Non-contact boxing and chronotropic incompetence in Parkinson's disease

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Abstract

Non-contact boxing training (NCBT) is a recent addition to exercise interventions suitable for people with Parkinson's disease (PwPD). Although NCBT is considered a form of high-intensity interval training (HIIT) for PwPD, it has not been verified as such in this population. This is especially the case if autonomic disturbance, in particular chronotropic incompetence (CI) is present. CI attenuates heart rate (HR) response during aerobic exercise despite increasing demand, thereby limiting the potential for high-intensity zone training. The primary question underpinning this thesis examines this issue and asks whether PwPD can train at high intensity when undertaking NCBT. A second, related question concerns the influence of CI on cardiac and metabolic responses during HIIT and the implications of this for monitoring exercise intensity.

The first study in this programme of research is a narrative review of aerobic exercise protocols for PwPD. The review concludes that although the effect of exercise intensity on aerobic performance in PwPD is positive overall, there is inconsistency in reporting training protocols (including lack of agreement around the definition and use of training zones) which limits generalisability, study replication and understanding the mechanisms causing any observed effect. A standardised approach is recommended to optimise outcome. A second finding is that CI appears to have a marked effect on aerobic performance and further research is required to enhance understanding of the phenomenon.

This body of work then informed an exploratory study examining the impact of CI on HR and metabolic responses and exercise intensity profiles during a cardiopulmonary exercise test (CPET) in PwPD with and without CI, and age-matched controls. HR and metabolic responses during CPET were significantly attenuated for the CI group, suggesting the need to first classify participants for CI prior to programming aerobic training protocols, and to monitor response throughout training.

The third study incorporates individualised physiological measures of exercise intensity obtained from the CPET study to investigate the effect of CI on physiological and clinical responses during NCBT. The results show that PwPD who present with CI, exhibit lower HR responses during NCBT than PD non-CI and controls. However, PwPD with and without CI do meet high-intensity training criteria and spend significant time exercising at and above the threshold zone.

In conclusion, this thesis highlights the need for consideration of autonomic dysfunction, in particular CI, when administering aerobic training programmes for PwPD. The results also show that despite attenuated HR and metabolic responses, people with CI are able to exercise in

high-intensity zones during NCBT. There is a need for comprehensive reporting of aerobic training protocols for PwPD and the adoption of standardised thresholds for training zones.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signature	28/03/024 Date

Co-Authored Works

Tone Ricardo Benevides Panassollo developed the thesis's original proposal after working with non-contact boxing in people with PwPD. Subsequently, in collaboration with a team of experts in PD and aerobic exercise programming from Auckland University of Technology, the research questions were tailored to explore physiological markers of exercise intensity in people with PwPD during CPET and NCBT.

Co-Autorship

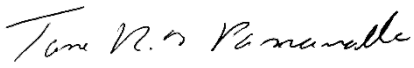
Chapter 1 Background and review of the literature Panassollo, T. R. B., Mawston, G., Lord, S.	**Panassollo** (80%): Conducted a thorough review of existing literature, drafted the chapter. **Mawston** (10%) provided supervision (oversight and leadership) and a key role in editing and revising the content. **Lord** (10%) provided supervision (oversight and leadership) and a key role in editing and revising the content.

Chapter 2 Panassollo, T. R. B., Mawston, G., Taylor, D., & Lord, S. (2024). Targeting exercise intensity and aerobic training to improve outcomes in Parkinson's disease. Sport Sciences for Health. https://doi.org/10.1007/s11332-024-01165-0	**Panassollo** (78%): Conducted a thorough review of existing literature, drafted the manuscript, and created figures and tables. **Mawston** (10%) provided supervision (oversight and leadership) and a key role in editing and revising the content. **Taylor** (2%) provided supervision (oversight and leadership) review of the final draft. **Lord** (10%) provided supervision (oversight and leadership) and a key role in editing and revising the content.

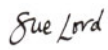
Chapter 3 Cardiopulmonary exercise testing Panassollo, T. R. B., Mawston, G., Lord, S.	**Panassollo** (85%): Conducted a thorough review of existing literature, drafted the chapter. **Mawston** (10%) provided supervision (oversight and leadership) and a key role in editing and revising the content. **Lord** (5%) provided supervision (oversight and leadership) and a key role in editing and revising the content.

Chapter 4 The effect of chronotropic incompetence on physiological responses during progressive exercise in people with Parkinson's disease Panassollo, T. R. B., Lord, S., Rashid, U. Taylor, D., Mawston, G.	**Panassollo** (80%): Conceptualised the study, designed the methodology, wrote and submitted ethics application, conducted data interpretation and analysis. **Mawston** (10%) Conceptualised the study, provided supervision (oversight and leadership), and collaborated on designing the methodology, ethics application, data interpretation and analysis. A key role in data collection, editing, and revising the content. **Rashid** (2%) Conducted statistical analysis, collaborated on data interpretation, provided feedback on manuscript drafts. **Taylor** (1%) provided supervision (oversight and leadership) review of the final draft. **Lord** (7%) Conceptualised the study, provided supervision (oversight and leadership), collaborated on designing the methodology, ethics application, data interpretation and analysis, and a key role in editing and revising the content.

Chapter 5 Chronotropic incompetence does not impede attainment of high-intensity exercise during non-contact boxing in Parkinson's disease Panassollo, T. R. B., Lord, S., Rashid, U. Taylor, D., Mawston, G.	**Panassollo** (80%): Conceptualised the study, designed the methodology, wrote and submitted ethics application, conducted data interpretation and analysis. **Mawston** (10%) Conceptualised the study, provided supervision (oversight and leadership), collaborated on designing the methodology, ethics application, data interpretation and analysis, and a key role in editing and revising the content. **Rashid** (2%) Conducted statistical analysis, collaborated on data interpretation, provided feedback on manuscript drafts. **Taylor** (1%) provided supervision (oversight and leadership) review of the final draft. **Lord** (7%) Conceptualised the study, provided supervision (oversight and leadership), collaborated on designing the methodology, ethics application, data interpretation and analysis, and a key role in editing and revising the content

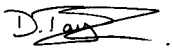


Tone Panassollo



Dr Sue Lord

Dr Grant Mawston



Prof. Denise Taylor

Dr Usman Rashid

Publications and presentations

The findings and research detailed in this thesis have been shared through publication and/or presentation on the following platforms:

Published papers

Panassollo, T. R. B., Mawston, G., Taylor, D., & Lord, S. (2024). Targeting exercise intensity and aerobic training to improve outcomes in Parkinson's disease. *Sport Sciences for Health*, *20*(2), 287-297. https://doi.org/10.1007/s11332-024-01165-0 (Chapter 2 of the thesis)

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Conference presentations

Panassollo, T. R. B., Lord, S., Taylor, Mawston, G. Non-contact boxing for people with Parkinson's disease. International Society of Gait & Posture Research (ISPGR). 3-minute presentation. Jul 2021

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Panassollo, T. R. B., Lord, S., Taylor, Rashid, U., D., Mawston, G. Autonomic dysfunction alters heart rate responses during non-contact boxing in Parkinson's disease. International Society of Gait & Posture Research (ISPGR) World Congress. Poster presentation, Montreal, Canada. Jul 2022

Panassollo, T. R. B., Lord, S., Taylor, D., Rashid, U., Mawston, G. Autonomic dysfunction alters heart rate responses during non-contact boxing in Parkinson's disease. Physiotherapy New Zealand Conference. Presented by Mawston, G. Sep 2022.

Panassollo, T. R. B., Lord, S., Taylor, D., Rashid, U., Mawston, G. The influence of chronotropic incompetence on maximum aerobic capacity and heart rate responses during boxing in Parkinson's disease. Postgraduate Research Symposium. Nov 2022.

Panassollo, T. R. B., Lord, S., Taylor, D., Rashid, U., Mawston, G. Autonomic dysfunction alters heart rate responses during non-contact boxing in Parkinson's disease. Sport Exercise Science New Zealand conference. Nov 2022.

Panassollo, T. R. B., Lord, S., Taylor, D., Rashid, U., Mawston, G. Non-contact boxing and Parkinson's disease: Balancing the hype. Neurology Special Interest Group (NSIG) presentation with Dr Sue Lord. Sep 2023.

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Ethics Approval

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Abbreviations

6MWT	6-minutes walking test
ACSM	American College of Sports Medicine
ANS	Autonomic nervous system
AUTEC	Auckland University of Technology Ethics Committees
BG	Basal ganglia
BMI	Body Max Index
BP	blood pressure
bpm	Beats per minute
CI	Chronotropic incompetence
CPET	Cardiopulmonary exercise test
CVD	cardiovascular diseases
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FITT-VP	Frequency, Intensity, Time, Type, Volume, and Progression
H&Y	Hoehn and Yahr
HDEC	Health and Disability Ethics Committees
HIIT	High-intensity interval training
HR	Heart rate
HRmax	Heart rate maximum
HRR	Heart rate reserve
HRrest	Heart rate rest
HRV	Heart rate variability

IPAQ-E	The International Physical Activity Questionnaire for the Elderly
MA-PHR	Maximum predicted heart rate
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MIIT	Moderate-intensity interval training
NCBT	non-contact boxing training
NSIG	Neurology Special Interest Group of Physiotherapy New Zealand
NZ	New Zealand
PD	Parkinson's disease
$PETCO_2$	Partial end-tidal carbon dioxide tension
$PETVO_2$	Partial end-tidal oxygen tension
PIGD	Postural instability and gait difficulty predominant
PNS	Parasympathetic nervous system
PNZ	Parkinson's New Zealand
QoL	Quality of life
RER	Respiratory exchange ratio
RPE	Rate of perceived exertion
rpm	Revolutions per minute
RSB	Rock Steady Boxing ™
SBP	Systolic blood pressure
SN	Substantia nigra
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticulata
SNS	Sympathetic nervous system

TD	Tremor dominant
TUG	Timed up and go
UPDRS	Unified Parkinson's disease rating scale
VCO_2	Volume of carbon dioxide production
VE	Minute ventilation
VIF	Variance inflation factor
VO_2	Volume of oxygen consumption
VO_2/HR	Oxygen pulse
VO_2max	Maximum oxygen consumption
VO_2peak	Peak oxygen consumption
VT1	First ventilatory threshold
VT2	Second ventilatory threshold
WR	Workload
WRpeak	Peak workload

Introduction

Parkinson's disease (PD) is a neurogenerative disorder characterized by a complex array of motor and non-motor symptoms. The cause of PD is predominantly idiopathic, although genetic, immunological, environmental, and age-related factors also contribute. Symptoms such as bradykinesia, hypokinesia, and impaired executive function arise from death of dopaminergic neurons in the substantia nigra and basal ganglia pathology (Fazl & Fleisher, 2018; Lanciego et al., 2012; Middleton & Strick, 2000; Rodriguez-Oroz et al., 2009); Steiner and Tseng (2017).

General physical exercises, including aerobic exercises, have been a longstanding component of the management of PD, mitigating symptoms and age-related changes including the decline in aerobic capacity and muscle strength. They also enhance quality of life (QoL), function, mobility, balance, and gait performance of people with PD (PwPD) (Cui et al., 2023; Gamborg et al., 2022; Ramazzina et al., 2017; Song et al., 2017; Thrue et al., 2023; Wu et al., 2017; Zhen et al., 2022).

As a form of aerobic exercise, non-contact boxing training (NCBT) has become increasingly popular among PwPD. The basis for including NCBT as a feature of exercise for PD is multi-faceted. It is acceptable as a form of high-intensity interval training (HIIT), an important training method used to improve aerobic capacity in healthy and clinical populations (Arseneau et al., 2011; Liguori et al., 2022; Nikolaidis et al., 2017). This aerobic exercise mode also comprises footwork, visual cueing (pad work and bags), and cognitive (mental) aspects - all of which are important in PD (Arseneau et al., 2011; Kruszewski et al., 2016; Peterson et al., 2016; Rzepko et al., 2014). Although NCBT in PD is considered vigorous to high-intensity aerobic training (Combs et al., 2013; Combs et al., 2011; Hermanns et al., 2021; King & Horak, 2009; Larson et al., 2021; Lowery et al., 2023; Moore et al., 2021; Sonne et al., 2021), and PwPD assume this is the case, this claim has not been formally substantiated. Questions remain concerning the effect of PD symptoms on NCBT performance. For example, the presence of bradykinesia and cognitive dysfunction may hinder the ability to perform sequential movements quickly enough to achieve the required exercise intensity (Ma et al., 2012; Morberg et al., 2014).

Autonomic dysfunction, particularly a blunted heart rate (HR) response (chronotropic incompetence), may also compromise performance. Chronotropic incompetence (CI) can lead to inaccurate measurement of exercise intensity, especially when it is based on predicted maximum HR. Exercise intensity is a key aerobic exercise training variable, and accuracy is critical for NCBT programming and to outcomes. CI is associated with lower peak aerobic capacity (VO_2peak) in the clinical population, and has recently been associated with exercise intolerance in PwPD (Brubaker et al., 2006; Brubaker & Kitzman, 2011; Davenport et al., 2019;

Herbsleb et al., 2019; Herbsleb et al., 2018; Liguori et al., 2022; Mavrommati et al., 2017; Penko et al., 2021).

A recent study by Griffith et al. (2024) showed significantly lower HR and VO_2peak during a maximal incremental test in PwPD, classified as having CI compared to those without CI. However, its impact on submaximal measures of exercise intensity (ventilatory thresholds), which are important for HIIT programming, was not reported. Additionally, the study included participants who were diagnosed with PD within the last five years and were not on dopaminergic medication for the management of PD. Therefore, the impact of CI on maximal and submaximal physiological measures to incremental exercise up to maximal intensity and during NCBT, still needs to be further investigated in PwPD.

Statement of the problem:

Although NCBT is a popular aerobic method for managing PD symptoms, the ability of PwPD to perform this activity in the high-intensity training zone, remains unknown. Additionally, the potential impact of a CI on cardiac and on metabolic responses and its implications for monitoring exercise intensity during HIIT in PwPD has yet to be explored.

Research questions:

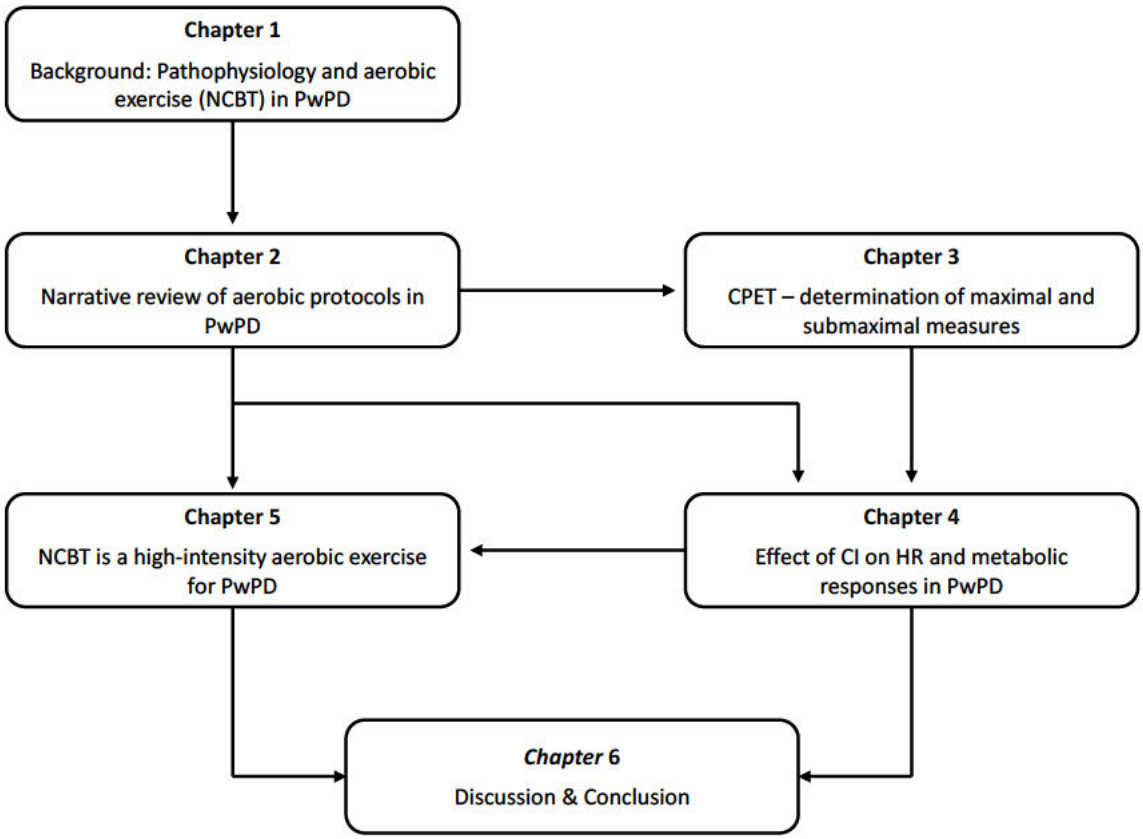
1. *Are there significant differences in HR and metabolic responses between PwPD with and without CI during progressive incremental exercise to maximal effort?*
    a. *Is there a significant difference in aerobic capacity in PwPD with and without CI?*
2. *Can PwPD reach high-intensity training zones during NCBT that incorporate only boxing related drills?*
3. *Are there significant differences in HR and metabolic responses between PwPD with and without CI during NCBT?*

Structure of the thesis

The programme of study was planned a year prior to COVID-19. Consequently, specific components had to be adjusted due to COVID-19 restrictions. Initially, we aimed to recruit 30 PwPD and 30 healthy controls for an exploratory study examining the key responses to the physiological outcome measures (cardiopulmonary exercise testing and close kinetic chain rate of force development and muscle power) and during two sessions of NCBT in PwPD. Subsequently, 20 PWPD were to be invited to participate in a feasibility study. This study was intended to assess the feasibility and acceptability of a 12-week of NCBT program (with two sessions per week) and to explore its effects on aerobic capacity, muscle strength and power, and functional performance in PwPD.

Unfortunately, due to COVID-19 restrictions, the feasibility study was cancelled and the exploratory study became our primary focus. Despite the challenges encountered in recruiting participants during the pandemic and the restrictions imposed to contain the virus, we managed to recruit 28 PwPD and 17 controls for the exploratory study. Data collection took place over three days per participant. In addition to the CPET and NCBT tests, participants performed a series of muscle strength, power, and functional tests. Due to time constraints, this data will be analysed at a future date. The final structure of the thesis is presented in the following flowchart (**Figure 1**).

Figure 1 *Structure of the thesis*



Chapter 1. Background: This chapter presents a brief review of the pathogenesis and pathophysiological aspects of PD and introduces motor and non-motor symptoms affecting exercise performance. The importance of autonomic dysfunction (a critical feature for some PwPD) to heart rate response and exercise intensity monitoring, is then considered in depth in the following chapters of this thesis. The role of aerobic exercise, mainly NCBT, as a form of HIIT in managing PD symptoms and improving general health is also reviewed.

Chapter 2 (study 1): Exercise intensity in aerobic training protocols in PD is considered key to improving outcomes for PwPD. This chapter presents a narrative review of some concerns associated with aerobic protocols and exercise intensity monitoring in the PD literature. These concerns include inconsistent exercise intensity reporting, training programs based on general guidelines instead of individualized physiological markers, inadequate correspondence between

intended exercise intensities and training zones, and the potential effect of CI on exercise programming. Furthermore, the selective impact of exercise intensity on aerobic capacity, motor symptoms, disease progression, and the recent aerobic exercise guidelines for PwPD, are reviewed.

Chapter 3. This chapter provides insight into methods used to identify maximal and submaximal measures during CPET in PwPD. Additionally, this chapter provides an outline of the significance of normative values for everyday tasks and aerobic exercise training.

Chapter 4 (study 2): In this cross-sectional study of 28 PwPD and 17 healthy aged-match controls, the impact of CI on HR and metabolic responses during a maximum cardiopulmonary exercise test in PwPD is explored, along with the implications of these markers for exercise intensity prescription. The individualized maximal and submaximal physiological markers of exercise intensity accessed in this study, are then used to determine the threshold for high intensity training required during the NCBT session, which is discussed in the subsequent study.

Chapter 5 (study 3): In this study, the ability of 11 PwPD with CI and 14 PwPD without CI to attain a high-intensity training zone during NCBT sessions incorporating boxing-related drills is assessed. Metabolic responses and percentage of time spent in high-intensity training zones, an essential HIIT training component for improving aerobic capacity, are also examined. The rate of perceived exertion is used as a clinical measure of exercise intensity during the sessions.

Chapter 6. Integrated findings from the three studies are combined with findings from current literature in the discussion and conclusion to this thesis. Recommendations for future research in the field are also made.

1 Background

1.1 Prologue

The principal focus of this thesis is to examine the ability of PwPD to attain high-intensity zones during NCBT. In order to give context to this aim, this chapter sets out the following discussion points.

Firstly, the pathogenesis and pathophysiology of PD are outlined, including a review of PD symptoms that are particularly relevant to the topic under investigation. These include motor symptoms such as bradykinesia, hypokinesia and postural instability, and non-motor symptoms including cognitive dysfunction and autonomic dysfunction.

Secondly, the significance of physical exercise, especially aerobic training and NCBT in managing PD symptoms and enhancing general health is reviewed, given their contribution to the management of PD. This discussion leads onto an overview of essential aerobic training principle, also important for HIIT programming. It then outlines the potential effect of aerobic exercises and NCBT for managing PD symptoms based on the recent literature. The chapter concludes with a summary of key issues that arise from this body of work as a basis for the studies then undertaken.

1.2 Aetiology and pathogenesis

Dr James Parkinson was the first person to observe resting tremor, festination, and flexed posture in six of his patients in London in 1817. He used the term paralysis agitans to describe these signs and symptoms. Later, Jean-Martin Charcot noticed that people affected by paralysis agitans, presented with a variable set of symptoms, including rigidity and bradykinesia, and subsequently renamed the disorder to Parkinson's disease or maladie of Parkinson (Cuenca et al., 2019; Elbaz et al., 2016; Jankovic, 2008; Obeso et al., 2017). Since these observations, PD has been studied extensively. Although progress has been made in the last century, there is still no cure for PD and many unknown questions persist more than 200 years later (Cuenca et al., 2019; Obeso et al., 2017).

PD is an age-related disease, with an average age onset of 68 years for men and 70 years for women, with 10% of cases diagnosed between the ages of 20 and 50 years. Globally, an estimated seven to ten million people are affected by the condition (Dexter & Jenner, 2013; Joshi et al., 2017; Latella et al., 2019; Lizoń et al., 2017). Between 2006 and 2017, approximately 15,500 PD cases were diagnosed in New Zealand (NZ), representing around 0.5% of the total population (Le Heron et al., 2021). Projections indicate a doubling of PD cases in NZ over the next 25 years (Myall et al., 2017; Parr-Brownlie et al., 2020). Europeans have

the highest prevalence and incidence of PD, followed by Asian, Pasifika, and Māori groups (Pitcher et al., 2018). As the ageing population continues to grow, the number of PwPD is expected to increase proportionally, significantly impacting on healthcare resources. Over time, the disease progresses, leading to an increase in associated costs (Bohingamu Mudiyanselage et al., 2017; Cuenca et al., 2019).

PD is more common in men (Dexter & Jenner, 2013; Elbaz et al., 2016; Popat et al., 2005; Tolosa et al., 2021), with oestrogen exerting a protective effect in women through its influence on dopamine syntheses uptake and release (Dexter & Jenner, 2013; Elbaz et al., 2016; Popat et al., 2005). Also, women are generally less exposed than men to environmental factors that may be a causal factor (Elbaz et al., 2016; Le Heron et al., 2021). Exposure to chemical substances, such as pesticides and solvents, along with lifestyle factors like diet, smoking, head injuries, and physical activity behaviour, has been associated with the risk of developing PD (Marras et al., 2019; Pan-Montojo & Reichmann, 2014). However, these factors do not definitively explain PD's origin; instead, they are more likely to contribute to the disorder's myriad development.

An earlier theory by Braak, hypothesised that an unknown virus or bacteria caused PD, affecting neurons of the gut and nasal cavity. Pathological change then progresses upwards from the brainstem to the nasal cavity and delineates different disease (Braak) stages (Braak & Braak, 2000; Braak et al., 2004; Braak et al., 2003; Del Tredici et al., 2002; Rietdijk et al., 2017; Visanji et al., 2013). This theory still holds today, although the effect of environment on gut health is now more prominent (Chen et al., 2022). The cause of PD is unlikely to be singular, given the heterogeneity of symptom presentation. Chen and Ritz (2018) propose that a complex interaction of environmental, genetic, and individual factors manifest to trigger the disease. Individuals who are genetically predisposed may encounter in their lifespan environmental factors such as air pollutants, viruses, or pesticides that enter the body either through the nasal cavity or gut. External impacts such as physical exercise, anti-inflammatory treatment, or nutrition may then accelerate (or alternatively decelerate) this pathological progression, thereby influencing the onset of motor symptoms. However, despite extensive efforts to understand, the aetiology of PD is still unclear (Cuenca et al., 2019; Obeso et al., 2017).

The pathogenesis of PD is characterized by the deterioration of mitochondrial function leading to oxidative stress inside the substantia nigra causing death of dopaminergic cells (Isaias et al., 2016; Jankovic, 2008; Obeso et al., 2000; Schapira et al., 1992; Shimizu & Hanajima, 2023). Mitochondria dysfunction has also been reported in skeletal muscle in PwPD and animal models of PD (Blin et al., 1994; Mendes et al., 2023; Pechstein et al., 2020). However, deterioration of muscle mitochondria occurs naturally with the ageing process and can be exacerbated by physical inactivity (Burtscher et al., 2021; Short et al., 2005), which, as discussed below, is common in PwPD. Although mitochondrial dysfunction in skeletal muscles has been suggested

to reduce energy supply and contribute to exercise intolerance in PwPD, there is no significant evidence to indicate that it can lead to a decrease in aerobic capacity specifically for this population (Kanegusuku et al., 2016; Mavrommati et al., 2017; Schapira & Gegg, 2011; Schapira et al., 1992).

A conclusive understanding of the pathogenesis of PD continues to absorb scientists, neurologists, and the research community. Research to date implicates genetic and other factors, including immunological, environmental, and age-related processes (Gillies et al., 2014; Graham et al., 2014; Pan-Montojo & Reichmann, 2014; Pringsheim et al., 2014; Venda et al., 2010).

1.3 Pathophysiology

The primary pathophysiological hallmark of PD is progressive degeneration of dopaminergic cells in the substantia nigra pars compacta (SNpc). Lewy body formations, composed of mis-folded clusters of a protein, α-synuclein, are also found in synaptic transmissions within hippocampal neurons and in the degeneration of the basal ganglia (BG) circuitry (Dexter & Jenner, 2013; Gaig & Tolosa, 2009; Jankovic, 2008; Rodriguez-Oroz et al., 2009; Schapira et al., 2017). However, the full extent of this pathology is still incompletely understood (Goedert, 2001; Goncalves et al., 2021; Markesbery et al., 2009; Schluter et al., 2003; Venda et al., 2010).

Deterioration of the BG circuitry is a pivotal aspect of the pathophysiology of motor symptoms in PD. The BG are a cluster of neurones including the corpus striatum (caudate nucleus, putamen, and nucleus accumbens), globus pallidus, substantia nigra (SN), and subthalamic nuclei. The globus pallidus comprises both internus and externus segments, while the SN comprises the pars compacta (SNpc) and pars reticulata (SNpr). BG operate as a key link between the cerebral cortex and subcortical systems, such as the thalamus, cerebellum, and supplementary motor area, and play a significant role in motor control and learning, planning, working memory, emotions, and habit formation (Fazl & Fleisher, 2018; Lanciego et al., 2012; Middleton & Strick, 2000; Rodriguez-Oroz et al., 2009; Steiner & Tseng, 2017). The supplementary motor area connects with various parts of the brain and primarily receives input from the BG and dentate nucleus. Supplementary motor area pathology slows movement initiation and impairs the timing and execution of motor tasks, impoverishing motor functions such as walking (Rahimpour et al., 2022).

The BG are also involved in initiating movement and stabilizing excitatory and inhibitory stimulus through direct and indirect neural pathways. A reduction in dopamine levels within the SNpc initiates a sequence of events that disturbs this pathway (Lanciego et al., 2012; Palakurthi & Burugupally, 2019; Sulzer & Surmeier, 2013). The predominance of the indirect over the direct neural pathway, results in increased activity in the output nuclei of the BG, leading to

inhibition exerted upon the thalamocortical and brainstem motor systems, producing common symptoms such as bradykinesia, hypokinesia, and impaired executive function. Conversely, the predominance of direct over indirect pathways results in inhibition of BG, causing dyskinesia (Fazl & Fleisher, 2018; Magrinelli et al., 2016; McGregor & Nelson, 2019).

PD is a multifocal, neurodegenerative disease not only affecting dopaminergic pathways, but also involving central, peripherical and enteric nervous systems, all of which are associated with PD symptoms (Braak & Braak, 2000; Del Tredici et al., 2002; Park et al., 2014). Disruption of the dopaminergic, cholinergic, noradrenergic and serotonergic neurotransmitters is also associated with non-motor symptoms such as depression, anxiety, sleep disorder, and blurred vision (Bartels & Leenders, 2009; Bohnen & Albin, 2011; Cosgrove & Alty, 2018; Goldman & Postuma, 2014; Klein et al., 2019; R. Morris et al., 2019; Schluter et al., 2003; Tolosa et al., 2021). Norepinephrine (noradrenergic neurotransmitter) deficiency may actually precede the loss of dopamine in PwPD, which would help to explain the emergence of some non-motor symptoms such as gastrointestinal dysfunction, olfactory and sleep disorders, and blunted HR before motor symptoms first present (Delaville et al., 2011; Espay et al., 2014; Palma & Kaufmann, 2014; Roos et al., 2022; Torrente et al., 2023). Of particular relevance to this thesis is an awareness of norepinephrine as a critical neurotransmitter for moderating heart rate in response to exercise see section; see section 1.5.4 on Page 31 for further details.

1.4 Clinical diagnosis

PD is diagnosed principally via clinical tests which focus on different aspects of movement and motor control, administered by a general practitioner and subsequently verified by a neurologist or gerontologist. Early signs such as anosmia (loss of smell) or veering during walking are sensitive but not specific early signs. Although neuro-imaging techniques are not routinely used as diagnostic tools, a dopamine activity transporter scan may be administered to provide diagnostic certainty (Jankovic et al., 2000; Rizzo et al., 2016; Shih et al., 2006). A diagnosis of PD is usually confirmed when at least 50-80% of dopaminergic neurons in the SNpc have been lost (Karapinar Senturk, 2020; Schapira et al., 2017; Ugrumov, 2020). These clinical signs and symptoms are also similar to those presenting with ‘Parkinsonian plus’ syndromes such as multiple system atrophy and progressive supranuclear palsy (Olfati et al., 2019). Both retrospective and prospective longitudinal studies suggest that non-motor symptoms are indicative of a prodromal phase of PD, whereby pathophysiological changes are evident without the notable presence of motor signs (Pont-Sunyer et al., 2017; Tolosa et al., 2021).

Recent advancements in machine learning and imaging techniques, aid early detection of non-motor symptoms and changes in brain structure before significant loss of dopaminergic neurons, potentially improving early management and prognosis (Sankineni et al., 2023; Tolosa et al., 2021). However, further refinement is needed before an accurate prodromal or early-stage

diagnosis is incorporated into clinical use. Despite there being no cure for PD, an earlier diagnosis would enable better management and enhance overall well-being of PwPD.

1.5 Motor and non-motor symptoms

The cardinal motor symptoms of PD, encompass resting tremor, rigidity, bradykinesia, hypokinesia, gait impairment, and postural instability (Jankovic, 2008; Latella et al., 2019; Moustafa et al., 2016). Initial motor symptoms are typically unilateral but become bilateral as the disease progresses. This phenomenon results from increased degeneration and diminished dopamine uptake in the contralateral substantia nigra and putamen. Eventually, both sides are affected, with the initially affected side often experiences greater severity (Heinrichs-Graham et al., 2017; Rodriguez-Oroz et al., 2009; Yagi et al., 2010).

Disease progression and secondary symptoms may also differ among PwPD based on whether a person is right or left dominant (Baumann et al., 2014). While all PD symptoms are significant and can affect an individual's QoL and function, this thesis focuses on those that have the greatest impact on the performance of cardiopulmonary exercise test (CPET) and NCBT. For example, although tremor is common and considered a debilitating symptom for many, it usually disappears during movement. Similarly, although rigidity is also a common motor symptom, it is more noticeable during passive or slow movements (stretching) compared with fast movements such as boxing (Rodriguez-Oroz et al., 2009).

1.5.1 Bradykinesia and Hypokinesia

In the literature, the terms bradykinesia and hypokinesia are used interchangeably. However, in this thesis, bradykinesia refers to the slowness of movement and occurs in all patients diagnosed with PD, while a reduction of frequency and range of motion, characterizes hypokinesia (Ling et al., 2012; Schilder et al., 2017). Although the cause of these symptoms is not fully understood, bradykinesia is associated with dopamine deficiency impairing direct and indirect pathways in the BG. Conversely, hypokinesia appears to be unrelated to the functioning of dopaminergic pathways and is instead more likely to reflect impaired timing mechanisms affected by loss of dopamine and catecholamines (Rodriguez-Oroz et al., 2009).

Berardelli et al. (2001) suggests that bradykinesia occurs in conjunction with hypokinesia and may result from tremors, muscle weakness, and rigidity. The authors explain that rigidity in antagonist muscles can slow the performance of agonist muscles. Some features of bradykinesia & hypokinesia include reduced arm swing (amplitude and frequency), decreased off-ground foot elevation, and stride length (Berardelli et al., 2001; Rodriguez-Oroz et al., 2009; Spay et al., 2019). These features significantly impact gait and balance in PwPD (Cheng-Chieh & Wagenaar, 2018; Hu et al., 2012; Ortega et al., 2008; Wagenaar & Van Emmerik, 2000; Yang et al., 2008; Zampier et al., 2018). Bradykinesia results in insufficiently recruited muscle fibres to

produce force when movement is initiated, increasing when more muscles are activated from different parts of the body during complex movements (Allen et al., 2009; Berardelli et al., 2001; Hallett & Rothwell, 2011; Hammond et al., 2017; Helgerud et al., 2020; Ma et al., 2012; Pelicioni et al., 2021; Rodriguez-Oroz et al., 2009).

According to Penko et al. (2021), bradykinesia may limit the ability of PwPD to reach their maximum aerobic capacity during CPET, and it may also hinder the improvement of aerobic capacity after aerobic exercise interventions. The authors suggest that bradykinesia limits PwPD to achieve their maximal effort. Similarly, bradykinesia may impact power performance during boxing movements, potentially influencing the ability of PwPD to reach high-intensity zones. Exercise intensity depends on movement speed and resistance (workload or inclination) that can be adjusted accordingly for each individual during aerobic training, such as that performed on the bike or treadmill (Laursen & Buchheit, 2019; Liguori et al., 2022). However, in NCBT, these tools are unavailable, making it challenging to control exercise intensity. Therefore, movement speed is critical to increasing exercise intensity during this activity, and bradykinesia can significantly impact PwPD's performance, including the ability of the upper body to reach a target, which is an essential movement during NCBT training, specially during focus pad drills (Ma et al., 2012). Bradykinesia, alongside dyskinesias and rigidity, may also affect energy expenditure (EE) in PwPD (Barichella et al., 2022; Katzel et al., 2012; Kempster & Perju-Dumbrava, 2021; Toth et al., 1997).

1.5.2 Cognitive impairment

In boxing, athletes must be able to move in diverse ways and rapidly adjust to changing situations using deft footwork and cognitive alertness. Sustained attention, or vigilance, is crucial for athletes to perform boxing drills whilst in motion at a close viewing distance, where they receive most of their visual information (Lesiakowski et al., 2013). NCBT for PwPD does not include an opponent, but the change in direction is standard during focus pad drills. Also, different boxing combinations and the rapid response to change from one combination to another (along with footwork) increases the demand for cognitive input.

Cognitive impairment manifests as attentional deficit such as the inability to allocate attention (resource allocation), divide attention, and switch attention. PwPD also present with an inability to dual task, reduced executive function, and visuospatial disorders, all of which are key to effective daily functioning and exercise performance (Heremans et al., 2013; Hillman et al., 2008; Intzandt et al., 2018; Murray et al., 2014; Peterson et al., 2016). Cognitive impairment affects around 42% to 57% of PwPD and often progresses to dementia (Anang et al., 2014; Williams-Gray et al., 2007; Yarnall et al., 2014; Yarnall et al., 2013). Deterioration of cognitive function in PD is linked to the degeneration of dopaminergic (fronto-striatal) and non-

dopaminergic (particularly cholinergic) systems (Klein et al., 2019; Schapira et al., 2017; Tsai et al., 2024).

Executive function, which includes the action of planning, initiating and inhibiting movements, is one of the most common forms of cognitive dysfunctions in PwPD and is associated with inactivity in this population (Foster & Hershey, 2011; Khalil et al., 2017; Nadeau et al., 2017). PwPD are slower in changing their focus on what they are working on to start a new task, such as processing and executing a new boxing combination (Ravizza et al., 2012), which may in turn impact on the ability to train in a high-intensity zone.

Visuospatial function is governed by a complex interaction of processes comprising 'top-down' (attentional) drivers and 'bottom-up' saccadic eye movements, both affected in PD. Prefrontal and parietal cortices, basal ganglia, thalamus, and brainstem structures are all implicated and deteriorate through loss of dopamine, leading to impairment in visuospatial and visuo-perception function (Archibald et al., 2013).

1.5.3 Postural instability and gait impairment

Postural instability and gait impairment are the most common and debilitating symptom in PwPD (*the 'signature' feature*), evident early in the disease (Lord et al., 2016). Decreased levels of dopamine and acetylcholine can help to explain the pathophysiology behind postural instability and gait impairment, though the *'signature' feature* of PD remains insufficiently understood (Bohnen et al., 2012; Grabli et al., 2012; Lewis & Barker, 2009; Roytman et al., 2023). The BG also has an important role in controlling postural reflexes and postural control by selecting appropriate muscles for activation or inhibition (Kim et al., 2013; Mille et al., 2007; Nallegowda et al., 2004; Palakurthi & Burugupally, 2019).

A sufficient level of coordination between sensory and motor systems is essential to adjust and maintain the centre of mass over the base of support during static and dynamic conditions. PwPD rely on greater input from visual, vestibular, and cognitive systems to augment sensory and motor deficit, and any disruption in these circuits exacerbates postural instability (Feng et al., 2020; Palakurthi & Burugupally, 2019). Postural instability can significantly impact an individual's mobility and exercise performance (particularly NCBT), as discussed below.

Gait performance demands continuous monitoring of bilateral coordination and dynamic postural control (Caetano et al., 2019). Walking is a mostly automatic activity, even in older adults. However, in PwPD it is a more demanding task, one that requires 'top-down' control via fronto-executive pathways. Walking is attentionally driven, which in turn compromises the capacity for dual task activity (Redgrave et al., 2010). Cognitive function is essential to initiating and coordinating the sequence of movements and continuously monitoring the environment required for walking (Bohnen et al., 2012; King & Horak, 2009; Lord et al., 2014;

R. Morris et al., 2019). Dysfunction of the supplementary motor area implicates in the performance of sequential movements such as gait and NCBT drills, and in the timing of the anticipatory postural adjustment in the start stages of gait (Jacobs et al., 2009; Rahimpour et al., 2022). Bradykinesia and hypokinesia are also noteworthy features impacting gait performance, by reducing the speed and range of motion of the movement (Cheng-Chieh & Wagenaar, 2018; Hu et al., 2012; Ortega et al., 2008; Rafferty, Prodoehl, et al., 2017; Wagenaar & Van Emmerik, 2000; Yang et al., 2008; Zampier et al., 2018).

The natural sequelae of postural instability and gait impairment in PwPD, is falls. Around 45%-75% of PwPD fall annually and about 50% of these falls are recurrent (Canning et al., 2015; Fasano et al., 2017; Kim et al., 2013; Li et al., 2012; Lord et al., 2016). Falls are debilitating, resulting in injury or fracture, which is one of the most common causes of hospitalisation in this population. Falls and fear of falling also result in reduced physical activity and lower QoL in PwPD (Canning et al., 2015; Kerr et al., 2010; Khalil et al., 2022; Okunoye et al., 2020; Palakurthi & Burugupally, 2019).

Falls in PwPD are associated with disease severity, and although the cause of falls is multifactorial, there is a robust link between falls and motor and cognitive impairment. (Lord et al., 2016). Nonnekes et al. (2019) identified two primary causes of falls. The first is due to a sequential reduction in step length and a corresponding increase in cadence, and the second is forward flexion of the trunk on the lower limbs, which the authors describe as two phenotypes of festination. This differs from freezing of gait, which is characterized by shuffling or trembling movements of the legs that temporarily prevent PwPD from walking forward, despite intending to do so. Freezing of gait is also highly associated with falling episodes and may be triggered by various situations such as turning, walking, tight spaces, and multitasking (Mitchell et al., 2019; Peterson et al., 2016; Spildooren et al., 2019).

NCBT is a complex motor and cognitive task which lies beyond most PwPD who present with advanced disease symptoms such as marked postural instability (Hoehn & Yahr IV, V), falls, gait festination and freezing, cognitive dysfunction, and dyskinesia. The complexity of this activity and the increased risk of falls and injuries are key factors explaining why studies evaluating NCBT in PwPD primarily include participants with mild to moderate disease severity (H&Y I-III) (Blacker et al., 2024; Combs et al., 2013; Combs et al., 2011; Shearin et al., 2021). H&Y III represents the threshold between moderate and severe PD. At this stage, individuals typically exhibit some degree of postural instability but remain capable of independent function (Goetz et al., 2019; Goetz et al., 2004; Lord et al., 2016; Palakurthi & Burugupally, 2019). However, including participants beyond this stage of the disease in NCBT may significantly increase the risk of falling, although to date this has not been formally evaluated.

NCBT incorporates upper body strikes to bags and focus pads, and rapid footwork changes in direction and pace change. Boxing rounds also incorporate different punches and order of punches. These all require robust cognitive, motor and sensory responsiveness. External cues and activities also impact on performance. Boxers must continually assess and update the environmental context in which they are exercising. General noise, instructions, music, and activities within the gym are all potential distractors for PWPD who are challenged by dual task performance (Heremans et al., 2013; Hillman et al., 2008; Intzandt et al., 2018; Murray et al., 2014; Peterson et al., 2016). All of these features have the potential to impact on the ability of PwPD to generate the skills required for a successful session of NCBT (Dinu & Louis, 2020; Kruszewski et al., 2016; Lesiakowski et al., 2013; Peterson et al., 2016; Rzepko et al., 2014).

Aerobic exercises and NCBT are discussed further in this thesis (Chapter four and five). However, it is beyond the brief of this thesis to extend this discussion to examine, for example the effect of NCBT on postural instability and gait impairment or the impact of motor symptoms on boxing performance. Participants recruited for the studies outlined in Chapter four and five are all H&Y I to III, comparable to earlier work (as noted above). This suggests that NCBT is preferentially suited to younger people with early to moderate disease onset.

1.5.4 Autonomic nervous system dysfunction

The ANS consists of the enteric, parasympathetic (PNS), sympathetic (SNS), and adreno-medullary hormonal components. PD pathology has been linked to a failure or dysregulation of multiple components within the ANS, with symptoms including constipation, urinary incontinence, orthostatic hypotension, and impaired HR response (Amino et al., 2005; Appenzeller & Goss, 1971; Goldstein, 2003; Goldstein et al., 2005; Palma & Kaufmann, 2020; Sabino-Carvalho et al., 2018; Shibata et al., 2009). Although dysfunction of the ANS seriously impacts an individual's QoL, this thesis focuses on inadequate increase in HR in response to maximum CPET and NCBT. Blunted HR response is often overlooked in the PD literature applying aerobic training protocols, despite reports of cardiac autonomic abnormalities in this population (Goldstein, 2003; Kanegusuku et al., 2016; Mavrommati et al., 2017; Oka et al., 2006).

During aerobic exercises and cardiopulmonary exercise testing, there is an increase in the demand for oxygenated blood to working muscles, resulting in an increasing HR and stroke volume leading to an increase in cardiac output to supply the demand (McArdle, 2015; Schmid et al., 2013). These physiological changes are governed by the ANS using two primary neurotransmitters: acetylcholine (cholinergic) and norepinephrine (noradrenergic). During rest, acetylcholine is released by the PNS and binds to the muscarinic receptors within the heart

muscle cells, decreasing atrioventricular conduction and reducing HR and contractility. With an increase in exercise intensity, the SNS becomes more active, leading to the release of norepinephrine, which binds with beta-1 adrenergic receptors of the heart muscle, increasing HR and contractile force (Gordan et al., 2015; Marieb & Hoehn, 2016; Menezes-Rodrigues et al., 2023; Rizzi & Tan, 2017; Sabino-Carvalho et al., 2021; Sulzer & Surmeier, 2013; Wichit et al., 2021). As exercise intensity decreases, SNS activity diminishes, while an increase in PNS activity occurs, leading to slower atrioventricular conduction and a decrease in HR. Therefore, a balance between the SNS (levels of norepinephrine) and PNS in controlling HR responses, is critical for aerobic exercise training, including HIIT (Buchheit et al., 2007; Foulon & De Backer, 2018; Goldstein, 2003; Goncalves et al., 2021; Ravens et al., 2011; Tessa et al., 2019).

Wichit and colleagues found significantly higher resting levels of plasma norepinephrine in PwPD than in health controls (n = 40 per group). In this study, PwPD were tested during their 'off-period' (12 hrs prior to analysis), and the effects of increasing exercise intensity on norepinephrine levels were not examined (Wichit et al., 2021). In contrast, DiFrancisco-Donoghue et al. (2009) reported significantly lower levels of plasma norepinephrine in PwPD (n=14) both at rest and during peak exercise, regardless of whether they were on or off medication. This finding suggests that blunted HR response observed in this population, is less likely to be attributed to levodopa use but to dysfunction of the SNS. Despite having lower norepinephrine levels and a significantly lower HR at peak exercise, PwPD attained a similar VO_2peak to healthy control participants, and their aerobic capacity was similar both while on or off medication (DiFrancisco-Donoghue et al., 2009). Aerobic capacity in PwPD is further discussed in the following chapters of this thesis. While plasma norepinephrine levels change during exercise, data from healthy populations shows that this depends on the exercise intensity and type of exercise being performed (Athanasiou et al., 2023; Greiwe et al., 1999). Increase in norepinephrine at rest and during exercise in PwPD warrant further evaluation, specifically in those with and without CI.

Due to the complex multisystem nature of PD, the exact pathophysiology of impaired HR in PwPD and its influence in exercise performance remains unknown in this population. It can involve both central and peripheral systems and changes in cardiac receptors located in the heart (Cuenca-Bermejo et al., 2021; Delaville et al., 2011; Espay et al., 2014; Goncalves et al., 2021; Rizzi & Tan, 2017). However, recent studies have shown a link between cardiac dysfunction and damage to the SNS and PNS. For example, impaired HR is associated with postganglionic sympathetic efference damage, α-synuclein aggregation in the sympathetic ganglia, and alteration of dorsal vagal motor activity (DiFrancisco-Donoghue et al., 2009; Goldstein, 2003; Oka et al., 2006; Sabino-Carvalho et al., 2021; Speelman et al., 2012; Suzuki et al., 2017; Ziemssen & Reichmann, 2010). According to Braak et al. (2004) the dorsal motor of the vagal nerve may be involved in the early stages of the disease. However, research suggests that the

degeneration of the cardiac sympathetic nerve occurs early in PD, before neuronal cell loss in the dorsal vagal nucleus and before the onset of cardiac parasympathetic and vasomotor peripheral sympathetic dysfunction in the sinus node (Amino et al., 2005; Oka et al., 2006; Orimo et al., 2007; Shibata et al., 2009). The cause of parasympathetic nervous dysfunction in PD is not fully understood.

As with other non-motor symptoms, blunted HR response may be a prodromal feature of PD, preceding the onset of motor symptoms (Amino et al., 2005; Fujishiro et al., 2008; Iniguez et al., 2022; Palma & Kaufmann, 2014), although again it appears to be a sensitive rather than a specific marker. In a retrospective cohort study of 2,739 patients undergoing CPET from 2001 to 2010, those who later developed PD, had significantly lower maximum HR (HRmax) at peak exercise compared with controls. Over a four-year period, the sensitivity for predicting PD was 83%, with a specificity of 62% (Palma et al., 2013).

It is unclear how impaired HR responses progress in different stages of PD. A decline in cardiac sympathetic activity, at a rate comparable to the loss of nigrostriatal dopamine terminals, and changes in cardiovagal function as the disease becomes more severe, have been reported (Kim et al., 2014; Li et al., 2002). However, Bryant et al. (2016) reported no difference between an impaired increase in HR and disease severity during a treadmill test to volitional exhaustion, and Shibata et al. (2009) suggest that cardiac autonomic dysfunction occurs independently of dopaminergic degeneration by examining ^{123}I-MIBG myocardial scintigraphy in PwPD.

1.5.4.1 Chronotropic incompetence

CI is defined as the inability to raise HR to an arbitrary threshold of 85% maximum age-predicted heart rate (MA-PHR) during peak exercise despite clinical and physiological markers indicating that maximal effort has occurred (Brubaker et al., 2006; Brubaker & Kitzman, 2011; Penko et al., 2021). A commonly used method of identifying CI is the chronotropic index equation: [(HRmax – HRrest)/(220 – age – HRrest)], which takes into consideration resting HR (HRrest). HRmax in this equation represents the maximum HR attained during CPET. A failure to achieve a chronotropic index above 0.8 indicates CI (Lauer et al., 2005; von Scheidt et al., 2019). An alternative approach for detecting CI involves examining the relationship between HR and metabolic reserve at various stages during the treadmill test, as suggested by Wilkoff and colleagues (Wilkoff & Miller, 1992). For consistency, the term CI is referred to if criteria for its determination were used; otherwise, impaired or blunted HR response is used.

In the general population, CI is associated with reduced aerobic capacity, increased risk of cardiovascular diseases and mortality (Brubaker et al., 2006; Brubaker & Kitzman, 2011; DiFrancisco-Donoghue et al., 2009; Herbsleb et al., 2018; Kanegusuku et al., 2016; Miyasato et al., 2018; Myers et al., 2007; Penko et al., 2021; Schmid et al., 2013; Werner et al., 2006).

Several studies have reported that a substantial percentage of PwPD are unable to reach their HRmax during a CPET designed to elicit maximal effort (Bryant et al., 2016; Kanegusuku et al., 2016; Mavrommati et al., 2017; Speelman et al., 2012). Penko et al. (2021) reported that 40% of 100 PwPD (H&Y II-III) under PD medication, were identified with CI during a stationary bike test. The authors suggested that CI may impact improvement in aerobic capacity in PwPD. However, participants from this study were not stratified according to the presence or absence of CI, to understand whether aerobic fitness levels differed between PwPD and without CI. By contrast, Griffith et al. (2024) identified only 13 PwPD with CI (±10%) during a treadmill test in a study involving 128 individuals diagnosed with drug-naïve PD (H&Y I-II) with disease duration under 5 years. Aerobic capacity was significantly lower in those who presented with CI than without.

Potential factors that may compromise aerobic capacity in PwPD are blunted HR response, which can reduce maximal cardiac output, and the malfunctioning of mitochondria, which can reduce the arterio-venous oxygen difference (DiFrancisco-Donoghue et al., 2009; Glaab & Taube, 2022; Gordan et al., 2015; Kanegusuku et al., 2016; Larsen et al., 2020; Penko et al., 2021).

Another issue associated with this feature of ANS dysfunction, is that although recent studies provide evidence for a beneficial effect of vigorous to high-intensity exercise in PD (Bouca-Machado et al., 2020; Schenkman et al., 2017; Shulman et al., 2013), researchers often fail to consider the implications of CI for exercise-intensity programming, which may impact the outcome. Traditional MA-PHR equations (e.g., 220-age) can be inaccurate at determining training intensity in PD with CI. This general approach may lead to under or overestimation of training intensity, which has implications for training effectiveness as well as from a safety perspective (Liguori et al., 2022).

1.6 Disease severity classification

Validated clinical instruments are used to classify disease stages. The Unified Parkinson's Disease Rating Scale (UPDRS) was developed in 1987 to monitor responses to medication and is also widely used to assess clinical changes following aerobic training protocols (Sacheli et al., 2019; Schenkman et al., 2017; Schootemeijer et al., 2020; van der Kolk et al., 2019). The Movement Disorder Society (MDS) addressed limitations in the original UPDRS. The MDS-UPDRS is a multi-domain assessment commonly used to assess symptom presentation and function, including subscales for gait, postural control, cognitive function, and mood. Lower scores on the test indicate milder disease severity (Goetz et al., 2019; Martinez-Martin et al., 2013). While the MDS-UPDRS is a reliable and valid evaluation instrument, it is a performance-based, clinical assessment taken on one occasion (Sangarapillai et al., 2021).

The Hoehn and Yahr Scale (H&Y) is derived from the motor sub-scale of the MDS-UPDRS and measures the severity of PD. The scale is comprised of 5 stages: Stage 1 indicates unilateral motor symptoms; Stage II shows that motor symptoms are bilateral, although balance and postural control are still intact; Stage III indicates attenuation of postural control and balance following an inability to recover from retropulsion. This is an important threshold to reach, suggesting a marked decline in the disease. By stage IV, symptoms become severe and impact on an individual's QoL and function, with mobility still preserved to some extent. By stage V, bed or wheelchair use is necessary unless assistance is provided (Combs-Miller & Moore, 2019; Goetz et al., 2004). PwPD who are classified as H&Y stage III or lower, tend to be more physically activity, and generally experience better QoL, mobility, physical function, and less cognitive decline (Oguh et al., 2014).

1.7 PD phenotypes

PD is a heterogeneous disorder with respect to clinical presentation, progression rates, and risk of disease complication (Lawton et al., 2018). Clinical phenotypes help inform about disease progression and management, and are generally based on age at onset (early-onset versus late-onset), motor (tremor vs non-tremor dominant, or postural instability and gait disorders), non-motor features (such as autonomic disturbance and cognitive dysfunction), and the rate of progression (Fereshtehnejad et al., 2015; Marras & Chaudhuri, 2016; Mu et al., 2017). Nonetheless, ongoing debates arise as to whether one subtype presents a more favourable prognosis and slower disease progression than another (Lee et al., 2019).

Two phenotypes are commonly (although not universally) referred to: the postural instability and gait difficulty predominant (PIGD) subtype, and the more benign form of the disorder, the tremor-dominant (TD) subtype. Gait and balance performance are worse in those classified as PIGD, and are predicted to have greater motor deficit and propensity for future falls (Herman et al., 2014). Further refinement of these subtypes has been carried out. Lawton et al. (2018) analysed data of 2000 PwPD over 5 years and identified four major clusters or phenotypes. The results showed some overlap between the subtypes, with some distinct patterns emerging. The first cluster (31% of participants) had faster motor progression and poor response to levodopa medication. The second cluster (29%) responded well to medication and presented intermediate motor progression. The third cluster (21%) had higher postural instability and gait impairment and presented an intermediate response to medication and motor progression. The fourth cluster (20%) was more tremor-dominant, had poor response to levodopa and had the slowest motor progression. Non-motor symptoms were more predominant in clusters 1 and 3 than in clusters 2 and 4.

1.8 PD treatment and management

A multi-disciplinary approach is necessary for effective management given the range of presenting symptoms. Levodopa medication is primary treatment for all, and is given orally or via an infusion pump in later disease stages (Graham et al., 2014; S. S. Paul et al., 2019; Rabin et al., 2015). Levodopa therapy is effective in providing symptomatic relief, especially in the early stages, but it does not prevent disease progression (Baker et al., 2009; Dexter & Jenner, 2013; Philippens et al., 2019). Long-term levodopa therapy has significant drawbacks, including the onset of dyskinesia and the wearing-off phenomenon (Beckers et al., 2022; Ribot et al., 2019; Shetty et al., 2019). Levodopa also has a selective effect. For example, it ameliorates bradykinesia, hypokinesia, and some gait patterns, such as gait speed and step length, but has minimal effect on freezing of gait and postural control (Dirkx & Bologna, 2022; Ling et al., 2012; Lord et al., 2014; Palakurthi & Burugupally, 2019). Tremors can respond well to levodopa treatment in some cases but not always (Beckers et al., 2022).

Dopaminergic replacement therapy does not appear to affect HR responses or the measurement of aerobic capacity in PwPD (DiFrancisco-Donoghue et al., 2009). Generally, aerobic exercise training in the 'on' state is considered optimal, with some individuals taking an extra dose to enhance performance (Schootemeijer et al., 2020). However, it remains uncertain whether the timing of medication intake has a positive or negative impact on improvements in aerobic capacity.

It is important to note that PwPD are actively involved in finding a cure and the best therapy approach to tackle the disorder. This is apparent, for instance, in events such as the World Parkinson Congress, where PwPD, caregivers and others take a prominent role in research, assisting with study design, evaluation and interpretation (World Parkinson Congress, 2024).

1.9 Physical exercise

Physical exercise, including aerobic exercise training, is also a mainstay of therapy for PwPD. It has proven efficacy in managing both motor and non-motor symptoms of PD and can enhance overall QoL and general health (Chen et al., 2020; Lamotte et al., 2015; Lauzé et al., 2016; Liguori et al., 2022). However, exercise also presents limitations. For example, while targeted physical exercise can reduce the rate of falls, efficacy is reported for the early stages of the disease only, with fall rates increasing in later stages (Canning et al., 2015; Morris et al., 2015).

While being physically active is important, this term is not the same as physical exercise. Physical activity involves any bodily movement that increases caloric requirements, whereas physical exercise is a planned, structured activity aimed at improving or maintaining physical fitness components (Liguori et al., 2022). The literature extensively documents the benefits of

physical exercise in managing PD (Chen et al., 2020; Cui et al., 2023; Gamborg et al., 2022; Li et al., 2021). However, most studies are randomized controlled trials with a maximum of 12 weeks duration, with only a few studies extending beyond this.

The health benefits of physical exercise go beyond managing PD symptoms. It can also improve cardiorespiratory function and muscle strength, help ameliorate social and psychological distress, and decrease the risk of osteoporosis, cardiovascular disease, diabetes mellitus, and other comorbid disorders (Ahlskog, 2011; Garber et al., 2011; Helmer et al., 2018; Kanegusuku et al., 2017; Kränkel et al., 2019; Liguori et al., 2022; Mavrommati et al., 2017; McNeill et al., 2006; McPhee et al., 2016; Powell et al., 2011; Russell et al., 1995; Sargeant et al., 2018; van Nimwegen et al., 2011; Xu et al., 2010).

Despite being well-informed about the advantages of physical exercises, PwPD tends to be less physically active than age-matched healthy controls (Afshari et al., 2017). Lord et al. (2013) showed that PwPD, even in the early stages (H&Y I), walk less than age-matched controls, both in terms of volume and frequency. This decline persists with increasing disease severity, implying that it is irreversible. A study with 108 PwPD (H&Y I-III) showed that as the severity of the disease measured progresses, PwPD tend to spend more time sitting and less time being physically active (Gorzkowska et al., 2020). A sedentary lifestyle is associated with fatigue in PwPD. Garber and Friedman (2003) concluded that PwPD with higher levels of fatigue are more likely to be sedentary and, therefore have poorer aerobic capacity (VO_2peak) compared to those with lower levels of fatigue. Pechstein et al. (2020) suggested that fatigue contributes to exercise performance, but the exact factors associated with exercise intolerance in PwPD, remain unknown.

A recent study of 30 PwPD and 30 healthy controls who wore a commercial device (FitBit charge HR, Fitbit Inc.) with a triaxial accelerometer to monitor their physical activity levels over 14 days, also revealed that PwPD are more sedentary, and that their activities also exhibit lower intensity compared to a healthy control group (Pradhan & Kelly, 2019). This finding is further supported by a study that interviewed 138 PwPD (Lockwich et al., 2022), who perceived their own exercise intensity as moderate, which was defined as the ‘ability to maintain a short conversation while exercising’.

Reasons for lack of engagement in physical activities and exercise vary, related to embarrassment over presenting PD symptoms such as tremor, impaired balance with the potential to fall, and fatigue. Non-disease related aspects also contribute, such as the absence of an 'exercise buddy' for motivation, fear of slowing down exercise classes due to being more affected than peers, low expectation with exercise, financial constraints, and travel distance posing barriers to engagement (Afshari et al., 2017; Borrero et al., 2022; Paul et al., 2021).

On the other hand, confidence in the ability to overcome personal, social, and environmental obstacles, was linked to increased participation in exercise, along with level of education and age (Ellis et al., 2011; Gorzkowska et al., 2020). Group-based exercise programs (e.g. NCBT) is suggested to promote camaraderie and social cohesion among PwPD. Such programs are recognized as essential elements for sustaining long-term participation in exercise regimens (Borrero et al., 2022; Lowery et al., 2023; M. E. Morris et al., 2019).

1.9.1 Aerobic exercise training

Aerobic exercise training comprises dynamic exercise involving major muscle groups, leading to a notable increase in HR and energy expenditure (Howley, 2001). The primary goal of aerobic training is to improve aerobic capacity, which refers to the body's ability to perform exercise involving large muscle groups at moderate-to-vigorous intensity for extended periods (Liguori et al., 2022). Aerobic capacity is typically represented by peak oxygen consumption (VO_2peak). Chapters Two and Three present an overview of the measurement, determination, and application of VO_2peak in PwPD.

Improvements in aerobic capacity from aerobic exercise training, rely on central and peripheral adaptations, such as nervous system efficiency in recruiting motor units, elevated stroke volume and cardiac output, blood flow, muscle mitochondrial content, and capillary density (Atakan et al., 2021; Laursen & Buchheit, 2019; Liguori et al., 2022). One of the most evident central physiological adaptions following aerobic interventions, is increased blood volume, which increases stroke volume (volume of blood ejected from the left ventricle per heartbeat) and the ability to supply oxygenated blood to the working muscles. This significantly contributes to the augmentation of cardiac output, reflected by a lower resting heart rate and a greater efficiency of pumping blood around the body at submaximal and maximal workloads. Increased cardiac output has been shown to have a direct relationship with increased VO_2peak following aerobic training (Astorino et al., 2017; Beltz et al., 2016; F.N. Daussin et al., 2007; Hellsten & Nyberg, 2015; Lepretre et al., 2004; Older, 2013).

The evidence is strong for the beneficial effect of aerobic training on aerobic capacity in PwPD. Schootemeijer et al. (2020) in a systematic and meta-analysis review, reported level 1 evidence that aerobic training has the potential to improve aerobic capacity in PwPD. The authors also highlighted the benefits of aerobic training in cardiovascular function and mortality for PwPD. According to a recent systematic review, improvement in VO_2peak in PwPW can vary from nil to up to 22%, after 6-12 weeks of aerobic training protocols (Thrue et al., 2023). However, studies included in these reviews did not consider CI affecting improvement in VO_2peak in PwPW, which, as mentioned above, can significantly hinder aerobic performance. Moreover, gender, age, baseline fitness level, and genetic factors may also contribute to lack of improvement in aerobic capacity (Meyler et al., 2021).

In addition to improving aerobic capacity and other health-related outcomes, aerobic training has been shown to significantly improve PD symptoms, although this is not a universal finding (Panassollo et al., 2024). Two recent systematic reviews report improvements in balance, motor function, and some gait parameters (velocity and step length) in PwPW after aerobic training protocols but no significant improvement in QoL (de Oliveira et al., 2021; Zhen et al., 2022). By contrast, a systematic review and meta-analysis reported a significant improvement in QoL after a minimum of 12 weeks of aerobic activities, including martial arts and dance (Chen et al., 2020). In another systematic review, Schootemeijer et al. (2020) found insufficient evidence for the effectiveness of aerobic training in improving gait, balance, and falls in PwPD. The contradictory results likely indicate a lack of consistency in measuring training variables, variability, and reporting within the PD literature (Bouça-Machado et al., 2020; Li et al., 2021).

Aerobic exercise training has also been the focus in PwPD due to its potential neuroprotective effect in mitigating disease progression. Mechanistic evidence suggests that high-intensity aerobic exercise training in particular, may afford neuroprotection and slow disease progression in PD, and more recently evidence has been supported by small clinical studies (Ahlskog, 2018; Alberts & Rosenfeldt, 2020; Ellis & Rochester, 2018). This is an emergent area of research, one that is highly relevant to PwPD who are motivated by an intervention that may help slow disease progression, especially given the limits of pharmacology (discussed on subsection 1.8).

Although challenging to tease apart, improvement in functional performance and motor symptoms after aerobic exercise training, is most likely due to a combination of exercise (or activity) to ameliorate PD-specific impairments and the favourable physiological adaptations associated with improvements in aerobic fitness. Gains in both may outweigh the benefits of one in isolation (Amateis et al., 2019; Ellis & Rochester, 2018; Gamborg et al., 2022; Lang & Espay, 2018; Tollar et al., 2019).

1.9.1.1 Aerobic fitness and comorbid disorders in PD

Enhancing overall fitness is also crucial for PwPD because there is a strong association between VO_2peak and reduced risk of cardiovascular diseases and mortality in the general population (Kunutsor et al., 2017; Liguori et al., 2022; Riebe et al., 2018; Satoru et al., 2009), although whether the effects are comparable in PD has yet to be determined. In a study examining cause of death in 143 PwPD, Pennington et al. (2010) reported that 12% of participants died of ischaemic heart disease, 12% of malignancy, 11% of pneumonia, and 9% of cerebrovascular disease. However, when compared to controls, PwPD were more likely to die from pneumonia and less likely to die from malignancy or ischaemic heart disease (Pennington et al., 2010). A recent systematic review and meta-analysis found that cardiovascular co-morbidities, are among the most common reasons for hospitalization in PwPD after infections, complications related to motor symptoms, and falls or fractures (Okunoye et al., 2020). However, not all studies

included in this review incorporate control groups into their research design. Guttman et al. (2004) reported that hospitalization cases in PwPD are 1.44 times higher than controls adjusted for survival rate. According to the authors, PwPD present higher hospitalization rates for pneumonia and fracture, but similar to cardiac disease.

Piqueras-Flores et al. (2018) found that heart problems intensify as the disease progresses, although the reasons for this are unclear. K. C. Paul et al. (2019) evaluated the lifestyle and mortality of 360 PwPD over 15 years and suggested that lifestyle behaviours such as coffee and alcohol consumption, smoking, and level of physical activity may influence the outcome. Therefore, it is unclear whether the increase in cardiovascular diseases in PwPD is related to the disease itself, a consequence of the inactivity (reduced aerobic capacity) or other lifestyle choices, or a combination of multiple factors.

1.9.2 Aerobic exercise training principles

Structured aerobic exercise protocols based on key training principles, is critical to promote improvement in aerobic capacity in PwPD. A comprehensive overview of all training principles exceeds the scope of this thesis. Nonetheless, we delve into three crucial training principles for general aerobic exercise and HIIT protocols. These include FITT-VP, specificity, and individuality principles, which are recommended for PwPD (Alberts & Rosenfeldt, 2020; Cheng et al., 2016; Liguori et al., 2022).

FITT-VP stands for Frequency, Intensity, Time, Type, Volume, and Progression. Although the ACMS describes it as a principle, the FITT-VP contains different training components that are also considered training variables (e.g. time, intensity, frequency) by other authors (Laursen & Buchheit, 2019; Stanton & Reaburn, 2014; Stoggl & Sperlich, 2014). These components (variables) can be manipulated to tailor aerobic exercises to individual needs and goals. The ACSM also defines *progression* as a separated training principle, which serves to adjusting other aerobic exercise training variables (e.g., intensity, frequency, and time), to advance the overall training program (Bushman, 2018). To enhance clarity in this thesis, the term 'principle' or 'variable' of training will precede the use of terminology (e.g., FITT-VP principle or training variable intensity). Below we describe FITT-VP principle and its training components following by the principle of specificity and individuality. **Table 2** in Chapter Two includes frequency, intensity, type, time, and volume of training of aerobic training protocols in PwPD.

Time refers to the duration of each session, while *type* refers to the aerobic exercise mode, such as continuous or interval, and includes modality such as treadmill or bike. In a recent study of 215 PwPD (Afshari et al., 2017), walking was reported as the most common exercise (73.3%), followed by strength training (34.9%), physical therapy (29.8%), and cycling (23.3%). The optimal aerobic exercise type for PwPD has not been established (Alvarez-Bueno et al., 2021).

However, the most suitable depends on individual needs, guided by the principle of specificity and individuality, which are further presented in this session.

The frequency of training, or how often the person exercises, is key to success, because of the cumulative physiological change that occurs after each session and the necessary recovery time between the sessions (Bushman, 2018; Liguori et al., 2022). Cumulative physiological change refers to the accumulation of short-term responses (e.g., an increase in HR), that lead to long-term changes in the body, such as an increase in left ventricular contractile force, which are critical for improvement in aerobic capacity. These changes vary depending on a person's level of fitness. For instance, someone who is unfit may need two 15-minute sessions to see improvements, while a fitter person may require five sessions to improve performance (Laursen & Buchheit, 2019; Liguori et al., 2022).

The recommended exercise frequency for PwPD ranges from three times per week to daily and may vary, based on disease severity (Alberts & Rosenfeldt, 2020; Kim et al., 2019; Liguori et al., 2022; Martignon, Pedrinolla, et al., 2021). The impact of training frequency on improving aerobic capacity in PwPD has yet to be evaluated, as most protocols have focused on exercise intensity as the key aerobic training variable (Alberts & Rosenfeldt, 2020; Martignon, Pedrinolla, et al., 2021; Panassollo et al., 2024; Schootemeijer et al., 2020). Training frequency is greatly influenced by exercise intensity, as adequate recovery periods between sessions are necessary. The recovery phase also depends on the type of training, strength training or continuous or interval aerobic training (Dias et al., 2022; Kraemer et al., 2016; Laursen & Buchheit, 2019; Liguori et al., 2022; Powers & Howley, 2018).

Training volume represents the product of duration (time per session) and frequency of training (Bushman, 2018; Laursen & Buchheit, 2019). Although not well understood in PD, training volume also appears to be critical to outcome. Studies show that PwpD who engage in exercise for at least 2.5 hours (150 minutes) per week for more than a year experience significant improvements in their QoL, functionality, and a reduction in caregiver burden, compared to those with a lower training volume (Oguh et al., 2014; Rafferty, Schmidt, et al., 2017). Shulman et al. (2013) found that PwPD who exercised on the treadmill for 150 minutes, improved more in the 6-minute walking test than those who performed the same type of exercise for 90 minutes weekly. Volume of training may also influence improvement in aerobic capacity in PwPD (Panassollo et al., 2024), but studies where intensity is equated are necessary to evaluate the effect of training volume in PwPD.

Training intensity is defined as the amount of physical effort, quantified as a percentage of an individual’s maximal physiological and clinical response to exercise (Laursen & Buchheit, 2019; McArdle, 2015). Despite low-intensity activities such as walking being the most popular form of aerobic exercise in PwPD, exercise intensity has been the primary focus of attention in

the PD literature (Afshari et al., 2017; Mantri et al., 2019). Exercise intensity and its importance for improving aerobic capacity, function, and motor and non-motor symptoms is reviewed in detail in Chapter Three. In a two-year longitudinal study in PwPD, Combs-Miller and Moore (2019) reported that a one-point increase in the rating of perceived exertion (RPE) ratings corresponded to a 1.55-point improvement in self-perceived health-related QoL, indicating that an increase in exercise intensity improves QoL. Schenkman et al. (2017) reported a significantly lower change in the UPDRS part III in those exercising at higher intensity, compared to lower exercise intensity, showing stability in motor symptoms and therefore less disease progression, rather than worsening of symptoms.

In a recent systematic review and meta-analysis of randomized controlled trials, Cui et al. (2023) reported a significant improvement in motor function (other than balance), mobility, and QoL in PwPD who had higher compliance to the ACSM minimum recommendations for training volume and intensity, than those with low compliance or when the compliance was unknown. Although these results underscore the impact of these two components of the FITT-VP principle in enhancing performance, the authors concluded that to date a specific type of exercise program has not been shown to be superior to others.

Training progression refers to a gradual increase in the other components of the FITT-VP principle, such as intensity and time. This feature is important for novice and advanced exercisers. For example, the recommendations from the ACSM for PwPD is to start with an exercise intensity of 60-65% HRmax and progress to 80-85% HRmax as they improve their fitness level (Liguori et al., 2022). Progression is not very common in studies with PwPD, due to time constraints. Most interventions are 12 weeks or less. However, Shulman et al. (2013) integrated training progression into their 12-week high-intensity aerobic exercise protocol in 23 PwPD, progressing the duration of the session from 15 to 30 min and the intensity from 40–50% of heart rate reserve (HRR) to 70–80% HRR. In the low-intensity protocol (n=22 PwPD), the duration progressed from 15 to 50 min, but there was no change in the exercise intensity, which was constantly at 40-50% of HRR. Despite differences in protocols, improvement in VO_2peak was similar in both groups (Shulman et al., 2013). Training progression is a critical component of aerobic training as it introduces new challenges to the body, promoting adaptation and continual improvement in performance. The time necessary for new stimulus depends on individual fitness and training goals (Dias et al., 2022; Laursen & Buchheit, 2019; Liguori et al., 2022).

The principle of specificity, also recommended for PwPD, suggests that the physiological adaptations resulting from aerobic exercises depend on other training components, such as exercise type and intensity (Dias et al., 2022; Lamotte et al., 2015; Laursen & Buchheit, 2019; Liguori et al., 2022). Repeatedly performing specific tasks is necessary for optimal therapeutic

outcomes in task-specific movement improvement or physiological adaptations (Cheng et al., 2016; Lamotte et al., 2015). For example, Demonceau et al. (2017) found that while aerobic exercise improved aerobic capacity in PwPD after 12 weeks, strength training did not show significant improvement. Exercise on the treadmill is suggested to provide greater improvement in gait performance in PwPD, due to the specificity of the task, than non-specific exercises (Bello et al., 2013; Cheng et al., 2016; Herman et al., 2007; Kurtais et al., 2008). However, a systematic review by Schootemeijer et al. (2020) could not confirm that treadmill exercise is more effective than other types of aerobic exercises in improving gait performance in PwPD.

The principle of individuality considers that each person is unique and emphasizes the need for personalized and tailored training protocols (França et al., 2022). Based on this principle, age, fitness level, health status, and individual goals are taken into account when planning a regime (Bushman, 2018). This is also the case in PD. A qualitative study involving 790 PwPD highlighted tremors as the number one symptom of concern for people, especially in the earlier stages of the disease. As the disease progressed, walking difficulties, balance, and falls became more critical for this population (Port et al., 2021). Therefore, training programs for PwPD might consider not only age, fitness level, and health status (e.g. elevated blood pressure and diabetes) but also the possibility that the goals of this population may change as the disease progresses.

1.9.3 High-intensity interval training

HIIT was used initially to enhance athletic performance and achieve record-breaking results across various sports (Atakan et al., 2021; Laursen & Buchheit, 2019). Its application expanded to the clinical realm, gaining popularity for a range of health outcomes. In a seminal study in 1975, HIIT demonstrated significant increases in aerobic power among post-coronary patients, with interval training outperforming moderate intensity continuous training (Atakan et al., 2021). Recent research examining the acceptability and efficacy of HIIT protocols has supported this early work for different health conditions, including PD (Cardozo et al., 2015; Demonceau et al., 2017; Harvey et al., 2019; Uc et al., 2014; Wen et al., 2019).

HIIT involves vigorous to maximum-intensity exercise interspersed with passive or low-intensity activity recovery between sets. Recovery time and type and work intervals are three specific HIIT training variables. It is generally classified into long intervals (2-4 minutes of work), low volume or short intervals (45 – 60 seconds of work), and sprint intervals (10 – 20 seconds of work). Recovery time and type (active or passive), work intervals, exercise volume, and intensity significantly influence the outcome, with work intervals and recovery time depending on the chosen intensity (Laursen & Buchheit, 2019; Liguori et al., 2022; Wen et al., 2019; Williams et al., 2019).

To date, the optimal training volume and the ideal time frames for work and recovery phases for HIIT protocols have not yet been defined for PD. Recent evidence from general and selected clinical populations, suggests that work phases should be 2 to 4 mins, and a total time in high-intensity zone should be at least 15 min per session to maximize gains in aerobic capacity. However, even shorter durations have been found to enhance fitness levels in both general and clinical populations, including those with heart conditions (Lehtonen et al., 2022; Quindry et al., 2019; Taylor et al., 2019; Wen et al., 2019). The optimal exercise intensity for HIIT protocols is uncertain, but generally agreed to be above 85% of HRmax, 80% of heart rate reserve, or 85% of peak aerobic capacity (Guiraud et al., 2012; Norton et al., 2010; StØren et al., 2017; Wen et al., 2019).

The literature suggests that HIIT elicits more significant changes in central adaptations (e.g. elevated stroke volume and cardiac output) than moderate training, associated with mainly peripheral changes, such as muscle mitochondrial content, and capillary density (Atakan et al., 2021; Laursen & Buchheit, 2019; Liguori et al., 2022; MacInnis & Gibala, 2017). However, for HIIT, central and peripherical adaptation can differ according to the duration of the bouts at the intensity performed. For example, game-based HIIT (including change in directions) and short intervals are associated with predominantly peripheral changes, while longer durations elicit more central adaptation (Buchheit & Laursen, 2013; Ksoll et al., 2021).

1.9.4 Non-contact boxing training

NCBT was originally developed in the United of States by former boxers as a HIIT fitness program for the general population. The program consisted of shadow boxing and drills incorporating bags or focus pads (Bellinger et al., 1997). In the mid-2000s, this activity gained popularity among PwPD mainly through the Rock Steady Boxing ™ (RSB) program. This group-based exercise regimen, incorporates various activities such as jumping rope, cycling, walking (treadmill or outdoor), calisthenic activities, push-ups, footwork, and punch activities using different bags and focus pads. The main goal of the RSB program, which has been used in recent studies evaluating the benefits of NCBT for PwPD, is to improve strength, fitness level, and balance (Combs et al., 2013; Combs et al., 2011; Lowery et al., 2023; M. E. Morris et al., 2019).

A key feature of NCBT is the use of external cues such as focus pads or boxing bags to help focus attention and in doing so, engage frontal and pre-frontal neural pathways (such as the dorso-lateral pre-frontal cortex) to bypass affected basal ganglia and activate the cerebellar circuit to enhance motor control (Morris et al., 2001; Philippens et al., 2019).

Combs and colleagues were the first to evaluate the feasibility and safety of NCBT in PwPD in a case series published in 2011 and a randomized clinical trial in 2013 (Combs et al., 2013;

Combs et al., 2011). Both studies reported improvement in balance, gait and QoL. The authors concluded that NCBT (based on the RSB program) was feasible and safe for PwPD. However, the increased dropout rates and decreased adherence to the program observed in the randomized clinical trial suggest that NCBT may not suit all (Combs et al., 2013).

Following on from Comb's studies, further research has been carried out to assess the impact of NCBT in improving PD symptoms. The results show improvements in cognitive function, balance, gait performance, mobility, bradykinesia, depression, social life, and overall QoL (Hermanns et al., 2021; Larson et al., 2021; Moore et al., 2021; Shearin et al., 2021; Sonne et al., 2021). While these studies highlight the potential benefits of NCBT for PwPD, identifying the selective effect of NCBT is challenging, as most studies base their protocols on the RBS program, which, as mentioned above, includes a series of other exercises that can influence outcomes.

Work intervals and recovery time vary significantly, and exercise intensity is not always reported in the literature evaluating NCBT in PwPD. The duration of rounds (interval training) ranges from 30 seconds to four minutes, while the recovery time varies from 30 seconds to 2 minutes (Blacker et al., 2024; Brunet et al., 2021; Campo-Prieto et al., 2022; Dawson et al., 2020; Lowery et al., 2023; MacCosham B et al., 2019; Moore et al., 2021; Sangarapillai et al., 2021).

The level of exercise intensity is less clear. In a recent study, PwPD were instructed to perform NCBT at an RPE of 15/17 out of 20, representing vigorous intensity according to the ACSM classification of exercise intensity. However, the study did not report whether this intensity was achieved (Moore et al., 2021). Blacker et al. (2024), in a recent feasibility study, reported that PwPD (n=10) were able to box at intensity relative to 80-90% of their predicted HRmax and an RPE of 14-18 during the high-intensity block of the 15-week periodized program. However, this study had a small sample size, did not consider the presence of CI, and estimated %HRmax for training purposes instead of using individualised physiological markers (Blacker et al., 2024).

The level of intensity attained during NCBT varies with respect to the specifics of training such as type of exercise (e.g., boxing drills), duration of rounds, and recovery time (Laursen & Buchheit, 2019; Liguori et al., 2022). For example, in a study with nine experienced male amateur boxers, participants engaging in pad work attained 83.6% of HRmax, those on the boxing bag reached 86.9% of HRmax, and during sparring, it was 91.7% of HRmax (Arseneau et al., 2011). Although not measured in their study, Domingos et al. (2019) highlighted the importance of exercise intensity along with the volume of training to understand the mechanisms contributing to the effectiveness of NCBT in PwPD.

In a recent review, M. E. Morris et al. (2019) emphasized that not all activities incorporating NCBT in PwPD fall within a high-intensity training zone. The authors recommend providing more precise and detailed explanations of the components of NCBT interventions, to increase understanding of the efficacy of this activity for PwPD. The absence of information regarding the exercise intensity achieved during NCBT protocols raises, doubts about whether PwPD can attain high intensity during this activity. Chapter Four discusses these issues in greater depth.

Summary

PD is a complex, progressive neurodegenerative disorder characterized by a range of motor and non-motor symptoms that significantly affect the ability of PwPD to engage in physical exercise, including aerobic exercise training. As a key feature of autonomic dysfunction, the presence of CI is poorly understood with respect to its impact on HR responses during high intensity aerobic training protocols, including NCBT.

Recent literature highlights the efficacy of NCBT in ameliorating motor and non-motor symptoms in PwPD. However, identifying the selective effect of NCBT is challenging, because reports do not consistently provide detail of the training regime and whether participants attained the targeted exercise intensity. Teasing out the selective effect of high intensity training during NCBT is difficult because most protocols include a range of exercises that can also influence outcomes.

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3 Cardiopulmonary exercise testing

3.1 Prologue

As reported in the narrative review, CPET effectively measures change in VO_2peak in PwPD using submaximal physiological markers such as ventilatory thresholds. Although CPET provides a variety of physiological measures, this chapter provides insight into the measurement and interpretation of maximal and submaximal physiological measures, which were used as outcomes of choice in the studies outlined in Chapters Four and Five. An overview of normative values and their importance for daily activities and aerobic training is also presented.

3.2 CPET protocol

CPET is considered the gold standard method to evaluate an individual's aerobic capacity. The test is usually performed on the treadmill or stationary bike (**Figure 4**), by incrementally increasing exercise intensity to maximal effort in a controlled laboratory environment (Liguori et al., 2022; Wasserman, 2012). Although CPET performed on the treadmill activates more muscles and yields higher aerobic capacity in healthy cohorts, this may not be the case in PwPD, due to gait impairments and balance issues, potentially hindering the attainment of maximum effort during testing (Glaab & Taube, 2022; Katzel et al., 2011; Liguori et al., 2022). Stationary bike is therefore the predominant ergometer used during CPET to evaluate maximum aerobic capacity in PwPD (Alberts & Rosenfeldt, 2020; Khalil et al., 2022; Liguori et al., 2022; Thrue et al., 2023).

Figure 4 *Cardiopulmonary exercise test using a stationary bike*

CPET protocols are usually selected according to the clinician's expertise and the objective of the test. However, the ramp protocol is the most common method used to increase exercise intensity (Herdy et al., 2016; Neder et al., 2021). The ramp protocol applies a continuous incremental increase in workload (WR) approximately every 2-15 seconds. In contrast, during the step protocol, the WR is increased by a predetermined wattage for a set period of between 1-3 minutes (Glaab & Taube, 2022; Liguori et al., 2022; Wasserman, 2012). The ramp protocol has several benefits, such as a uniform continuous increase in workload increments which leads to a smoother exercise experience and hemodynamic and physiological responses. The ramp protocol also provides more accurate estimations of exercise capacity and ventilatory threshold (Glaab & Taube, 2022; Liguori et al., 2022).

Ramp protocols typically involve an initial resting phase lasting 2-3 minutes, followed by unloaded cycling (no or low resistance) for 2-3 minutes, then an incremental exercise phase (lasting approximately 8-12 minutes), and a recovery phase of 3-5 min. The cycling cadence during unloaded cycling and exercise phases, typically ranges from 55 to 70 revolutions per minute. The workload increment during the exercise phase is adjusted based on the individual's predicted fitness level based on equations or clinician expertise, but ramp slopes of 15, 20, or 25 watts per minute are frequently used for healthy and active adults. The appropriate selection of the incremental workload is important because the target time during the ramp phase of the CPET should be between 8-12 minutes. An incremental workload that is too high for an individual during the ramp phase, can result in hyperventilation, difficulty determining ventilatory thresholds, and premature test termination (Glaab & Taube, 2022; Herdy et al., 2016; Levett et al., 2018; Liguori et al., 2022; Wasserman, 2012). The increments in workload during CPET protocols using stationary bike vary from 3 to 40 watts in PwPD (Table 5).

Termination of CPET tests is usually based on the following criteria: 1) the individual can no longer maintain a cadence of 60 RPM; 2) experiences an adverse reaction (such as chest pain, dizziness, and shortness of breath); 3) requests to stop; 4) or if the researchers feel the test is unsafe to continue based on the participant’s ECG and BP responses. These signs and symptoms include significant ST depression and elevation changes; significant arrhythmias causing symptoms; fall in systolic blood pressure (>20mmHg); hypertension (>250 mm Hg systolic; >115 mm Hg diastolic and severe desaturation (SpO2 <80%); loss of coordination; mental confusion; dizziness or faintness (Liguori et al., 2022; Weisman et al., 2012).

3.3 Peak and maximum oxygen consumption

Maximum aerobic capacity is represented by peak or maximal oxygen consumption (VO_2peak/max), which is the interaction of cardiac output (the product of HR frequency and

stroke volume), arterial oxygen content, and muscle oxygen diffusing capacity (F. N. Daussin et al., 2007; Kinnear & Blakely, 2013; Wasserman, 2012). Although VO_2peak and VO_2max are used interchangeably throughout literature, they do not represent the same physiological response. VO_2peak is the 'highest' (peak) value attained during CPET, whilst VO_2max is the maximum physiological value achieved and maintained, even if the workload continues to increase - a physiological response known as a plateau (Beltz et al., 2016; Midgley et al., 2007; Older, 2013). For consistency, the term VO_2peak will be used instead of VO_2 max, as the latter is often difficult to achieve in clinical populations (Green & Askew, 2018; Liguori et al., 2022; Wasserman, 2012).

VO_2peak is established by assessing several physiological parameters indicating maximal or quasi-maximal effort that may vary according to the population performing the test (Glaab & Taube, 2022; Laveneziana et al., 2021; Wagner et al., 2020). However, it is generally accepted that a respiratory exchange ratio (RER) of ≥1.10, an RPE above 18, and attainment of 95% of predicted HRmax at the end of the CPET, are indicative of maximum effort for adults without cardiorespiratory conditions (Boutou et al., 2020; Franssen et al., 2022; Herdy et al., 2016; Liguori et al., 2022; Robergs et al., 2010; Wasserman, 2012). RER represents the ratio between the volume of carbon dioxide production (VCO_2) and the volume of oxygen consumed (VO_2), and it is currently the best non-invasive indicator of maximal effort (Wasserman, 2012). For a valid assessment of VO_2peak, it has been suggested that data should be filtered using a 20 to 30 second moving time interval average. However, this can differ depending on protocols and clinician preference (Franssen et al., 2022; Herdy et al., 2016; Robergs et al., 2010). **Figure 5** shows a plot graph of VO_2 in Liters per minute (L/min) over time for determination of VO_2peak in one participant. Data points are plotted using the 20 second moving time interval average approach used in the studies in this thesis. According to a recent systematic review, studies evaluating VO_2peak in PwPD lack consistency in the measurement and reporting of maximum effort, leading to inadequate data reporting (Thrue et al., 2023). **Table 5** shows the mean RER recorded at the conclusion of CPET performed in PwPD.

Figure 5 *Determination of VO_2peak 20 seconds moving time interval average*

The first 3 minutes of the protocol represent the resting time (pink). The following 3 minutes represent the warm-up stage using 20 watts of resistance (yellow). The green represents the loaded stage with 15 watts incremental resistance per minute. The last 5 minutes (blue) represent the recovery phase using 20 watts of resistance. The purple bar demonstrates VO_2peak.

While there is some evidence to suggest a decrease in VO_2peak amongst PwPD compared with age-matched controls (Kanegusuku et al., 2016; Mavrommati et al., 2017; Penko et al., 2021), a recent systematic review of randomized control trials and cross sectional studies, reported comparable values (Thrue et al., 2023). The earlier studies tended to recruit PD participants who were sedentary or had low levels of physical activity, which may account for some of the difference. An important aspect of this body of work is that CI was not measured, and participants were not stratified accordingly.

Griffith et al. (2024) first examined VO_2peak in a subset of PwPD with CI. The authors found a significantly lower VO_2peak in PwPD classified as having CI than those without CI. However, the ability to generalise from the results is limited, due to the targeted inclusion criteria and lack of a control group. PD participants were early onset (< 5 years since diagnosis), dopa-naïve, and practised a maximum of three days of moderate-intensity exercise. The authors did not report physiological measures attained at the first and second ventilatory thresholds limiting interpretation. Table 5 shows VO_2peak values from recent cross-sectional studies in PwPD.

3.4 Submaximal physiological markers

In addition to the VO_2peak, CPET provides key submaximal physiological markers denoting the first and the second ventilatory thresholds (VT1 and VT2), in which physiological homeostasis is interrupted. A change in source of energy production from predominantly aerobic to anaerobic metabolism occurs at VT1 (McArdle, 2015; Wasserman, 2012), whilst a disproportionate increase in respiratory frequency at VT2, is most likely due to metabolic acidosis from exercise demand (Nicolo et al., 2020). The most reliable methods for determining VT1 involve the V-slope method and identification of hyperventilation relative to VO_2 or VCO_2 using the ventilatory equivalent methods. VT1 can also be confirmed by observing a significant increase in the partial end-tidal oxygen tension ($PETO_2$) without substantial change in partial end-tidal carbon dioxide tension ($PETCO_2$) (Figure 6). The determination of VT2 (Figure 7), involves the observation of a sharp increase in minute ventilation (VE) in relation to VCO_2 production due to metabolic acidosis, and a significant increase in the ventilatory equivalent for CO_2 (VE/VCO_2). The verification of VT2 occurs when a significant decrease in $PETCO_2$ is observed in the $PETO_2$ and $PETCO_2$ plot (Binder et al., 2008; Cannon et al., 2009; Franssen et al., 2022; Glaab & Taube, 2022; Herdy et al., 2016; Wasserman, 2012).

Figure 6 *Determination of the first ventilatory threshold*

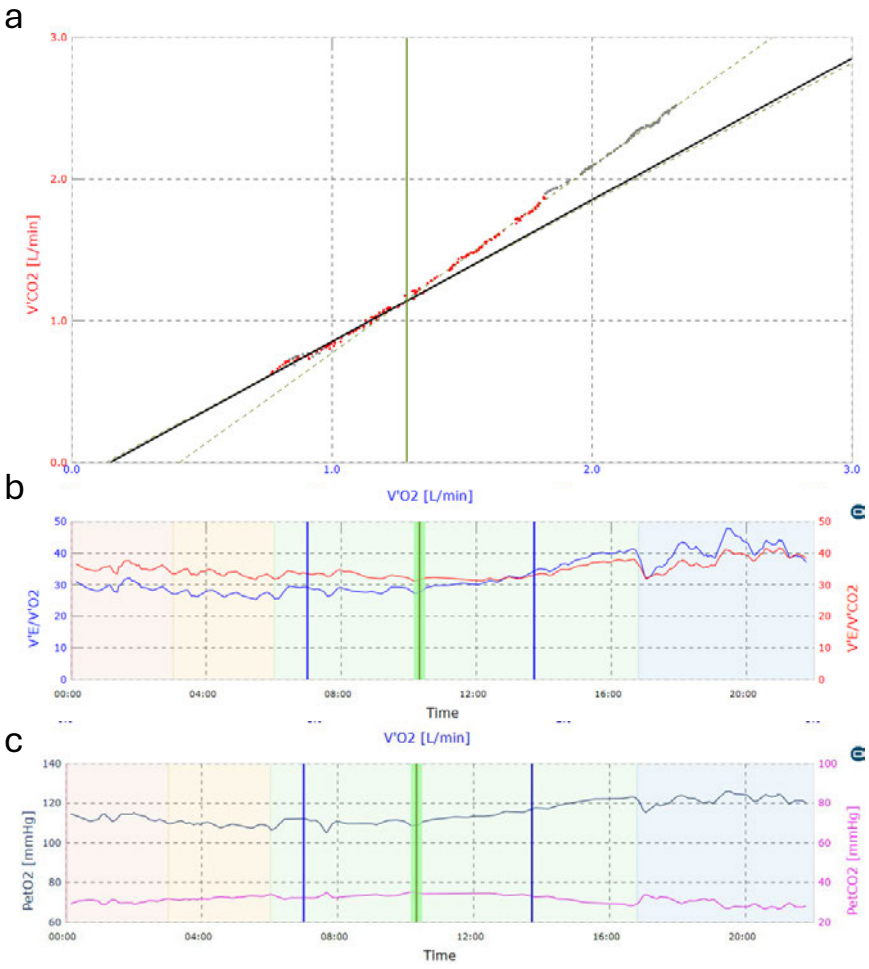
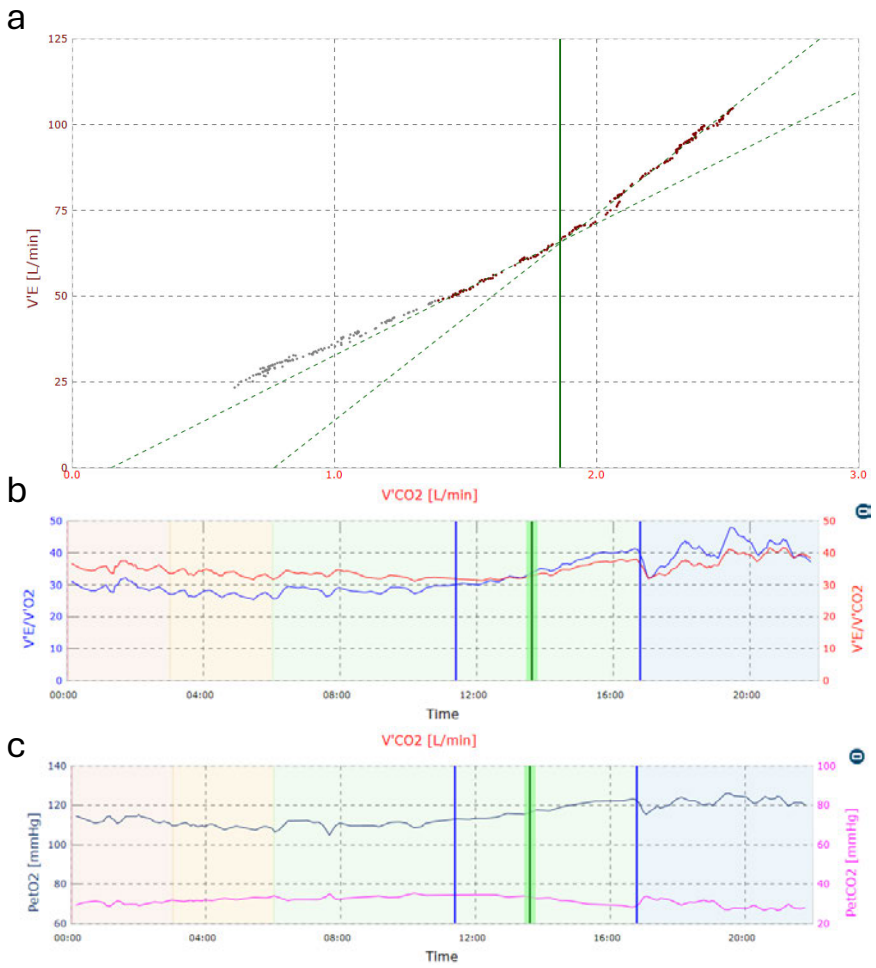


Figure 6A highlights the intersection where carbon dioxide production (VCO_2) significantly increases compared to oxygen consumption (VO_2) based on the V-slope method. In Figure 6B, the green line marks where the ratio of ventilatory equivalent for oxygen (VE/VO_2) increases and stays elevated, while the ventilatory equivalent for carbon dioxide (VE/VCO_2) remains constant or decreases. In Figure 6C, the green line signifies the point where partial end-tidal oxygen tension ($PETO_2$) rises without a significant change in partial end-tidal carbon dioxide tension ($PETCO_2$), confirming the first ventilatory threshold (VT1).

According to Penko et al. (2021), VT1 is a valuable indicator of individuals' aerobic capacity at submaximal levels for PwPD. Improving this physiological marker can significantly increase energy efficiency during daily activities. VT1 is expected to range between 40% and 65% VO_2peak in healthy adults, and it refers to the highest level of physical exertion during exercise that can be sustained for a prolonged period without a continuous increase in blood lactate levels and subsequent hyperventilation. It is influenced by genetic factors, diseases, and training methods (Herdy et al., 2016; Liguori et al., 2022; Wasserman, 2012). Daily activities generally tend to induce intensities that are lower than VT1. However, these activities may represent intensities above VT1 in individuals with poor fitness levels.

Figure 7 *Determination of the second ventilatory threshold*



The green line in Figure 7A shows a deviation in the linear VE-VCO2 relationship, where there is a disproportional increase in minute ventilation (VE) in relation to carbon dioxide production (VCO_2). The green line in Figure 7B shows where the VE/VCO2 ratio (red line) increases and does not return to baseline values (ventilatory equivalents method). To confirm the second ventilatory threshold (VT2), PETCO2 should decrease after a period of flattening or increasing (Green line in Figure 7C).

Kanegusuku et al. (2016) reported that sedentary PwPD (n=48, age 67, H&Y II-III) reached VT1 at approximately 60% of their VO_2peak, which was similar to the healthy controls (n=20, age 65) who achieved VT1 at 56% of their VO_2peak. In this study, VT2 was also similar between PwPD and healthy controls, achieved at approximately 82% and 83% of their VO_2peak. Penko et al. (2021) reported similar results in sedentary PwPD (n=90, age 63, H&Y II-III), where VO_2 at VT1 represented approximately 62% of their VO_2peak. VT2 was not reported in this study. VT1 and VT2 are critical for aerobic exercise training, including HIIT protocols, as these markers represent physiological thresholds where there is a perturbation in homeostasis (Jamnick et al., 2020). The importance of VT1 and VT2 for setting exercise intensity, is further discussed in Chapters Four and Five. Recent literature indicates that aerobic interventions using individualized threshold-based training led to a greater percentage of participants improving aerobic capacity compared to traditional training methods (Lehtonen et al., 2022; Weatherwax et al., 2019; Wolpern et al., 2015).

Individuals with limited aerobic capacity or impaired gait, face significant challenges in performing daily activities such as walking (Blokland et al., 2023). Katzel et al. (2012) found that when asked to walk at a self-selected pace, oxygen consumption in PwPD (H&Y I-III) was 51% higher than the expected values for non-PD. Not surprisingly, people with more advanced disease experienced higher oxygen consumption, indicating poor economy of gait. Oxygen consumption was highly variable amongst the 79 participants, ranging from 31% to 89% of their VO_2peak (Katzel et al., 2012). Shulman et al. (2013) reported that oxygen consumption in PwPD was on average 64% of their VO_2peak when walking at comfortable pace. This result is comparable to older adults walking at their self-selected pace, accounting for approximately 67% of their VO_2peak (Wert et al., 2013).

3.5 Heart rate response during CPET

During the incremental test (CPET), HR rises gradually in a linear relationship with WR. However, it may vary influenced by factors such as age, fitness level, gender, and clinical conditions (Cooper et al., 2014; Yoshida et al., 2017). Until VT1, the increase in HR occurs mainly due to PNS withdrawal, while after this point, the increase reflects more excellent SNS activity (Perini & Veicsteinas, 2003; Yamamoto et al., 1991). During the first recovery minute, a decrease in HR is attributed mainly to the reactivation of PNS, while a further decrease in HR is associated with the withdrawal of SNS activity (Perini & Veicsteinas, 2003; Villelabeitia-Jaureguizar et al., 2017).

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6 Integrated Discussion and Conclusion

6.1 Prologue

This thesis set out to answer questions chiefly concerning the effect of exercise intensity during aerobic protocols, particularly NCBT, in PwPD. They arose initially from the author's own clinical and personal experiences of working with PwPD who attended non-contact boxing classes at community-based gyms in NZ. As with many PhD programmes of study, the initial questions evolved to become both larger in scope and granular in nature, and more complex to comprehend. Although the role of autonomic dysfunction, particularly CI, had not initially been a dominant line of inquiry, it came into focus after the narrative review highlighting the lack of awareness of this feature in the PD literature evaluating VO_2peak and changes in aerobic capacity after exercise protocols in PwPD despite its high prevalence in this population.

A second feature of this PhD was the effect of COVID-19 on the programme of study, as outlined on Page 21 (Structure of the thesis). Although the feasibility study could not go ahead as planned, data obtained from the exploratory studies presented in Chapters Four and Five offer valuable insights for clinicians and researchers passionate about aerobic exercise as a tool to alleviate PD-related symptoms and for enhancing general fitness and overall well-being.

This final chapter provides a comprehensive overview of the thesis, integrating the findings from the studies and offering recommendations for future research and clinical practice.

6.2 Overview of the thesis

Exercise intensity is crucial for enhancing aerobic capacity (VO_2peak) and has been a central focus in recent PD literature evaluating the effect of aerobic exercise protocols (in particular moderate and high intensity protocols) on symptom management. NCBT is a popular example of high intensity exercise. However, an assumption underpinning this practice is that PwPD actually attain the threshold for high-intensity exercise which they then maintain, as healthy adults do. Given the complexity of PD and knowledge of the effect of autonomic disturbance on performance, this assumption motivated the ideas for this thesis.

The first step of this journey, was the narrative review which appraised exercise intensity as a key component of aerobic training with respect to aerobic capacity, functional performance, and motor symptoms in PD. The findings indicate that vigorous to high-intensity aerobic regimes, may result in a notable enhancement in VO_2peak compared to moderate-intensity protocols, highlighting the significance of exercise intensity for improvement in aerobic capacity. However, they also revealed that the influence of exercise intensity in improving function and motor symptoms, is less clear.

Further critical learning from the review was the role of exercise intensity as the pre-eminent training variable compared with other variables (training duration, modality), if improvement in aerobic capacity is not the study's primary outcome or the session's objective in clinical practice. The focus on exercise intensity stems from its potential neuroprotective effect, often overshadowing other training variables (Panassollo et al., 2024). The role of high intensity exercise as a neuroprotective agent is briefly discussed on Page 65, but a question of growing importance. The mechanisms that underpin improvement in PD symptoms following intense aerobic exercise are under scrutiny. Crotty and Schwarzschild (2020) concluded that despite some progress in understanding the effects of exercise in PwPD, there are still many unresolved questions, such as whether exercise provides long-term benefits by protecting the nervous system and altering the course of the disease itself, or if its benefits are merely temporary and limited to symptom relief that may disappear once exercise is stopped. This statement reiterates the training principle of reversibility, which underscores that fitness levels may revert to their initial state when exercise ceases (Bouca-Machado et al., 2020).

Another important point highlighted in the review, is the lack of clarity around specific goals of training protocols and the need to target protocols more effectively to improve outcomes in PwPD. Ellis and Rochester (2018) reported that physical exercise protocols in the PD literature, including aerobic training, often adopt a "one size fits all" strategy, disregarding individual differences and hindering the understanding of optimal interventions. To enhance and optimize the effectiveness of exercise for PwPD, Bouca-Machado et al. (2020) suggest that future studies should prescribe exercises based on sports science principles. *Section 1.9.2* - Aerobic Exercises Principles of Training highlights some of these principles in this document. It is recommended that physical exercises, including aerobic training protocols, target the activity according to individuals ‘needs, which can change as the disease progresses (Alberts & Rosenfeldt, 2020; Liguori et al., 2022; Port et al., 2021). Another important aspect of future research is to explore the effect of other training variables, such as training duration and exercise modality, on PwPD.

Notably, the review shows that there is an emphasis on the importance of exercise until PwPD reach stage H&Y III, after which gait and balance challenges may seem insurmountable. This in turn leads to the view that research examining the effect of aerobic exercise for people with advanced disease lacks value. This view also underscores the prevalent focus in PD literature on the potential neuroprotective effects of physical exercise, with less attention given to the broader physical and well-being benefits associated with maintaining an active lifestyle. Community boxing classes for PD frequently accommodate individuals in wheelchairs, demonstrating the willingness of PwPD to engage in exercise even as the disease progresses. However, further research is essential to guide clinicians and exercise physiologists working with this population regarding the impact of aerobic exercise in cases of limited mobility or severe balance impairment.

While the optimal exercise program (or programmes) and intensity for alleviating symptoms in PD still need to be determined (Alvarez-Bueno et al., 2021; Li et al., 2023), clinicians must consider the broader benefits of physical exercises. PD is an age-related disorder, and decline in aerobic capacity is a natural aspect of ageing. The current view expressed in the literature is that exercise professionals working with PwPD are best to integrate aerobic training as an essential component of exercise regimes to enhance VO_2peak, given the associated overall health benefits of aerobic exercise (Kunutsor et al., 2017; Liguori et al., 2022; Loe et al., 2014; Stathokostas et al., 2004).

Another important insight derived from the narrative review, is the overlooked aspect of CI in the PD literature assessing changes in VO_2peak after aerobic training protocols and that exercise intensity is programmed according to general guidelines rather than physiological measures obtained at the first and second ventilatory thresholds (VT1 and VT2). Although the use of general guidelines enables clinicians and researchers to replicate protocols, there is a lack of awareness regarding the importance of more accurate measurements of exercise intensity and the potential implications of setting exercise intensity based on predicted equations, to adhere to general guidelines. Consequently, there is a risk of exercising beyond the desired training zone or of PwPD exerting themselves excessively in pursuit of the potential benefits associated with vigorous to high-intensity training often promoted for this population (Liguori et al., 2022; Schenkman et al., 2017). The exploratory studies presented in Chapters Four and Five further expanded this feature of PD, contributing to a better understanding of CI in aerobic exercise programming.

The aim of the first exploratory study, was to examine HR and metabolic responses during CPET in PwPD with and without CI in order to understand its effect on key physiological markers and thereby enhance precision in setting exercise intensity parameters for aerobic exercise in this population. This aim was set to answer the following questions:

1. *Are there significant differences in HR and metabolic responses between PwPD with and without CI during progressive incremental exercise to maximal effort?*
2. *Is there a significant difference in aerobic capacity in PwPD with and without CI?*

The key findings of this exploratory study reveal that PwPD with CI exhibit blunted heart rate (HR) responses, particularly noticeable during high (VT2) and maximal intensity exercise but not at rest or during moderate intensity (VT1) exercise. Reduced HR may have contributed to the lower observed VO_2peak in this subgroup. Recent research by Griffith et al. (2024) shone some light on this issue by conducting a retrospective analysis of 128 PwPD involved in phase two of the Study in Parkinson's Disease of Exercise (SPARX) (Schenkman et al., 2017).

The authors highlighted a significant decrease in VO_2peak amongst PwPD with CI,

although their study reported a lower incidence of CI among participants (10%) compared to ours (46%) which is more comparable with earlier prevalence estimates (Penko et al., 2021). Notably, participants in the study by Griffith et al. (2024), had a median disease duration of 1.5 years, compared with a duration of around six years in our study: This prompts the question: Is CI a marker of disease progression? Research to date has not examined this fully. Prognostic studies on different PD cohorts are required to measure the onset of CI and the effect it has on symptomatology, progression, and mortality.

The SPARX study was designed to compare the effects of high-intensity continuous training (at 80-85% of maximum heart rate), with moderate-intensity continuous training (at 60-65% of maximum heart rate) conducted twice a week over 12 months on a treadmill. SPARX is currently in its Phase 3, aiming to recruit 370 participants (Patterson et al., 2022). The main objective of this ongoing study is to compare changes in UPDRS after 12 and 18 months of the exercise program in PwPD who are dopa-naïve at the outset of the study and aim to remain so over its duration. This longitudinal study will provide insights into the benefits of aerobic training in PwPD. However, it would be interesting to stratify participants according to the presence of CI to evaluate any potential effect of this feature on the study's secondary outcome – changes in VO_2peak.

In summary, research concerning the question of CI and its impact on aerobic performance is limited. Further work is required on a large sample to inform prevalence rates and to examine its effect on aerobic performance.

Physiological measures obtained from CPET in this study, served to identify individualised training zones for the next study presented in Chapter Five, which posed the following questions:

1. *Can PwPD reach high-intensity training zones during NCBT that incorporate only boxing related drills?*
2. *Are there significant differences in HR and metabolic responses between PwPD with and without CI during NCBT?*

The key findings from the second exploratory study, demonstrate that NCBT is a high-intensity exercise for PwPD with and without CI, based on individual physiological profiles and clinical measures rather than predicted equations. Despite lower HR and metabolic responses during rounds, RPE was similar amongst participants. RPE was also similar at peak exercise during CPET.

Although accurate identification of CI requires costly equipment (CPET) to ascertain maximal effort through physiological measurements, there is an alternative for clinical settings. The combination of RPE and HR monitoring can help estimate whether blunted HR responses occur

in PwPD. These are affordable tools for clinicians and exercise physiologists and allow the measurement of training intensity more accurately than predictive equations. This aids in tailoring aerobic exercise programs, including HIIT, for PwPD.

Despite the popularity of NCBT and the importance of exercise intensity, this type of training is not included in general exercise guidelines for PwPD (Panassollo et al., 2024). This may reflect the limited body of research examining the effect of HIIT protocols, where the exercise intensity remains within the high-intensity zones. Future studies may aim to investigate whether a more complex type of HIIT such as NCBT, has different effect on PD symptomatology than less complex HIIT type of training, such as that achieved using a stationary bike. To improve accuracy, training zones should be based on threshold zones rather than general guidelines. CI need to be accounted as a potential contributor to exercise intolerance in this population. Moreover, it is unknown whether CI is associated with the presence of other non-motor symptoms. Moreover, aerobic training has been show to improve chronotropic responsiveness in cardiac patients (Pimenta & Rocha, 2021; Zweerink et al., 2018), but the effect of aerobic training in CI in PwPD remains unknown.

6.3 Limitation of the thesis

The respective chapters have already discussed the limitations of each study. However, it is important to recognise that results from this thesis are exploratory, and despite studies being powered for the primary outcome (HRmax), the sample size was relatively small. This PhD study focused on the measurement of exercise intensity and attainment of high-intensity zones, which was previously described as critical for enhancing aerobic capacity. However, boxing is more than '*exercise intensity'*, and the focus of this activity cannot be limited to this or any other training variable. In addition to other features of boxing, such as a change in direction challenging balance, and involvement of complex combinations challenging cognition, NCBT sessions have an important social aspect, as stated by PD participants from Humphrey et al. (2020) who reported ‘At boxing everybody will give each other high fives and say good job-you couldn't do that before and now you can do it’ and ‘I feel like I'm in better shape mentally and physically than I was when I was diagnosed’. While the studies discussed in this thesis have provided valuable insights into exercise intensity during NCBT in PwPD, as noted earlier it is vital to recognize the multi-faceted nature of boxing. The varied components of the practice itself yields benefits well beyond those gained from high intensity exercise alone. Although this training variable is critical for aerobic exercise programming, its application must reflect the training goals both for clinical practice and research.

6.4 Conclusion

The findings of this thesis inform about exercise intensity and continuous and interval training aerobic protocols for PwPD. The narrative review concluded that exercise intensity positively impacts aerobic performance, but its effect on motor symptoms and function remains to be determined. Overemphasizing exercise intensity may undervalue the roles of volume and exercise modality.

The prevalence of CI was high in the exploratory study, affecting HR response at vigorous and peak exercise but not at moderate intensity. This is a new finding in a prospective cohort, albeit exploratory, that helps to inform the field. Reduced HR may be one of the primary factors influencing VO_2peak in this subgroup of PwPD. This thesis demonstrated that PwPD with and without CI, can exercise at high intensity during NCBT and sustain this intensity for a significant amount of time. HR response was also lower in PwPD with CI during NCBT sessions. Despite reduced HR during CPET and boxing, RPE was similar amongst participants during both activities, indicating that RPE and HR monitoring can better measure exercise intensity for PwPD compared with estimated HRmax.

Findings from these studies have paved the way for future research and have informed clinical practice. Areas to focus on include the impact of training variables other than intensity on relieving PD symptoms, and whether aerobic training, continuous or HIIT, is effective in improving chronotropic response in PwPD. Studies may also aim to investigate whether aerobic interventions based on individualized measures of exercise intensity (threshold zones) yield a greater improvement in aerobic capacity in PwPD compared to general guidelines.

Finally, working with PwPD in research and clinical practice has unveiled their extraordinary dedication amidst the challenges of their condition. Their unwavering commitment to research and engagement showcases their resilience, making them an exceptional and inspiring group to work with.

7 Chapter Addendum

Muscle strength, power, and functional performance in PD

7.1 Introduction

Recent studies, including systematic and meta-analysis reviews suggest that muscle strength and power are reduced in PwPD compared to age-matched healthy controls, adversely affecting their quality of life, functional performance, and increasing the risk of falling (Allen et al., 2010; Bavaresco Gambassi et al., 2019; Borde et al., 2015; Delmonico et al., 2009; Gamborg et al., 2023; Lambert et al., 2004; Ni et al., 2016; Ponsoni et al., 2023; Renee et al., 2021; Trombetti et al., 2016). Motor and non-motor symptoms contribute to inactivity in PwPD, which can lead to an accentuated decrease in muscle strength and aerobic capacity in this population (Afshari et al., 2017; Gorzkowska et al., 2020; Lord et al., 2013; Pechstein et al., 2020; Pescatello et al., 2014; Pradhan & Kelly, 2019).

Results from our studies (Chapters 4 and 5) showed that PDCI had reduced VO2peak and blunted HR responses during CPET and NCBT. This then raised the question during the examination of whether muscle strength and power are reduced in PwPD with CI compared to those without CI, and whether these measures serve as a simple proxy measure to identify the presence of CI in PwPD. To explore this, we tested muscle strength, power, and functional performance to investigate whether these measures differ between PDCI and PD non-CI.

7.2 Methods

Participants inclusion and exclusion criteria, and ethical approval are all described in Chapters 4 and 5. Participants underwent a CPET at least two days prior to strength and power testing to assess for the presence of CI. The CPET procedure and the determination of CI are also described in Chapters 4 and 5.

7.2.1 Muscle strength and power

7.2.1.1 Equipment

Upper body muscle strength and power using a bench press on a modified Smith-machine, while a modified horizontal leg-press machine was used to test muscle strength and power of lower limbs. Force was measured using a 7.5 x 7.5 cm and a 46 x 51 cm force plate (Advanced Mechanical Technology Inc., 179 Waltham Street, Watertown, MA 02172, USA) for bench and leg press respectively. Each force plate was calibrated to a known force (98.1 N) prior to testing. To measure force during the bench press, the force plate was positioned between two bars. Initially, the force plate was attached to a small bar, which was then connected to the barbell of

the Smith-machine. For the leg press, the force plate was attached to the footplate of the horizontal leg press machine.

A linear transducer (P-80A, Unimeasure, Oregon) measured bar displacement during the bench press exercise and displacement of the sliding frame of the horizontal leg press. For the bench press, the linear transducer was secured with one end fixed to the Smith-machine bar and the other end anchored to the ground. The linear transducer used for the horizontal leg press was attached to the footplate and the other end attached to the sliding frame. The linear transducer was calibrated to a known distance (0.3 m) prior to testing.

Signals from the force plate and the linear transducer were collected at a sampling frequency of 1000 Hz, amplified and filtered with a 10.5 Hz low pass cut-off Butterworth filter (Stavric & McNair, 2012) via computer-based data collection and analysis software (NI LabView software 2021-National Instruments). Bar and sliding frame velocity was calculated by differentiating displacement with respect to time (Δ displacement/Δ time). Power was calculated as the product of instantaneous force and velocity.

Both tests were performed with the participant in a supine position. For the bench press, the participants' feet were positioned flat on the bench. Shoulders were in a neutral position and abducted to 45 degrees with the elbows at 90 degrees of flexion. For the leg press, lower limbs were tested unilaterally, with hip and knee joints at 90 degrees of flexion. During lower limb testing, the untested limb was held secure via a supporting strap. Upper and lower limb muscle strength and power testing were performed in different days separated by at least 48 hrs.

7.2.1.2 One-repetition maximum test (1RM)

Participants warmed up on a stationary bike for five-minutes, set at a resistance of 40-60 watts at 60-70 revolutions per minute. The 1RM test started with a specific warmup consisting of10 repetitions at 40-60% of the participant's perceived maximum resistance. After a one-minute rest, participants performed three repetitions at 60-80%. Then, depending on the effort perceived by the participant and the observed effort, the load was increased by 5-15% until participants could perform a single repetition through a full range motion but were unable to complete two repetitions. Participants were given three minutes of rest between each attempt (Battista et al., 2018; Liguori et al., 2022; Stavric & McNair, 2012).

7.2.1.3 Muscle power assessment

Participants were positioned on the bench press or leg press machine as previously described and tested at 30%, 50%, and 70% of their 1RM (Stavric & McNair, 2012). Participants were instructed to perform the movement "as fast as possible," while imagining throwing the barbell (bench press) or jumping (leg press) as high as they could. Performing these movements on the

Smith and horizontal leg-press machine allowed participants to lose contact with the barbell and footplate during the throwing (bench press) and jumping (leg press) phases, respectively (Ferley & Vukovich, 2019; Vingren et al., 2011). After each trial, participants had a rest period of 1 minute. Three repetitions were completed at each load, and a rest of up to 3 minutes was provided when the loads were changed. The testing order for the three different loads was randomized prior to testing.

7.2.2 Functional performance tests

7.2.2.1 Seated medicine ball throw (SMBT)

Participants were asked to sit in an armless chair, leaning against the wall for safety, with their hip and knee joints flexed at approximately 90°. Different arm lengths were adjusted by measuring the start position, with participants extending their arms while holding a 3 kg medicine ball away from the chest and dropping it onto the floor. This point was established as a zero mark (Harris et al., 2011). From this point, a 5-meter tape measure was placed. Participants were requested to throw the 3 kg medicine ball “as far as they can”, performing a movement like the basketball chest pass. Participants had two familiarization trials before completing three attempts, with a one-minute rest period between each attempt. The highest score from these attempts was selected for analysis. The SMBT is a common clinical test used to assess upper limb power in older adults and has shown excellent test-retest reliability in older adults, with an ICC value of 0.96 (Harris et al., 2011).

7.2.2.2 Five times sit-to-stand (5STS)

Participants sat back against an armless chair (leaning against the wall for safety) with arms folded across their chest, and with their hip and knee joint angles at approximately 90°. Participants were asked to rise from the chair as fast as they could five times, to reach full hip extension in standing, and to then sit back down (start position) while keeping their feet flat on the floor during each repetition (Petersen et al., 2017). Time started when the researcher said "go" and stopped when participants' buttocks reached the chair's seat after the fifth stand. The 5STS is a clinical measure of lower limb strength and power in older populations and has been shown to have good to excellent interrater and test-retest reliability in PwPD, with an ICC value of 0.96 and 0.76 respectively (Duncan et al., 2011).

7.2.2.3 Six-minute walking test (6MWT)

Participants were instructed to walk at a self-comfortable pace (without running) for six minutes along a 30-meter corridor. They were allowed to stop and restart walking as needed during the 6MWT (Crapo et al., 2002). The maximum distance covered in that time was recorded. The 6MWT has shown excellent test-retest reliability in PwPD, with an ICC value of 0.96 (Steffen & Seney, 2008).

7.2.2.4 Data analysis

For demographic and clinical data, between-group differences (PD with (PDCI) and without CI (PD non-CI), and controls) were examined using analysis of variance (ANOVA) and post hoc tests (Tukey's HSD). For clinical data, between-group differences (PDCI and PD non-CI), time living with PD, levodopa equivalent (medication), and MDS-UPDRS were examined using t-tests, assuming equal variances and independent observations. These assumptions were examined using QQ, box plots, and histograms.

Mixed linear regression was used to investigate the effects of group (PD, PDCI, PD no-CI) and exercise level (30%, 50% and 70% RM) on outcomes (peak velocity, force, and power) while accounting for potential covariates and inter-individual variability. The fixed effect models included Group, level, and their interaction (Group*level) for the bench press, and Group, level, leg (right and left) and their interaction (Group*level*leg) for the leg press. Age, gender, MDS-UPDRS, and VO_2 peak were included as covariates. BMI was included as a covariate for peak velocity but was not included as a covariate for strength and power measures because peak force and power were normalized to body mass (kg) to improve data accuracy (Abdalla et al., 2021). ANOVA was conducted to assess the significance of independent variables in regression models. Pairwise comparisons between different levels of the 'Group' factor were also conducted. For functional tests (6MWT, 5STS, and SMBT), linear regression was used to assess the effects of group (PD, PDCI, PD no-CI) on performance, adjusting for covariates including Age, BMI, MDS-UPDRS, and VO_2peak. Pairwise comparisons of adjusted group means were performed to identify significant differences. Estimated means are reported with standard errors (SE) and 95% confidence intervals (CI). The level of significance was set at $p \leq 0.05$. Data analysis was performed on R-environment for statistical computing (Bates et al., 2015). Parametric statistics were used, despite being underpowered to detect a significant between-group difference, should one exist (see below). This decision was based on preliminary analysis which showed the data for each of the three groups were normal distributed for key outcomes.

The sample size was calculated using t-tests (GPower 3.1.9.7) with a significance level of 0.05 and a power of 80%. Based on knee extension muscle force (Renee et al., 2021) and knee extension muscle power (Lima et al., 2016), 23 participants per group were required to reveal group differences for muscle force and power as primary outcomes. Given an estimated prevalence of CI in PwPD of approximately 50%, a minimum total of 46 participants with PD was necessary to ensure adequate representation. However, due to COVID-19, budget, and time constraints, the required sample size of 46 individuals with PD could not be achieved.

7.2.3 Results

Twenty-four participants with mild to moderate PD (H&Y I-III) and seventeen healthy controls were included, with the demographic and clinical data presented in Table 1A. CI was identified in 11 (43%) PD participants who were included in the PDCI group. All other participants were included in the PD non-CI (n 13) or control group (n 17). No significant difference was observed in age, height, or weight among participants ($p \geq 0.05$). PDCI had a significantly higher BMI compared to PD non-CI ($p = 0.03$) but not controls ($p \geq 0.05$). For specific PD clinical outcomes, MDS-UPDRS part III was significantly higher in PDCI than PD non-CI ($p = 0.02$). However, no difference was observed between the years of living with PD and the levodopa dose equivalent ($p \geq 0.05$).

Table 1 Demographic and clinical data

	PDCI (n = 11)	**PD non-CI (n = 13)**	**Control (n = 17)**
Age; years	64 ±6.34 [55,72]	63 ±5.85 [52,70]	62 ±6.27 [52,70]
Height; cm	173 ±7.59 [162,188]	170 ±9.21 [153,185]	170 ±6.08 [157,179.5]
Weight; Kg	81 ±13.27 [54,97]	69 ±13.09 [47,95]	73 ±12.08 [58,96]
BMI; kg/m2	27 ±4.09 [20,32] †	24 ±3.23 [19,29]	25 ±2.81 [21,30]
MDS-UPDRS (part III)	34 ±7.38 [24,48] †	27 ±8.51 [11,39]	n/a
Years living with PD	5.8 ±3.98 [1.67,12.28]	6 ±4.21 [0.72,15.90]	n/a
Levodopa dose equivalent; mg/day	574 ±444 [225,1575]	579 ±397.03 [0, 1200]	n/a

*Data is presented in mean± SD [min, max] values. BMI: Body Max Index; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale. * p≤ 0.05 VS control † p≤ 0.05 VS PD non-CI*

7.2.3.1 Peak velocity

During bench press (Figure 1A), peak velocity was not significantly different between groups at 30%, 50%, and 70% of participants' 1RM ($p \geq 0.05$). During leg press (Figure 1B), peak velocity was not significantly different between groups ($p \geq 0.05$) or between the right and left legs within each group at 30%, 50%, and 70% 1RM ($p \geq 0.05$). In both exercises (bench press and leg press), peak velocity decreased significantly across 30%, 50%, and 70% 1RM ($p \leq 0.001$).

Figure 1A Peak velocity during bench press at 30%, 50%, and 70% of 1RM

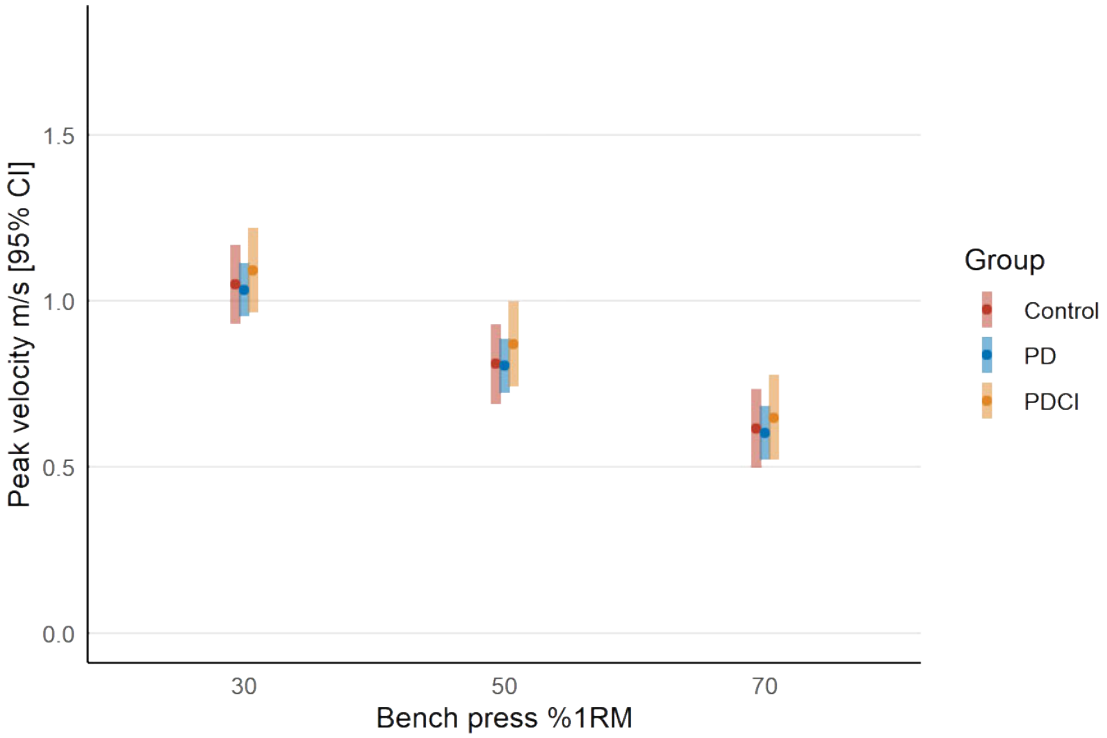
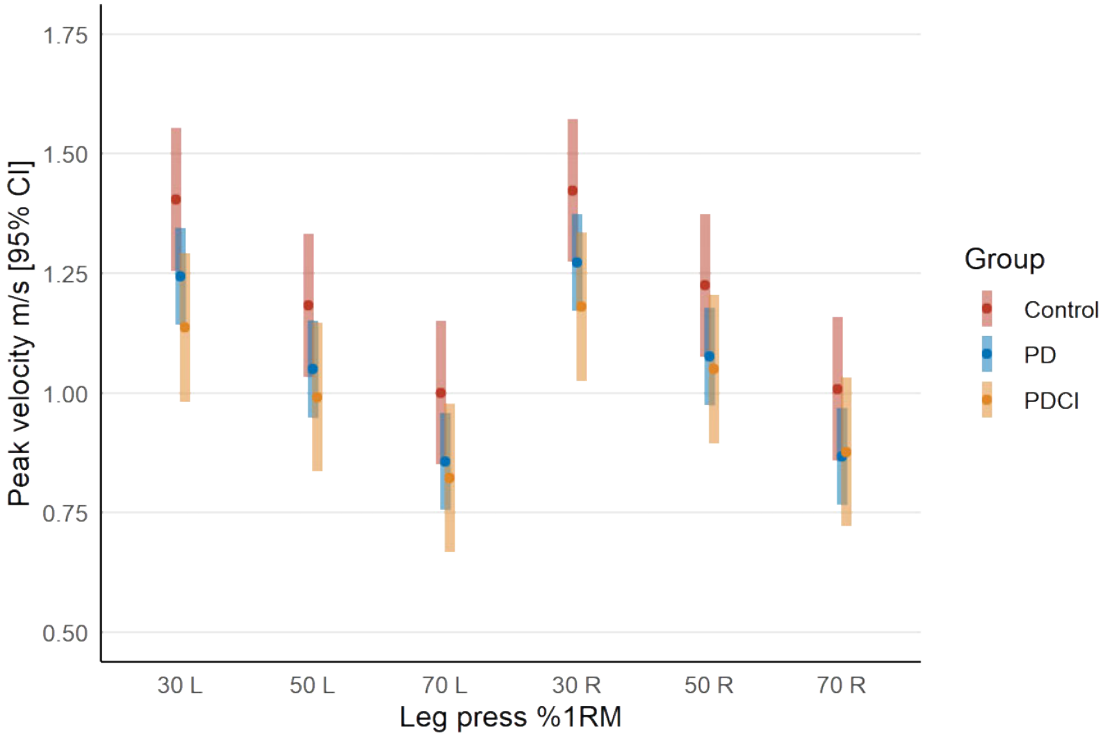


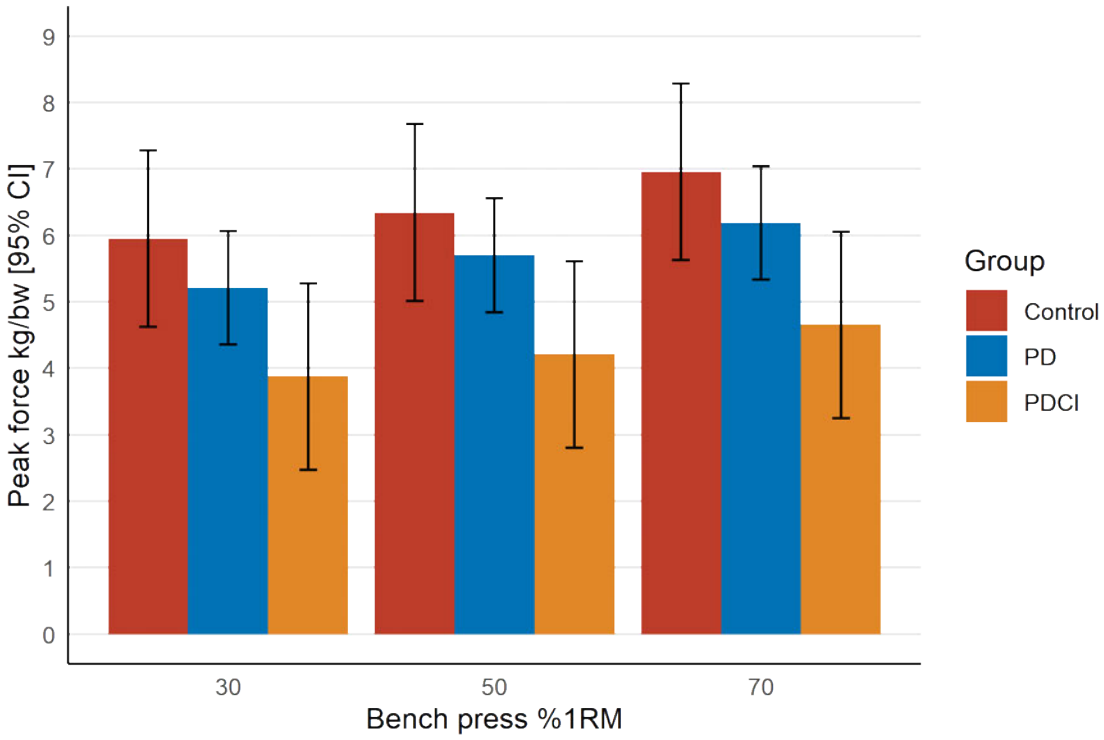
Figure 1B Peak velocity of the right (R) and left (L) lower limb during the horizontal leg press at 30%, 50%, and 70% of 1RM



7.2.3.2 Peak force

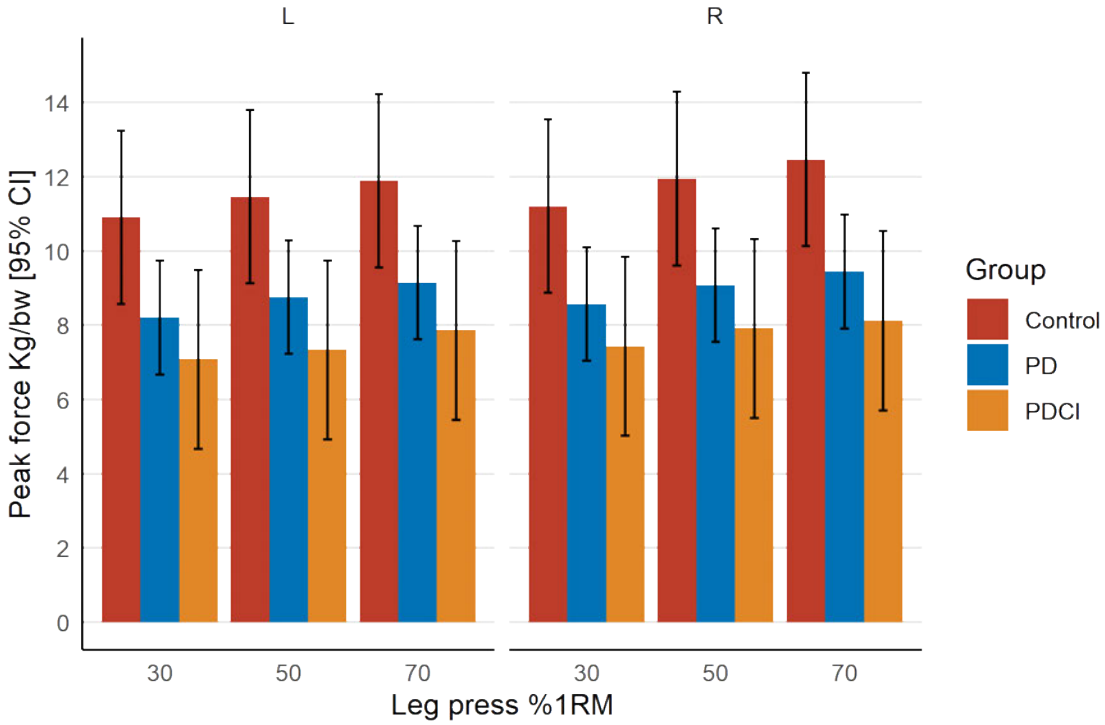
On the bench press, peak force was significantly lower in PDCI than PD non-CI at 30% (p =0.030), 50% (p =0.016) and 70% (p =0.014) of their 1RM (Figure 2). No significant differences were observed between PDCI and controls ($p \geq 0.05$) and PD non-CI and controls ($p \geq 0.05$) across different %1RM. Peak force was significantly higher at 70% compared to 50% and 30% ($p \leq 0.001$), and at 50% compared to 30% 1RM ($p \leq 0.001$) within each group.

Figure 2 Peak force during bench press at 30%, 50%, and 70% of 1RM



On the leg press, peak force was not significantly different amongst groups across different percentage of 1RM ($p \geq 0.05$) (Figure 3). In the PDCI group, peak force was significantly higher at 70% compared to 30% ($p \leq 0.05$) but not between 70% and 50% ($p \geq 0.05$), and 50% and 30% ($p \geq 0.05$) of their 1RM in both legs. In the PD non-CI and control groups, peak force was significantly higher at 70% compared 30% ($p \leq 0.05$), and 50% compared to 30% ($p \leq 0.05$), but not 70% compared to 50% ($p \leq 0.05$) of their 1RM in both legs. Peak force during leg press was not significantly different between right and left legs within PDCI and PD non-CI group at 30%, 50%, and 70% 1RM ($p \geq 0.05$). In the control group, peak force was significantly different between right and left legs at 50% and 70% ($p \leq 0.05$), but not at 30% ($p \geq 0.05$) of 1RM.

Figure 3 Peak force of the right (R) and left (L) lower limb during the horizontal leg press at 30%, 50%, and 70% of 1RM



7.2.3.3 Peak power

On the bench press, peak power was not significantly different amongst groups at 30%, 50%, and 70% 1RM ($p \geq 0.05$). Peak power was significantly higher at 30% compared to 50% and 70% ($p \leq 0.001$), and at 50% compared to 70% 1RM ($p \leq 0.001$) within each group (Figure 4).

On the leg press, peak power was also not significantly different amongst groups at 30%, 50%, and 70%1RM for both legs ($p \geq 0.05$) (Figure 5). In the PDCI group, peak power was significantly higher at 30% and 50% than 70% in both legs ($p \leq 0.05$), but no significant difference was observed between 30% and 50% 1RM ($p \geq 0.05$). In the PD non-CI and controls, peak power was significantly higher at 30% compared to 50% and 70% ($p \leq 0.05$), and at 50% compared to 70% ($p \leq 0.05$) of their 1RM in both legs. In the PDCI group, peak power was significantly different between the right and left legs at 50% 1RM (p =0.03), but not at 30% and 70% 1RM ($p \geq 0.05$). In the PD non-CI group, peak power was similar between left and right legs across different % 1RM ($p \geq 0.05$). In the control group, peak power was significantly different between right and left legs at 50% (p = 0.009) and 70% (p = 0.02), but not at 30% 1RM ($p \geq 0.05$).

Figure 4 Peak power during bench press at 30%, 50%, and 70% of 1RM

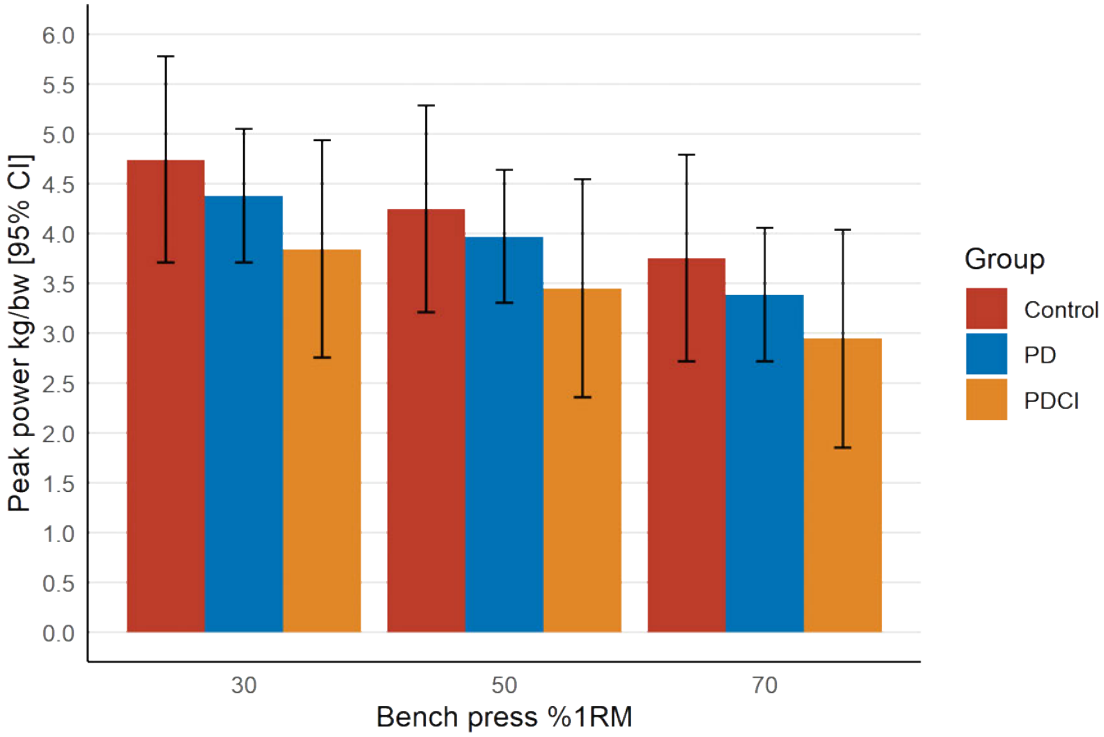
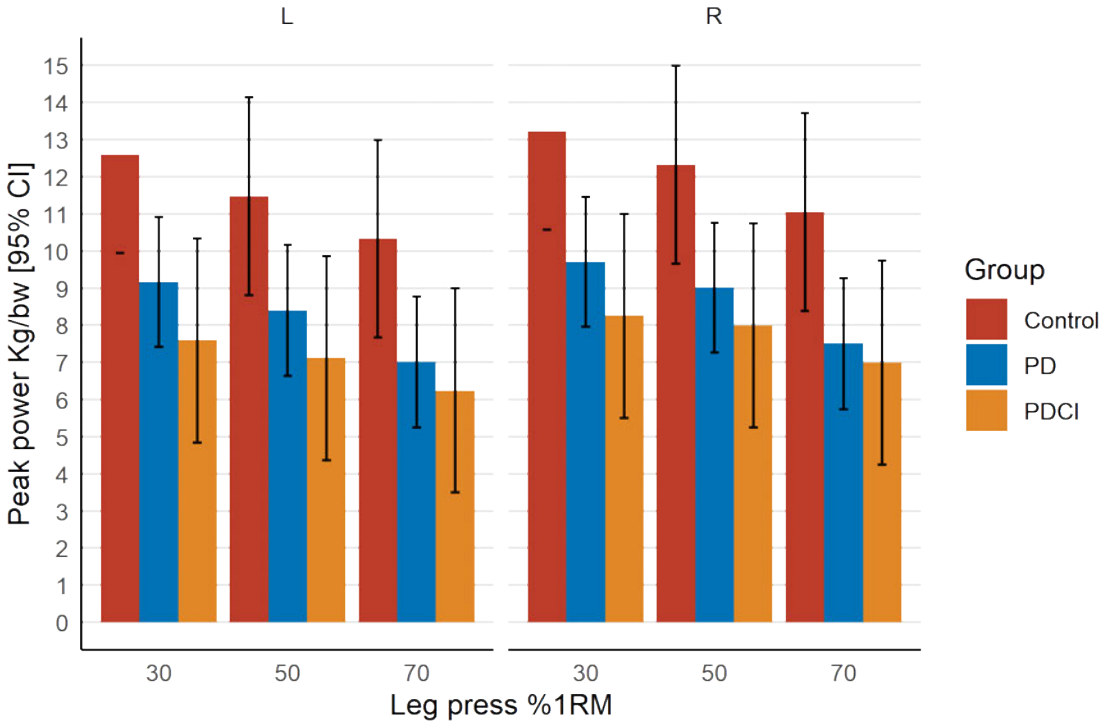


Figure 5 Peak power of the right (R) and left (L) lower limb during the horizontal leg press at 30%, 50%, and 70% of 1RM



7.2.3.4 Functional tests

SMBT, 5STS, and 6MWT was not significantly different amongst group ($p \geq 0.05$) (Table 2).

Table 2 Functional tests

	PDCI (n = 11)	PD non-CI (n = 13)	Control (n = 17)
SMBT (meters)	2.53±0.27 [1.97,3.08]	2.95±0.18 [2.58,3.32]	3.38±0.26 [2.84, 3.91]
5STS (seconds)	11.4±0.88 [9.60,12.2]	10.0±0.59 [8.81,11.2]	8.8±0.86 [7.05,10.6]
6MWT (meters)	538±30.8 [476,601]	564±20.7 [522,607]	667±29.90 [606,727]

*Data is presented in mean± SE [95% CI]. SMBT: Seated medicine ball throw; 5STS: five seconds sit-to-stand; 6MWT: six minutes walking test. * p≤ 0.05 VS control; † p≤ 0.05 VS PD non-CI*

7.3 Discussion

This chapter set out to answer two related questions raised during the examination: Do PwPD with CI produce less force and power than those without CI, and can muscle strength and power serve as a simple proxy measure for identifying the presence of CI in PwPD? Our results show that peak force was significantly lower in PDCI compared to PD non-CI during the bench press test, but no statistical difference was observed in the leg press test. Peak velocity was similar between groups, which may have influenced peak power, as no statistical difference was observed amongst participants for this outcome in either test. However, our results showed a trend toward lower peak power in PDCI compared to PD no-CI during the bench and leg press exercises. This trend may have contributed to the poorer, but not statistically significant, difference in functional performance observed in the PDCI participants compared to the PD no-CI group.

Martignon, Ruzzante, et al. (2021) reported no significant differences in muscle strength during isometric knee extension in PwPD compared to controls, which is similar to our results. In contrast, Skinner et al. (2019) found significantly lower isometric muscle strength in hip flexion, ankle dorsiflexion, and plantar flexion in PwPD compared to controls. The activity levels of participants and the specific muscles tested can partially explain these conflicting results. Physical activity level, training specificity, and exercise type (e.g. isometric, isotonic, and isokinetic) can be significant confounding factors when assessing muscle strength in PwPD and in the general population (Gamborg et al., 2023; Liguori et al., 2022). Participants in the study by Martignon and colleagues were physically active, whereas the activity levels of participants in the study by Skinner and colleagues were not reported. IPAQ-E findings and VO2peak (Chapters 4 and 5) indicate that participants from our study were physically active and involved in vigorous intensity training. However, it is unknown if weight training (upper and lower body) was included in each person's exercise routine.

The pathophysiology behind the potential decrease in muscle strength in PwPD compared to controls remains unknown. It is unclear whether muscle weakness originates centrally or peripherally and whether it is intrinsic to the disease or a consequence of progressive motor

impairment (Correa et al., 2020). Both central and peripheral factors may contribute to diminished mechanical muscle function in PwPD. Research shows decreased muscle activation, altered motor unit activity, and changes in muscle fibre morphology (Gamborg et al., 2023; Wilkinson et al., 2018). Reduced muscle quality can also be characterized by increased fat infiltration, linked to greater disease severity and frailty. However, these morphological changes may result more from reduced physical activity and mobility than from the disease itself (Gamborg et al., 2023). From the age of 60, there is a significant decrease in the number and diameter of alpha motor neurons and a decrease in the number of functioning motor units, resulting in loss of muscle mechanical function in healthy old adults. Additionally, there is a loss of cross-section area (muscle mass) primarily due to the reduction of fast-twitch muscle fibre hindering muscle power production (Aagaard et al., 2007; Aagaard et al., 2010; Ponsoni et al., 2023).

Our study found no significant difference in peak power across groups. Allen et al. (2009) who reported significantly lower peak low limb power in physically active PwPD compared to age-matched controls at different percentages of 1RM (30-90% 1RM at 10% increments). According to the authors, reduced peak power in PwPD arises from a combination of impaired muscle strength and velocity (due to bradykinesia) at low percentage of 1RM, while at a higher percentage of 1RM, it mainly results from muscle weakness. Paul et al. (2012), using the same pneumatic seated leg press machine (Keiser 420) to test muscle power from 30% to 80% 1RM (at 10% increments), acknowledged the role of bradykinesia but suggested reduced muscle strength as the primary contributor to diminished muscle power in PwPD compared to age-matched control. Our contrasting power results may partly be attributed to methodological differences between studies (Ferley & Vukovich, 2019; Gamborg et al., 2023). In Allen et al. (2009) study, it was unclear whether participants were instructed to jump or if they lost contact with the footplate during the exercises. This may have affected peak velocity, which is an important component of muscle power (Ferley & Vukovich, 2019; Vingren et al., 2011). Allen et al. (2009) reported significantly lower peak velocity in PwPD than controls at loads below 60% 1RM, but not at 70%, 80%, or 90% 1RM. In contrast, results from our study indicated no difference in peak velocity amongst participants across 30%, 50%, and 70% 1 RM.

Muscle strength and power can significantly impact functional performance in PwPD (Allen et al., 2010; Baizabal-Carvallo et al., 2023; Barbalho et al., 2019; Ni et al., 2016; Pääsuke et al., 2004; Ramsey et al., 2004; Strand et al., 2021). Our functional performance test results were similar to strength and power testing, showing no significant difference across groups. This may be partly due to the PD groups in the current study being more active and having a relatively high level of function. For example, PDCI in our study demonstrated better results compared to those reported in the literature for the SMBT (Strand et al., 2021), 5STS (Figueiredo et al., 2024), and 6MWT (Ugut et al., 2023), indicating that level of activity impact functional

performance in PwPD (Allen et al., 2010; Correa et al., 2020; Helgerud et al., 2020; Strand et al., 2021).

Taylor et al. (2022) suggested that factors such as gender, self-reported physical activity, BMI, waist circumference, and isometric grip strength are predictive of an abnormal chronotropic response to progressive exercise in non-PD participants aged 18 to 69 years. Despite the observed trend of decreased muscle force, power production, and functional performance, and the significantly higher BMI in PDCI compared to PD non-CI, our small sample size limits our ability to draw definitive conclusions or generalize these findings to the broader PD population. Furthermore, different types of muscle contractions (dynamic or isometric), equipment, muscle groups, and disease severity can produce varying results, making it challenging to accurately assess muscle strength in PwPD (Gamborg et al., 2023; Liguori et al., 2022).

7.4 Conclusion

Peak force was significantly lower in PDCI during the bench press but not during the leg press when compared to PD no-CI. This difference may be related to training specificity. Our results show no clear differences in peak velocity, force, and power across different percentages of 1RM between participants with and without CI, and age-matched controls. Additionally, functional performance did not show significant differences among our participants. However, this study was underpowered and future research with larger participant numbers is necessary to investigate the impact of CI on muscle strength, power, and overall functional capacity in PwPD. Additionally, studies should explore whether these outcomes, along with clinical measures such as BMI and MDS-UPDRS, could serve as useful proxies for identifying CI in PwPD.

7.5 Study limitations

Participants from this study were classified with mild to moderate disease severity (H&Y 1–3), limiting generalizability, and our study was underpowered to detect significant differences between the groups due to sample size limitations. Additionally, we tested compound movements using modified equipment found in community gyms rather than isolated muscles and equipment that use sophisticated technology such as pneumatic and isokinetic machines.

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Appendices

Appendices A. Health and disability ethics committees (HDEC)

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@health.govt.nz

17 August 2020

Mr Tone Ricardo Benevides Panassollo
School of Clinical Sciences
AUT University North Campus
90 Akoranga Drive
Auckland 0627

Dear Mr Benevides Panassollo,

Re:	Ethics ref:	20/NTB/154
	Study title:	Exercise intensity of non-contact boxing in people with Parkinson's disease

I am pleased to advise that this application has been *approved* by the Northern B Health and Disability Ethics Committee. This decision was made through the HDEC-Expedited Review pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Northern B Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.
2. Before the study commences at *each given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

Non-standard conditions:

- As per the Committees respond - Please correct the email contact to the HDC in the PIS to advocacy@advocacy.org.nz

Non-standard conditions must be completed before commencing your study, however, they do not need to be submitted to or reviewed by HDEC.

If you would like an acknowledgement of completion of your non-standard conditions you may submit a post approval form amendment through Online Forms. Please clearly identify in the amendment form that the changes relate to non-standard conditions and ensure that supporting documents (if requested) are tracked/highlighted with changes.

For information on non-standard conditions please see section 128 and 129 of the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz)

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

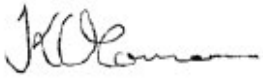
Your next progress report is due by 17 August 2021.

Participant access to ACC

The Northern B Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,



Mrs Kate O'Connor
Chairperson
Northern B Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@health.govt.nz

12 October 2020

Mr Tone Ricardo Benevides Panassollo
School of Clinical Sciences
AUT University North Campus
90 Akoranga Drive
Auckland 0627

Dear Mr Benevides Panassollo

Re:	**Ethics ref:**	**20/NTB/154/AM01**
	Study title:	Exercise intensity of non-contact boxing in people with Parkinson's disease

I am pleased to advise that this amendment has been *approved* by the Northern B Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Mrs Kate O'Connor
Chairperson
Northern B Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendices C. AUT Ethics Committee (AUTEC)

22 September 2020
Sue Lord
Faculty of Health and Environmental Sciences
Dear Sue
Re Ethics Application: **20/307 Exercise intensity of non-contact boxing in people with Parkinson's disease**
Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).
Your ethics application has been approved for three years until 22 September 2023.
Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard and that all the dates on the documents are updated.

AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.
Please quote the application number and title on all future correspondence related to this project.
For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

(This is a computer-generated letter for which no signature is required)
The AUTEC Secretariat
Auckland University of Technology Ethics Committee
Cc: tone.panassollo@autuni.ac.nz; Grant Mawston; Denise Taylor

Appendices D. Consent Form

Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
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www.aut.ac.nz

Consent Form

Project title: Exercise intensity of non-contact boxing in people with Parkinson's disease

Principal investigator: Tone Ricardo Benevides Panassollo

Project Supervisors: Dr. Seu Lord; Dr. Grant Mawston; Prof Denise Taylor

☐ I have read and understood the information provided about this research project in the Information sheet dated ____/_____/_____.

☐ I have had an opportunity to ask questions and to have them answered.

☐ I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without being disadvantaged in any way.

☐ I understand that if I withdraw from the study then I will be offered the choice between having any data that is identifiable as belonging to me removed or allowing it to continue to be used. However, once the findings have been produced, removal of my data may not be possible.

I consent to the use of my anonymised data by researchers in the future.
Yes ☐ No ☐

I agree to take part in this research.
Yes ☐ No ☐

I wish to receive a summary of the research findings, which will be provided in the end of the research project (please tick one): Yes ☐ No ☐

I wish to receive a copy of my assessment results (please tick one):
Yes ☐ No ☐

Participant's signature: _____

Participant's name: _____

Date:____/_____/_____

Approved by the HDEC on 17 of August of 2020
HDEC Reference number 20/NTB/154/AM01
Note: The Participant should retain a copy of this form, and of the participation information sheet.

Appendices E. Participant information form for participants with Parkinson's disease

Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999
www.aut.ac.nz

Participation Information Sheet

Project title: Exercise intensity of non-contact boxing in people with Parkinson's disease

Principal investigator: Tone Panassollo
Contact number: 022 361 5033
Organization: AUT – Auckland University of Technology

Introduction

Kia ora!

My name is Tone Panassollo and I am a PhD student at the Auckland University of Technology (AUT). I am looking for volunteers to take part in a study testing fitness levels in adults aged 50 to 70 years old. We will compare findings from people with Parkinson's disease, with adults of similar age who do not have Parkinson's disease. Volunteers will take part in 3 sessions of non-contact boxing, which is a high-intensity exercise. Please contact me if you would consider being part of the study or if you would like further information or clarification of any aspects of the study. Participation in this research is **voluntary**, and you do not have to decide immediately whether or not you would like to take part. Please take time to consider this information, and, if you wish, talk with relatives, whānau, friends, or healthcare workers before deciding whether or not to participate. You can find further details about the study below.

Purpose of the research

In recent years non-contact boxing training has become popular in people with Parkinson's disease (PD). However, our understanding about how people with PD can participate in a non-contact boxing training is limited, due to their physical level and symptoms caused by the disorder. People with PD may have limitations while participating in a high-intensity exercise such as non-contact boxing.
This study aims to measure levels of physical fitness by assessing aerobic capacity, muscle power and muscle strength in people with PD and adults aged 50 to 70 years old. This information will guide us to understand how different levels of fitness affect participation in non-contact boxing training.
The knowledge we gain from this study will be used to plan tailored non-contact boxing classes for this population.

Participation selection

We are inviting adults aged between 50 to 70 years old, who are mobile and able to walk without an aid. We will exclude people who present with any of the following:

- A neurodegenerative disease
- Cardiac pathology

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- Use of a pacemaker
- Chronic respiratory disease

Voluntary participation

Your participation in this research project is voluntary (tūao), with no obligation to take part in it. We encourage you to read this information and discuss the study with your whānau or friends If you do want to participate, you will be asked to provide a signed consent form before initiating this study. During this study, all participants will be in contact with specialists from neurological rehabilitation and specialists in exercise.
If you have any personal, cultural factors, or aspects of Māoritanga that you think are important to make you feel more comfortable during this research, please let us know either before or during the research project. You are welcome to bring whānau or friends to any of the sessions. You will be able to withdraw from the study if you change your mind later.

Type of research intervention

This study involves answering questionnaires and undertaking tests to evaluate aerobic capacity (maximal ability of your body to use oxygen), muscle power, muscle strength and balance. It also involves participating in 3 sessions of non-contact boxing training.

The test to evaluate aerobic capacity will be performed using a stationary bike. You will be required to wear a specific mask during the test. The mask is comfortable. We will be monitoring your heart rate and your blood pressure during the test. You will be able to stop the test at any time.
The tests to evaluate muscle power and muscle strength will be performed using a specific leg press and a bench press machine. These machines are commonly found in community gyms. Specific movements will be used to evaluate your balance ability. You will participate in three non-contact boxing sessions. During Session 1 we will teach basic boxing movements. In session 2 and 3 you will perform these movements, which include punching a boxing bag or focus pads.
The boxing sessions, tests and questionnaires will be conducted by an exercise specialist (and principal investigator Tone Panassollo) who has experience in instructing non-contact boxing exercises for people age above 65 years old. You will be able to stop the tests or the boxing exercises at any time if you feel pain, fatigue or any other discomfort.

Duration and venue

Assessments will take place over 3 days for approximately 2 hours per day at the Auckland University of Technology (AUT) North Campus, 90 Akoranga Drive, AA building.

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Benefits

For you personally: you will have your level of fitness evaluated. This information will be useful to plan your physical activities appropriately.
For the community: results from this study will inform the research community and people working with Parkinson's disease (PD) about the exercise intensity during a non-contact boxing session. This will help to plan the exercises more tailored for people with PD.
For the research community: Results from this study will be important for developing future research regarding exercise intensity in people with PD.

Risks

Participants may feel tired after the tests or during the non-contact boxing training. Muscle pain related to exercise may also occur; this is a natural process. You will be supervised during all the tests and during the non-contact boxing training sessions. Measures will be in place to reduce the risk of injuries.
If you were injured in this study, which is unlikely, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

Reimbursements (Koha)

A $20.00 petrol voucher will be offered to you each time you drive to AUT to cover your transport costs.

Confidentiality

Your privacy will be protected by identifying you only as a number in the final report. Access to the data is restricted to the researchers involved in this study and to external researches if appropriate, and only with your consent. Results from the study may be published in academic journals and used in conference presentations. Any data presented will be totally anonymised. Data obtained from this study will be stored at AUT for a period of 10 years, and after that it will be destroyed/shredded.

Sharing the results

If you would like to receive a brief summary of the main findings of the study, we will email or post these to you. Confidential information will not be shared.

Right to refuse or withdraw

You may withdraw from this study at any time and without any disadvantage.

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Concerns about this research project

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisors:
Dr Sue Lord – e-mail: sue.lord@aut.ac.nz Ph: 021 106 3172
Dr Grant Mawston – e-mail: gmawston@aut.ac.nz 09-9219999 extension 7180.

Concerns regarding the conduct of the research should be notified to:

Independent Health and Disability Advocate	0800 555 050 advocacy@advocacy.org.nz
HDEC Ethics Committee	0800 4 38442 (0800 4 ETHIC) hdecs@moh.govt.nz
Māori cultural contacts	Witeri Williams Phone: 0272098902 E-mail: witeri.williams@procare.co.nz Tammi Wilson Uluinayau Phone: 09 921 9999 ext 6201 E-mail: tuluinay@aut.ac.nz

Research is being funding

This research is being funding by:

- Parkinson's New Zealand
- Health and Rehabilitation Research Group (HRRI)

Contact for further information

Please feel free to ask me any more questions about any part of the research study, if you wish to.
Principal investigator: Tone Panassollo. Contact No. 022-361-5033
Email: tone.panassollo@autuni.ac.nz

Tone R B Panassollo

Appendices F. Participant information form for participants with Parkinson's disease – Amendment

Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
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www.aut.ac.nz

Participation Information Sheet

Project title: Exercise intensity of non-contact boxing in people with Parkinson's disease

Principal investigator: Tone Panassollo
Contact number: 022 361 5033
Organization: AUT – Auckland University of Technology

Introduction

Kia ora!

My name is Tone Panassollo and I am a PhD student at Auckland University of Technology (AUT). I am looking for volunteers to take part in a study testing fitness levels in people with Parkinson's disease. I will examine the effect that different levels of fitness has whilst engaging in non-contact boxing, which is a high-intensity exercise. Please contact me if you would consider being part of the study or, if you would like further information or clarification of any aspects of the study. Participation in this research is voluntary, and you do not have to decide immediately whether or not you would like to take part. Please take time to consider this information, and, if you wish, talk with relatives, whānau, friends, or healthcare workers before deciding whether or not to participate You can find further details about the study below.

Purpose of the research

In recent years non-contact boxing training has become popular in people with Parkinson's disease (PD). However, our understanding about how people with PD can participate in a non-contact boxing training is limited, due to their physical level and symptoms caused by the disorder. People with PD may have limitations while participating in a high-intensity exercise such as non-contact boxing.
This study aims to measure the level of physical fitness by assessing aerobic capacity, muscle power and muscle strength in people with PD. This information will guide us to understand how different levels of fitness affect participation in non-contact boxing training. The knowledge we gain from this study will be used to plan tailored non-contact boxing classes for this population.

Participation selection

We are inviting people clinically diagnosed with idiopathic Parkinson's disease aged between 45 to 75 years old, with mild to moderate disease severity. By this, we mean people who are able to walk without an aid, with or without medication, who do not experience freezing of gait, and who are not consistently falling.
We will exclude people who present with any of the following:

- A neurodegenerative disease other than PD
- Cardiac pathology
- Use of a pacemaker
- Chronic respiratory disease

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Voluntary participation

Your participation in this research project is **voluntary (tūao)**, with no obligation to take part in it. We encourage you to read this information and discuss the study with your whānau or friends If you do want to participate, you will be asked to provide a signed consent form before initiating this study. During this study, all participants will be in contact with specialists from neurological rehabilitation and specialists in exercise for people with Parkinson's disease.
If you have any personal, cultural factors, or aspects of Māoritanga that you think are important to make you feel more comfortable during this research, please let us know either before or during the research project. You are welcome to bring whānau or friends to any of the sessions. You will be able to withdraw from the study if you change your mind later.

Type of research intervention

This study involves questionnaires and tests to evaluate aerobic capacity maximal ability of your body to use oxygen), muscle power, muscle strength and balance. This study also involves participating in 3 sessions of non-contact boxing training.
During the first day of data collection we will evaluate your cognitive function using the Montreal Cognitive Assessment (MoCA). If you have any disfunction performing the test, you will be excluded from future data collection. After evaluating your cognition, you will answer questionnaires to evaluate disease severity and your quality of life, using specific questions regarding to PD.
The test to evaluate aerobic capacity will be performed using a stationary bike. You will be required to wear a specific mask during the test. The mask is comfortable. We will be monitoring your heart rate and your blood pressure during the test. You will be able to stop the test at any time.
The tests to evaluate muscle power and muscle strength will be performed using a specific leg press and a bench press machine. These machines are commonly found in community gyms. Specific movements will be used to evaluate your balance ability.
You will participate in three non-contact boxing sessions. During Session 1 we will teach basic boxing movements. Session 2 and 3 you will perform these movements, which include punching a boxing bag or focus pads. The boxing sessions, tests and questionnaires will be conducted by an exercise specialist (and principal investigator Tone Panassollo) who has experience in instructing non-contact boxing exercises for people with PD. You will be able to stop the tests or the boxing exercises at any time if you feel pain, fatigue or any other discomfort.

Duration and venue

Assessments will take place over 3 days for approximately 2 hours per day at the Auckland University of Technology (AUT) North Campus, 90 Akoranga Drive, AA building.

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Benefits

For you –> You will have your level of fitness evaluated. This information will be useful to plan your physical activities appropriately.
For the community -> Results from this study will inform the research community and people working with PD about the exercise intensity during a non-contact boxing session. This will help to plan the exercises more tailored for people with PD.
For the research community -> Results from this study will be important for developing future research regarding exercise intensity in people with PD.

Risks

Participants may feel tired after the tests or during the non-contact boxing training. Muscle pain related to exercise may also occur; this is a natural process. You will be supervised during all the tests and during the non-contact boxing training sessions. Measures will be in place to reduce the risk of injuries.
If you were injured in this study, which is unlikely, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

Reimbursements (Koha)

A $20.00 petrol voucher will be offered to you each time you drive to AUT to cover your transport costs.

Confidentiality

Your privacy will be protected by identifying you only as a number in the final report. Access to the data is restricted to the researchers involved in this study and to external researches if appropriated, and only with your consent. Results from the study may be published in academic journals and used in conference presentations. Any data presented will be totally anonymised. Data obtained from this study will be stored at AUT for a period of 10 years, and after that it will be destroyed/shredded.

Sharing the results

If you would like to receive a brief summary of the main findings of the study, we will email or post these to you. Confidential information will not be shared.

Right to refuse or withdraw

You may withdraw from this study at any time and without any disadvantage. Please make the researcher aware of your decision.

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Concerns about this research project

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisors:
Dr Sue Lord – e-mail: sue.lord@aut.ac.nz Ph: 021 106 3172
Dr Grant Mawston – e-mail: gmawston@aut.ac.nz 09-9219999 extension 7180.

Concerns regarding the conduct of the research should be notified to:

Independent Health and Disability Advocate	0800 555 050 advocacy@advocacy.org.nz
HDEC Ethics Committee	0800 4 38442 (0800 4 ETHIC) hdecs@moh.govt.nz
Māori cultural contacts	Witeri Williams Phone: 0272098902 E-mail: witeri.williams@procare.co.nz Tammi Wilson Uluinayau Phone: 09 921 9999 ext 6201 E-mail: tuluinay@aut.ac.nz

Research funding

This research is being funding by:

- Parkinson's New Zealand
- Health and Rehabilitation Research Group (HRRI)

Contact for further information

Please feel free to ask me any more questions about any part of the research study, if you wish to.
Principal researcher: Tone Panassollo. Contact No. 022-361-5033
Email: tone.panassollo@autuni.ac.nz

Tone R B Panassollo

Appendices G. Participant information form for participants control group

Auckland University of Technology
Private Bag 92006, Auckland 1142, NZ
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www.aut.ac.nz

Participation Information Sheet

Project title: Exercise intensity of non-contact boxing in people with Parkinson's disease

Principal investigator: Tone Panassollo
Contact number: 022 361 5033
Organization: AUT – Auckland University of Technology

Introduction

Kia ora!

My name is Tone Panassollo and I am a PhD student at the Auckland University of Technology (AUT). I am looking for volunteers to take part in a study testing fitness levels in adults aged 50 to 70 years old. We will compare findings from people with Parkinson's disease, with adults of similar age who do not have Parkinson's disease. Volunteers will take part in 3 sessions of non-contact boxing, which is a high-intensity exercise. Please contact me if you would consider being part of the study or if you would like further information or clarification of any aspects of the study. Participation in this research is **voluntary**, and you do not have to decide immediately whether or not you would like to take part. Please take time to consider this information, and, if you wish, talk with relatives, whānau, friends, or healthcare workers before deciding whether or not to participate. You can find further details about the study below.

Purpose of the research

In recent years non-contact boxing training has become popular in people with Parkinson's disease (PD). However, our understanding about how people with PD can participate in a non-contact boxing training is limited, due to their physical level and symptoms caused by the disorder. People with PD may have limitations while participating in a high-intensity exercise such as non-contact boxing.
This study aims to measure levels of physical fitness by assessing aerobic capacity, muscle power and muscle strength in people with PD and adults aged 50 to 70 years old. This information will guide us to understand how different levels of fitness affect participation in non-contact boxing training.
The knowledge we gain from this study will be used to plan tailored non-contact boxing classes for this population.

Participation selection

We are inviting adults aged between 50 to 70 years old, who are mobile and able to walk without an aid. We will exclude people who present with any of the following:

- A neurodegenerative disease
- Cardiac pathology

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- Use of a pacemaker
- Chronic respiratory disease

Voluntary participation

Your participation in this research project is **voluntary (tūao)**, with no obligation to take part in it. We encourage you to read this information and discuss the study with your whānau or friends If you do want to participate, you will be asked to provide a signed consent form before initiating this study. During this study, all participants will be in contact with specialists from neurological rehabilitation and specialists in exercise.
If you have any personal, cultural factors, or aspects of Māoritanga that you think are important to make you feel more comfortable during this research, please let us know either before or during the research project. You are welcome to bring whānau or friends to any of the sessions. You will be able to withdraw from the study if you change your mind later.

Type of research intervention

This study involves answering questionnaires and undertaking tests to evaluate aerobic capacity (maximal ability of your body to use oxygen), muscle power, muscle strength and balance. It also involves participating in 3 sessions of non-contact boxing training.

The test to evaluate aerobic capacity will be performed using a stationary bike. You will be required to wear a specific mask during the test. The mask is comfortable. We will be monitoring your heart rate and your blood pressure during the test. You will be able to stop the test at any time.
The tests to evaluate muscle power and muscle strength will be performed using a specific leg press and a bench press machine. These machines are commonly found in community gyms. Specific movements will be used to evaluate your balance ability. You will participate in three non-contact boxing sessions. During Session 1 we will teach basic boxing movements. In session 2 and 3 you will perform these movements, which include punching a boxing bag or focus pads.
The boxing sessions, tests and questionnaires will be conducted by an exercise specialist (and principal investigator Tone Panassollo) who has experience in instructing non-contact boxing exercises for people age above 65 years old. You will be able to stop the tests or the boxing exercises at any time if you feel pain, fatigue or any other discomfort.

Duration and venue

Assessments will take place over 3 days for approximately 2 hours per day at the Auckland University of Technology (AUT) North Campus, 90 Akoranga Drive, AA building.

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Benefits

For you personally: you will have your level of fitness evaluated. This information will be useful to plan your physical activities appropriately.
For the community: results from this study will inform the research community and people working with Parkinson's disease (PD) about the exercise intensity during a non-contact boxing session. This will help to plan the exercises more tailored for people with PD.
For the research community: Results from this study will be important for developing future research regarding exercise intensity in people with PD.

Risks

Participants may feel tired after the tests or during the non-contact boxing training. Muscle pain related to exercise may also occur; this is a natural process. You will be supervised during all the tests and during the non-contact boxing training sessions. Measures will be in place to reduce the risk of injuries.
If you were injured in this study, which is unlikely, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

Reimbursements (Koha)

A $20.00 petrol voucher will be offered to you each time you drive to AUT to cover your transport costs.

Confidentiality

Your privacy will be protected by identifying you only as a number in the final report. Access to the data is restricted to the researchers involved in this study and to external researches if appropriate, and only with your consent. Results from the study may be published in academic journals and used in conference presentations. Any data presented will be totally anonymised. Data obtained from this study will be stored at AUT for a period of 10 years, and after that it will be destroyed/shredded.

Sharing the results

If you would like to receive a brief summary of the main findings of the study, we will email or post these to you. Confidential information will not be shared.

Right to refuse or withdraw

You may withdraw from this study at any time and without any disadvantage.

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Concerns about this research project

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisors:
Dr Sue Lord – e-mail: sue.lord@aut.ac.nz Ph: 021 106 3172
Dr Grant Mawston – e-mail: gmawston@aut.ac.nz 09-9219999 extension 7180.

Concerns regarding the conduct of the research should be notified to:

Independent Health and Disability Advocate	0800 555 050 advocacy@advocacy.org.nz
HDEC Ethics Committee	0800 4 38442 (0800 4 ETHIC) hdecs@moh.govt.nz
Māori cultural contacts	Witeri Williams Phone: 0272098902 E-mail: witeri.williams@procare.co.nz Tammi Wilson Uluinayau Phone: 09 921 9999 ext 6201 E-mail: tuluinay@aut.ac.nz

Research is being funding

This research is being funding by:

- Parkinson's New Zealand
- Health and Rehabilitation Research Group (HRRI)

Contact for further information

Please feel free to ask me any more questions about any part of the research study, if you wish to.
Principal investigator: Tone Panassollo. Contact No. 022-361-5033
Email: tone.panassollo@autuni.ac.nz

Tone R B Panassollo

Appendices H. Poster Parkinson's disease

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Would you like to know about your level of fitness?

We are looking for people clinically diagnose with Parkinson's disease age 50 to 70 years old to participate in study about the level of fitness through non-contact boxing exercise.

You can not participate:	Participation in this study involve:
• If you make use of DBS or heart pacemaker • If you have any other neurodegenerative disease other than Parkinson's disease • If you have had a heart attack within the last year, or if you have chronic obstructive pulmonary disease	• Evaluation of aerobic capacity – oxygen consumption • Evaluation of muscle strength and muscle power • Evaluation of balance • Evaluation of disease severity • Participation in 3 sessions of non-contact boxing training

WHAT SHOULD I DO IF I AM INTERESTED?

For further information, please contact **Tone Panassollo** by phone **022-361-5033**, or by e-mail on tone.panassollo@autuni.ac.nz. Tone will answer any questions you may have about the study, and if you would like to participate, he will organise a date and time for your assessment at Auckland University of Technology (AUT), Akoranga Drive, Northcote.

Study supervisor:
Dr Sue Lord (suelord@aut.ac.nz) and Dr. Grant Mawston (grant.mawston@aut.ac.nz).

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Appendices I. Poster controls

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