the major motor symptoms of PD (tremor, rigidity, hypokinesia, freezing) nor disease progression were strongly related to exercise capacity. All participants were able to initially achieve the required 50 revolutions / minute during the stress test further highlighting in this mild-moderate group that hypokinesia may not have been a primary limiting factor to completing the test. Respiratory function was significantly lower than we would have expected from prediction equations. However, respiratory function was not associated with exercise capacity; previous research has provided contradictory findings, (Canning et al., 1997; Haas, Trew and Castle, 2004), which may be explained by the duration of the exercise increments.

Speelman et al. (2012) found that approximately half of the people with PD were not able to achieve the predicted heart rate increase during a submaximal exercise test whilst others (Haas, Trew and Castle, 2004) found that approximately a third of participants were able to reach >75% of their HR_{peak}. In the present study we found that 32% of the total population screened (n=37) and 66% of those tested (n=18) achieved HR_{peak} >75%.

Factors such as lower limb weakness and autonomic dysfunction may therefore limit the ability to achieve an adequate HR_{peak} (Speelman et al., 2012).

Stage 2: Feasibility of HIT in a purposive sample

This study showed that a small convenience sample of individuals with mild to moderate PD were able to participate safely in HIT over a 3 week period. All participants tolerated the exercise regimen and there were no dropouts, missed exercise sessions or adverse effects. It has been suggested that Wingate protocols can be extremely demanding and may not be safe (Gibala et al., 2012). We were concerned about applying 'all out' exercising to people with PD and therefore adopted the protocol suggested by Gibala et al. (2012). Typical Wingate protocols involve 'supra-maximal' workloads; our adopted protocol reduced the workload but increased duration and shortened the rest period between bouts. Feedback from the participants confirmed that this made for an enjoyable and positive exercise experience, with a preference for HIT compared to lower intensity exercise fo some. In addition, participants stated that they had an improved sense of wellbeing and that the HIT regime has inspired some to be more active six weeks after the conclusion of the programme and to purchase their own exercise bike. Thus, supervised initial training may therefore facilitate long term compliance by increasing people's confidence in their ability. In keeping with this Ellis et al. (2013) found that readiness and self-efficacy for exercise in people with PD rather than disability was associated with regular exercise behaviour.

We saw improvements in a number of outcomes measurements with HIT with effect sizes ranging from 0.001-0.73 . The largest effect size was seen for the ability to cycle for longer after training. Some subjectively reported improvements warrant more investigation, such as the effect on sleeping patterns, as this is a difficulty in PD [31]. The study is limited by lack of control group of low/no intensity exercise, the lack of rater blinding and long term follow-up measurements. However, our study was primarily designed to explore for the first time the possibility, safety and acceptability of HIT in people with PD.

This is the first report that HIT in a selected cohort people with PD is feasible and safe. The intensive nature of HIT does however require health screening and careful monitoring during exercise. It is therefore likely that participants will prefer to exercise in a facility with access to emergency equipment and trained staff. HIT in a group setting was been suggested by our participants and should be considered in a future trial. Subjective

reports suggest that HIT led to people adopting and/or increasing their amount of weekly unsupervised exercise possibly as a result of increased confidence in their ability. Therefore, the costs, as well as clinical effectiveness of HIT over other forms of exercise in the short and long term need to be evaluated. Although the purposive sampling of participants limits the generalisability of the data the results of the two stages suggest that ~33% of people with Parkinson's disease grade Hoehn and Yahr 1-4 may be able to exercise more intensively.

Acknowledgment and funding

This study was designed in response to a question posed by the local Parkinson's UK group to the University's VC's Community Research Awards. The group wanted to explore the potential of HIT as an option for their members. In consultation with the group we designed the study protocol and successfully applied for a grant from the VC's Community Research Award. The award body had no further influence on the design, conduct or publication of the study.

Conflict of Interest

We declare that there was no conflict of interest.

Key Points

- **High Intensity Interval Training (HIT) may be safe and feasible in people with mild to moderate Parkinson's disease**
- **Approximately 33% of people with mild to moderate Parkinson's disease may be able to participate in HIT**
- **Lower limb flexor muscle strength may be one of the limiting factors**
- **Disease progression may not limit ability to participate in HIT**
- **People with Parkinson's disease may prefer HIT to moderate/low intensity exercise**

References

Adamson, S. B., Lorimer, R., Cobley, J. N. and Babraj, J. A. (2014) 'Extremely short-duration High Intensity Training substantially improves the physical function and self reported health status of elderly adults', *JAGS*, 62(7), pp. 1380–1381.

Allen, N. E., Sherrington, C., Suriyarachchi, G. D., Paul, S. S., Song, J. and Canning, C. G. (2012) 'Exercise and motor training in people with Parkinson's disease: a systematic review of participant characteristics, intervention delivery, retention rates, adherence, and adverse events in clinical trials.', *Parkinson's disease*, 2012(doi 10.1155/2012/854328). doi: 10.1155/2012/854328.

American College of Sports Medicine (2014) *ACSM's Guidelines for Exercise Testing and Prescription*. 9th editio. Philadelphia: Lippincott Williams & Wilkins.

Bartlett, J. D., Close, G. L., MacLaren, D. P. M., Gregson, W., Drust, B. and Morton, J. P. (2011) 'High-intensity interval running is perceived to be more enjoyable than moderate-intensity continuous exercise: implications for exercise adherence.', *Journal of sports sciences*, 29(6), pp. 547–53. doi: 10.1080/02640414.2010.545427.

Borg, G. (1998) *Borg's Perceived Exertion and Pain Scales*. Illinois: Human Kinetics.

Burgomaster, K. a, Howarth, K. R., Phillips, S. M., Rakobowchuk, M., Macdonald, M. J., McGee, S. L. and Gibala, M. J. (2008) 'Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans.', *The Journal of physiology*, 586(1), pp. 151–60. doi: 10.1113/jphysiol.2007.142109.

Canning, C. G., Ada, L., Johnson, J. J. and McWhirter, S. (2006) 'Walking capacity in mild to moderate Parkinson's disease', *Archives of Physical Medicine and Rehabilitation*, 87(3), pp. 371–375. doi: 10.1016/j.apmr.2005.11.021.

Canning, C. G., Alison, A., Allen, N. E., Hans, B. and Groeller, H. (1997) 'Parkinson's Disease : An Investigation of Exercise Capacity, Respiratory Function and Gait', *Archives of Physical Medicine and Rehabilitation*, 78(February), pp. 199–207.

Ciolac, E. G. (2012) 'High-intensity interval training and hypertension: maximizing the benefits of exercise?', *American journal of cardiovascular disease*, 2(2), pp. 102–10. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3371620&tool=pmcentrez&rendertype=abstract.

Durstine, J. L. and Moore, G. E. (2003) *ACSM's Exersise Managment for Person's with Chronic Diseases and Disabilities*. 2nd ed. Champaign, Ilinois: Human Kinetics.

Ellis, T., Boudreau, J. K., Deangelis, T. R., Brown, L. E., Cavanaugh, J., Earhart, G., Ford, M. P., Foreman, K. B. and Dibble, L. E. (2013) 'Barriers to exercise in people with Parkinson's disease', *Physical Therapy*, 93(5), pp. 628–636.

Ellis, T., Cavanaugh, J. T., Earhart, G. M., Ford, M. P., Foreman, K. B., Fredman, L., Boudreau, J. K. and Dibble, L. E. (2011) 'Factors associated with exercise behavior in people with Parkinson disease.', *Physical therapy*, 91(12), pp. 1838–48. doi: 10.2522/ptj.20100390.

European Respiratory Society (1993) 'Standard lung function testing. Official statement of the European Respiratory Society', *The European Respiratory Journal*, 6(Supp.16), p. Appendix 2.

Gibala, M. J. and Little, J. P. (2010) 'Just HIT it! A time-efficient exercise strategy to improve muscle insulin sensitivity.', *The Journal of physiology*, 588(Pt 18), pp. 3341–2. doi: 10.1113/jphysiol.2010.196303.

Gibala, M. J., Little, J. P., Macdonald, M. J. and Hawley, J. A. (2012) 'Physiological adaptations to low-volume, high-intensity interval training in health and disease.', *The Journal of physiology*, 590(Pt 5), pp. 1077–84. doi: 10.1113/jphysiol.2011.224725.

Gibala, M. J. and McGee, S. L. (2008) 'Metabolic adaptations to short-term High-Intensity Interval Training: a little pain for a lot of gain', *Exercise and Sport Sciences Review*, 36(2), pp. 58–63.

Gill, D. P., Jones, G. R., Zou, G. Y. and Speechley, M. (2008) 'The Phone-FITT: a brief physical activity interview for older adults.', *Journal of aging and physical activity*, 16(3), pp. 292–315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18660552.

Goetz, C. G., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stebbins, G. T., Stern, M. B., Tilley, B. C., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., Van Hilten, J. J. and LaPelle, N. (2007) 'Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan.', *Movement Disorders*, 22(1), pp. 41–7. doi: 10.1002/mds.21198.

Goodwin, V. A., Richards, S. H., Taylor, R. S., Taylor, A. H. and Campbell, J. L. (2008) 'The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis.', *Movement disorders : official journal of the Movement Disorder Society*, 23(5), pp. 631–40. doi: 10.1002/mds.21922.

Haas, B. M., Trew, M. and Castle, P. C. (2004) 'Effects of respiratory muscle weakness on daily living function, quality of life, activity levels, and exercise capacity in mild to Parkinson's disease', *American Journal of Physical Medicine & Rehabilitation*, 83(8), pp. 601–607.

Hobson, P., Gallacher, J. and Meara, J. (2005) 'Cross-sectional survey of Parkinson's disease and parkinsonism in a rural area of the United Kingdom', *Movement Disorders*, 20(8), pp. 995–998. doi: 10.1002/mds.20489.

Hoehn, M. M. and Yahr, M. D. (1967) 'Parkinsonism: onset, progression and mortality', *Neurology*, 17(5), pp. 427–442.

Hood, M. S., Little, J. P., Tarnopolsky, M. a, Myslik, F. and Gibala, M. J. (2011) 'Low-volume interval training improves muscle oxidative capacity in sedentary adults.', *Medicine and science in sports and exercise*, 43(10), pp. 1849–56. doi: 10.1249/MSS.0b013e3182199834.

Jenkinson, C., Fitzpatrick, R., Peto, V. and Hyman, N. (1997) 'The Parkinson's disease questionnaire (PDQ - 39): development and validation of a Parkinson's disease summary index score', *Age and Ageing*, 26, pp. 353–357.

Jung, M. E., Bourne, J. E., Beauchamp, M. R., Robinson, E. and Little, J. P. (2015) 'High-Intensity Interval Training as an Efficacious Alternative to Moderate-Intensity Continuous Training for Adults with Prediabetes', *Journal of Diabetes Research*, 2015(Artice ID 191595), p. 9 pages. doi: http://dx.doi.org/10.1155/2015/191595.

Katzel, L. I., Sorkin, J. D., Macko, R. F., B., S., Ivey, F. M. and Shulman, L. M. (2011) 'Repeatability of aerobic capacity measurements in Parkinson's disease', *Med Sci Sports Exerc*.

Van der Kolk, N. M. and King, L. a. (2013) 'Effects of exercise on mobility in people with Parkinson's disease', *Movement Disorders*, 28(11), pp. 1587–1596. doi: 10.1002/mds.25658.

Murphy, S. M., Edwards, R. T., Williams, N., Raisanen, L., Moore, G., Linck, P., Hounsome, N., Din, N. U. and Moore, L. (2012) 'An evaluation of the effectiveness and cost effectiveness of the National Exercise Referral Scheme in Wales, UK: a randomised controlled trial of a public health policy initiative.', *Journal of Epidemiology and Community Health*, 66(8), pp. 745–753. doi: 10.1136/jech-2011-200689.

Murray, D. K., Sacheli, M. a, Eng, J. J. and Stoessl, a J. (2014) 'The effects of exercise on cognition in Parkinson's disease: a systematic review.', *Translational neurodegeneration*. Alzheimer's Research & Therapy, 3(1), p. 5. doi: 10.1186/2047-9158-3-5.

Nordin, E., Lindelof, N., Rosendahl, E., Jensen, J. and Lundin-olsson, L. (2008) 'Prognostic validity of the Timed Up-and-Go test, a modified Get-Up-and-Go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities', *Age Ageing*, 37(4), pp. 442–448. doi: 10.1093/ageing/afn101.

Pääsuke, M., Ereline, J., Gapeyeva, H., Joost, K., Mõttus, K. and Taba, P. (2004) 'Leg-extension strength and chair-rise performance in elderly women with Parkinson's disease', *Journal of Aging and Physical Activity*, 12(4), pp. 511–524.

Phillips, M., Flemming, N. and Tsintzas, K. (2009) 'An exploratory study of physical activity and perceived barriers to exercise in ambulant people with neuromuscular disease compared with unaffected controls', *Clinical Rehabilitation*, 23(8), pp. 746–755. doi: 10.1177/0269215509334838.

Prodoehl, J., Rafferty, M. R., David, F. J., Poon, C., Vaillancourt, D. E., Comella, C. L., Leurgans, S. E., Kohrt, W. M., Corcos, D. M. and Robichaud, J. a. (2014) 'Two-Year Exercise Program Improves Physical Function in Parkinson's Disease: The PRET-PD Randomized Clinical Trial', *Neurorehabilitation and Neural Repair*, 29(2), pp. 112–122. doi: 10.1177/1545968314539732.

Ridgel, A. L., Vitek, J. L. and Alberts, J. L. (2009) 'Forced, not voluntary, exercise improves motor function in Parkinson's disease patients.', *Neurorehabilitation and neural repair*, 23(6), pp. 600–8. doi: 10.1177/1545968308328726.

Rose, M. H., Løkkegaard, A., Sonne-Holm, S. and Jensen, B. R. (2013) 'Improved clinical status, quality of life, and walking capacity in Parkinson's disease after body weight-supported high-intensity locomotor training.', *Archives of physical medicine and rehabilitation*. Elsevier Ltd, 94(4), pp. 687–92. doi: 10.1016/j.apmr.2012.11.025.

Schmolesky, M. T., Webb, D. L. and Hansen, R. a (2013) 'The effects of aerobic exercise intensity and duration on levels of brain-derived neurotrophic factor in healthy men.', *Journal of sports science & medicine*, 12(3), pp. 502–11. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3772595&tool=pmcentrez&rendertype=abstract.

Shulman, L. M., Taback, R. L., Bean, J. and Weiner, W. J. (2001) 'Comorbidity of the nonmotor symptoms of Parkinson's disease', *Mov Disord*, 16(3), pp. 507–510. doi: 10.1002/mds.1099.

Smith, J. A. (1995) 'Semi-structured interviewing and qualitative analysis', in Smith, J. A., Hark, R., and Langenhove, L. Van (eds) *Rethinking Methods in Psychology*. London: Sage.

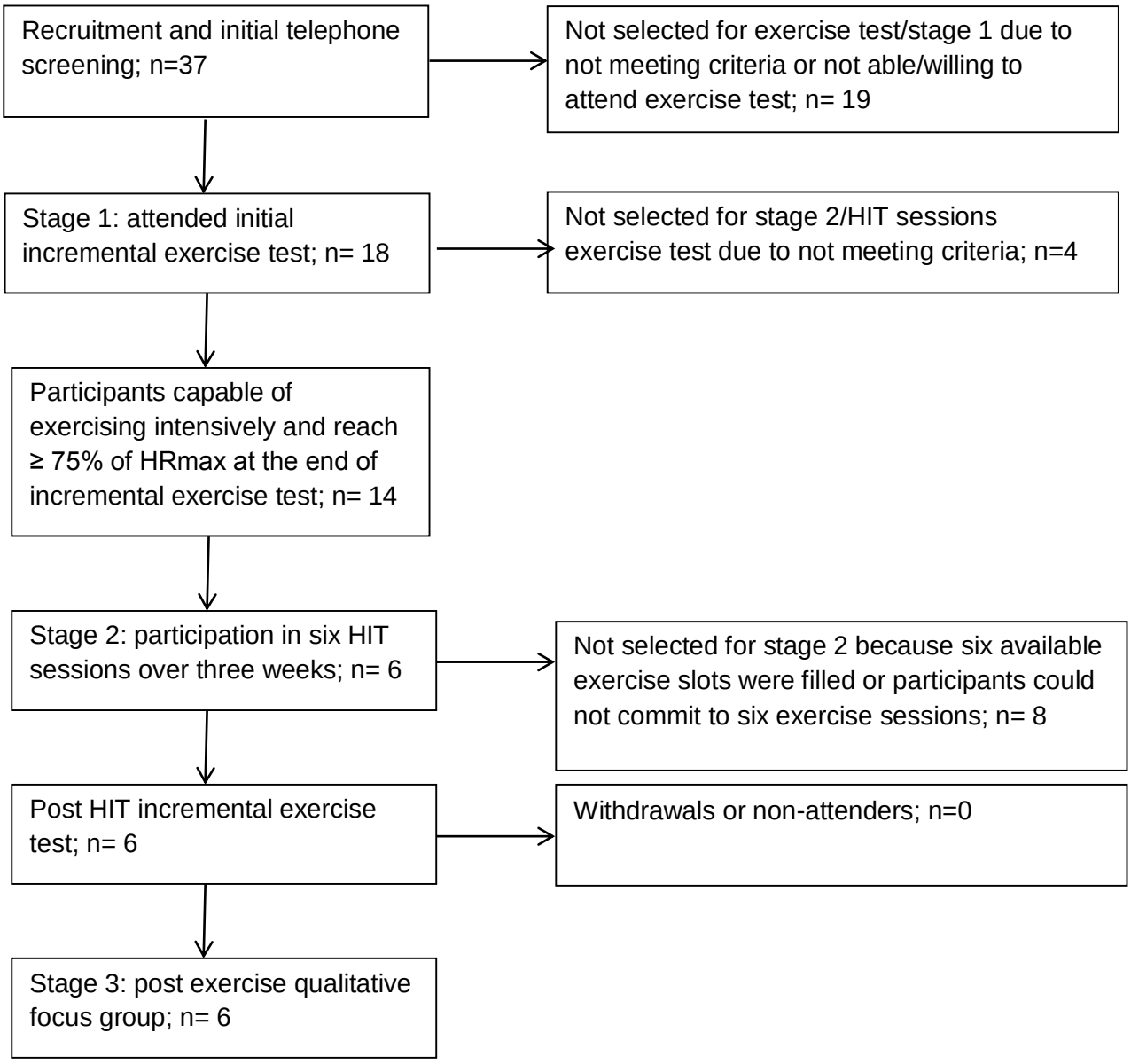
Speelman, A. D., Groothuis, J. T., van Nimwegen, M., van der Scheer, E. S., Borm, G. F., Bloom, B. R., Hopman, M. T. E. and Munneke, M. (2012) 'Cardiovascular responses during a submaximal exercise test in patients with Parkinson's disease', *Journal of Parkinson's Disease*, 2(3), pp. 241–247.

Wilson, S. H., Cokke, N. T., Edwards, R. H. T. and Spiro, S. G. (1984) 'Predicted normal values for maximal respiratory pressures in caucasion adults and children', *Thorax*, 39, pp. 535–538.

Wisløff, U., Støylen, A., Loennechen, J. P., Bruvold, M., Rognmo, Ø., Haram, P. M., Tjønna, A. E., Helgerud, J., Slørdahl, S. a, Lee, S. J., Videm, V., Bye, A., Smith, G. L., Najjar, S. M., Ellingsen, Ø. and Skjaerpe, T. (2007) 'Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study.', *Circulation*, 115(24), pp. 3086–94. doi: 10.1161/CIRCULATIONAHA.106.675041.

Zigmond, M. J., Cameron, J. L., Hoffer, B. J. and Smeyne, R. J. (2012) 'Neurorestoration by physical exercise: moving forward.', *Parkinsonism & related disorders*. Elsevier Ltd, 18 Suppl 1, pp. S147–50. doi: 10.1016/S1353-8020(11)70046-3.

Figure 1: Study design



Sample	gender	Age mean (Stdev)	PDQ-39[1] median (IQR)	H&Y[2] stages median (IQR)	UPDRS[3] scores - median (IQR)				Phone-FITT[4] median (IQR)	FVC[5] (ltr) mean (Stdev)	MIP[6] (cmH_2O) mean (Stdev)	Ext leg[7] (n·m) mean (Stdev)	Flex leg[7] (n·m) mean (Stdev)
					Tremor	Rigidity	Agility	Freezing					
All 18 partici-pants at stage 1	3 female 15 male	65.11 (6.17)	28.59 (19.86)	2 (1.25)	1 (2)	1 (1)	1 (2)	0 (1)	59.83 (11.68)	3.31 (0.95)	55.83 (25.06)	1.26 (0.42)	0.86 (0.34)
All 6 exercising volunteers in stage 2	2 female 4 male	63.00 (7.35)	25.21 (20.92)	2 (2)	1 (1)	1 (0.25)	0.5 (1.25)	1 (1.5)	68.00 (25.38)	3.38 (1.27)	57.83 (17.46)	1.27 (0.27)	0.99 (0.31)
All 12 partici-pants not selected for exercising	1 female 11 male	66.17 (5.54	30.89 (25.72)	2 (0.75)	1 (1)	0.5 (1)	1 (2)	0 (0.75)	55.25 (23.30)	3.28 (0.85)	54.83 (28.79)	1.26 (0.49)	0.79 (0.35)
		$	$	$	$	$	$	$	$	$	$	$	*

*Differences significant at $p< 0.05$; $^{\$}$Differences not significant with $p>0.05$

Table 1: Key body structure and function characteristics between participants in stage 1 and stage 2

Table 2: Changes in Fitness, QoL, mobility, activity levels, leg strength and cycle endurance before and after six sessions of cycle exercise; calculated effect sizes and estimated total sample size

Participant	HR_{max} (bt/min)		VO_{2max} (ml/min/kg)		Inspiratory Muscle strength (MIP)		PDQ-39 summary index		PhoneFITT activity score		Timed Up&Go test (sec)		Extensor muscle strength (N·m)		Flexor Muscle strength (N·m)		Cycle endurance (sec)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	91	89	27.14	24.84	48	48	28.85	25.47	76.08	81.08	13.22	13.2	1.19	1.222	0.54	0.714	510	506
2	89	100	24.25	30.11	39	56	13.02	23.54	63.5	74.13	8.71	9.35	0.97	1.208	0.99	1.034	423	424
3	79	89	40.07	34.57	42	44	38.28	28.54	99.66	94	11.49	11.05	1.37	1.593	1.14	1.141	544	612
4	84	85	26.8	33.07	72	68	21.56	19.84	35.91	40.91	12.31	11.55	1.71	1.95	0.9	1.106	519	645
5	77	80	34	33.73	82	81	15.42	56.46	66	77	11.19	11.1	1.03	0.567	1.47	0.718	607	650
6	94	102	20.6	22.76	64	98	34.9	41.3	70	70	9	8.8	1.33	1.057	0.96	1.057	507	600
Mean (±Stdev)	85.67 (6.80)	90.83 (8.57)	28.81 (7.05)	29.85 (4.96)	57.83 (17.46)	65.83 (20.79)	25.34 (10.35)	32.53 (13.84)	68.53 (20.61)	72.85 (17.68)	10.99 (1.80)	10.84 (1.59)	1.27 (0.27)	1.27 (0.47)	1.00 (0.30)	0.96 (0.19)	518.33 (59.68)	572.83 (89.50)
Effect size (at $p<0.05$; $\beta= 0.80$); *significant	0.34		0.08		0.21		0.30		0.11		0.04		0.001		0.08		*0.73	
Estimated total sample size	64		1222		173		82		643		4900		7848855		1221		10	