Aerobic exercise to improve cardiorespiratory function in Parkinson's

Aseel Aburub

Submitted to Keele University for the degree of Doctor of Philosophy,

December 2021

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Abstract

Introduction

Cardiopulmonary impairments are the leading cause of morbidity and mortality in advanced stages of Parkinson's. Although there is some evidence of pulmonary impairments in the earlier stages, symptoms remain asymptomatic until advanced stages. Aerobic exercise and lung function in people living with Parkinson's (PLwP) has not yet been investigated. This thesis aims to:

- Review prevalence of pulmonary function, cardiovascular response to exercise, and effects of aerobic exercise on cardiopulmonary function, in PLwP.
- Pilot and investigate feasibility of a trial of aerobic exercise to improve cardiopulmonary function in PLwP.
- Survey the effects of COVID-19 pandemic on physical activity in PLwP.

Methods

- Reviews of published literature with systematic search, quality assessment and narrative synthesis of findings
- Mixed-methods, single-blind feasibility study exploring: recruitment, attrition, intervention, outcome measures, inclusion and exclusion criteria. Pulmonary function, cardiac fitness, and physical activity were assessed at baseline, 8-weeks and 12-weeks. Participants' experiences and acceptability of intervention and outcome measures were explored in focus groups.
- Online questionnaire to explore effects of COVID-19 pandemic on physical activities in PLwP.

Results

- PLwP suffer from obstructive and/or restrictive pulmonary disease; cardiac fitness in PLwP is variable; aerobic exercise improves cardiac fitness but no studies have assessed effects of aerobic exercise on pulmonary function in Parkinson's.
- Twenty-four PLwP were recruited and 15 completed the EXoCARP trial, with low attrition (n=7), five due to the COVID-19 pandemic. Feasibility and acceptability of outcomes and intervention was confirmed.
- Outdoor and gym-based physical activity decreased in PLwP during the COVID-19 pandemic; many PLwP accessed online resources to exercise at home.

Conclusions

People with early stages of Parkinson's should be screened for asymptomatic pulmonary impairments that could be managed, to prevent late-stage complications. Feasibility of a larger trial of aerobic exercise and cardiopulmonary function in Parkinson's was confirmed. Considering remote/online or home-based exercises is warranted for future exercise trials.

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Publications arising from the research in this thesis:

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. (2020). Cardiopulmonary function and aerobic exercise in Parkinson's: a systematic review of the literature. *Movement Disorders Clinical Practice*, 7(6), 599-606.

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Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. (2021). The effects of community based aerobic exercise on cardiopulmonary and cognitive function in people with Parkinson’s disease. School of Allied Health Professions Research seminars, Keele University (oral presentation).

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. (2020). Aerobic exercise to improve cardiopulmonary function in Parkinson's: a systematic review. Physio UK (virtual poster presentation).

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. (2019). The effects of community based aerobic exercise on cardiopulmonary and cognitive function in people with Parkinson’s disease. The International Movement Disorders Society Congress, Dubai (oral presentation).

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. (2019). Community based aerobic exercise programme and cardiopulmonary function in people with Parkinson’s disease. Faculty of Medicine and Health Sciences PGR Symposium, Keele University (oral presentation).

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. (2018). The effects of community based aerobic exercise on cardiopulmonary and cognitive function in people with Parkinson's disease. Institute of Liberal Arts and Science (ILAS) Conference, Keele University (poster presentation).

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. (2018). The effects of community based aerobic exercise on cardiopulmonary and cognitive function in people with Parkinson's disease. School of Allied Health Professions Research seminars, Keele University (oral presentation).

Chapter 1: Introduction and Background

1.1. Overview

This introductory chapter will describe the general aspects of Parkinson's. The pathophysiology of Parkinson's will be explained, followed by a description of the major clinical features and the stages of Parkinson's, and then an overview of human pulmonary function and cardiovascular response to exercise. This will lead to an explanation of the aims of the thesis at the end of the chapter.

1.2. Parkinson's: epidemiology and general overview

Parkinson's is the most common age-related motor, neurodegenerative disorder, with unknown specific cause (Jankovic, 2008). Its incidence is 160 persons per 100,000 people in the UK per annum, with an incidence of 15 to 20 per 100,000 annually (National Institute for Health and Care Excellence, 2018). The prevalence of Parkinson's is 1.5% of people over 60 years old and increases with age up to 4.3% in people above 85 years old, and is expected to increase considerably within the next decades, leading to increases in health demands and, subsequently, costs (de Rijk et al., 1995).

1.3. Aetiology and pathophysiology

Parkinson's results from unknown (idiopathic) causes that lead to loss of neurons from the substantia nigra of the brain basal ganglia, which is responsible for producing dopamine, a neurotransmitter essential for controlling body movement and balance (Sethi, 2002). These neurons project to the striatum and their loss leads to a decrease in the activity of neural circuits within the basal ganglia and an increase in inhibitory signals leading to decrease in movement.

The main cause of mortality and morbidity in the advanced stages of Parkinson's is respiratory impairment including type 1 respiratory failure, type 2 respiratory failure, or both types together (Torsney, 2017). Hart (2008) categorises respiratory failure into either lung failure leading to type 1 respiratory failure ($PaO_2 \leq 8KPa$), or pump failure leading to type 2 respiratory failure ($PaO_2 \leq 8KPa$ concurrent with a $PaCO_2$ of $\geq 6PKa$).

Type 1 respiratory failure: Impaired diffusion might occur due to pulmonary oedema (West 2008), low partial pressure of inspired oxygen, or a pulmonary disease such as emphysema (Hari and Mackenzie 2007). Low partial pressure of inspired oxygen occurs in high altitudes, and alveolar hypoventilation occurs in atelectasis or pneumonia. PLwP may also suffer from aspiration pneumonia due to the swallowing problems they may have (Lanspa et al. 2013). When aspiration pneumonia is accompanied by weak cough, type 1 respiratory failure might occur (Ebihara et al. 2003). Additionally, PLwP generally have low levels of physical activity, which might lead to decreased lung volumes and, over time, development of atelectasis and subsequently type 1 respiratory failure (Torsney, 2017). If atelectasis happened frequently, this could increase the load on respiratory muscles and lead to type 2 respiratory failure over time (Torsney, 2017).

Type 2 respiratory failure results from an impairment in one or more of the following: central respiratory drive; load placed on the respiratory muscles; and the capacity of the respiratory muscles (Jones et al., 2016). It was reported previously that PLwP have an abnormal ventilatory response to hypercapnia, suggesting that their respiratory control is compromised (Seccombe et al., 2011).

PLwP have a kyphoscoliotic posture that, together with a swallowing impairment, might decrease the strength of the respiratory muscles (Torsney, 2017). The

decrease in the respiratory muscle strength together with the impairment in coordination of movements will affect the mechanics of ventilation (Torsney, 2017), specifically the “Bucket Handle Movement” (movement that happens due to the vertical arrangement of the lumbar and costal segments of the diaphragm) (Gatzoulis, 2008). Furthermore, rigidity of the chest wall muscles in PLwP might lead to ankylosis of the costosternal and thoracovertebral joints, and subsequently affect the mechanics of ventilation (Shill and Stacy, 2002). Moreover, kyphoscoliosis, together with chest wall muscle rigidity, might lead to decrease in the physical size of the thorax, and subsequently a decrease in lung volumes (O'Callaghan, 2018). All these factors might lead to the development of type 2 respiratory failure in PLwP. Figure 1 represents a summary of the main factors that might lead to type 1 and type 2 respiratory failure in PLwP.

Hypercapnic ventilatory response is mediated by the retrotrapezoid nucleus, located in the ventral medullary surface, and is expressed as the change in minute ventilation (the volume of gas inhaled or exhaled from a person's lungs per minute) per change in CO2 at the end of exhalation (Goldberg et al., 2017). The central respiratory drive including the medullary surface might be affected in PLwP. Seccombe et al. (2011) reported that PLwP are unable to maintain an adequate seal to complete the hypercapnic ventilatory response (reported as abnormal in 47% of their sample) due to medullary impairment. In a healthy population, respiratory drive is influenced by hypercapnia, but in PLwP reduced response to carbon dioxide was reported (Seccombe et al, 2011), due to medullary surface impairment. Findings of Seccombe and colleagues demonstrate impairments of the respiratory drive in response to hypercapnia. The impairment of the respiratory drive may also be explained by the Braak hypothesis, which suggests that Parkinson’s pathology is related to an unknown pathogen (virus or bacterium) that enters the body through the nasal cavity, and subsequently is swallowed and reaches the gut,

initiating Lewy pathology, and might spread via the olfactory tract and the vagal nerve, toward and within the central nervous system (CNS) (Braak et al., 2011). The Braak hypothesis suggests early brainstem involvement in PLwP with selective degeneration of the neurons in the pons and medulla oblongata in the brainstem, and subsequently, respiratory impairment (Braak et al., 2011). However, the Braak hypothesis is limited because not all PLwP have Lewy pathology (Rietdijk et al., 2017).

Another factor that might lead to respiratory impairment in PLwP is the diminished dopamine level. Dopamine is an important neurotransmitter not only in the brain but also in the carotid body. Dopamine plays an important role in the ventilatory response to hypoxia, as it has an inhibitory modulatory effect on the carotid body (Hovestadt et al., 1989). For example, dopamine infusion inhibits carotid body response to hypoxia and dopamine D2 receptor blockage causes an increased response of the carotid body to hypoxia (Bisgard et al., 2001). Onodera et al. (2000) studied the peripheral chemosensitivity to hypoxemia and hypercapnia in PLwP, and reported a blunted response to both oxygen and carbon dioxide changes, suggesting an impairment in the function of the carotid chemoreceptors.

In summary, swallowing impairment, weak cough, low level of physical activity, respiratory drive impairment, kyphoscoliosis, decreased strength of the respiratory muscles, impaired mechanics of ventilation, rigidity of chest wall muscles, and diminished dopamine levels, are the main factors related to the respiratory impairment in PLwP.

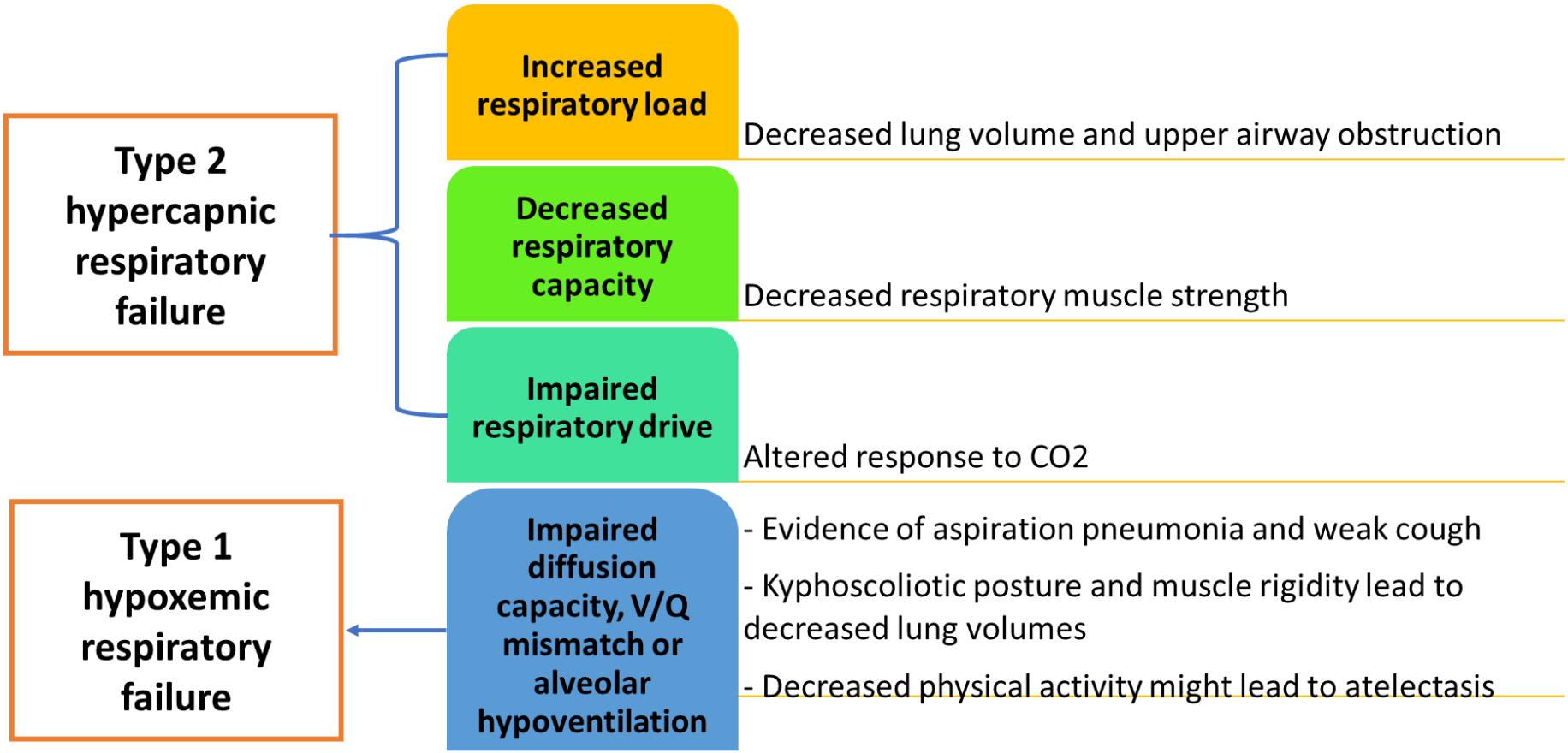


Figure 1: Summary for the main factors that affect respiratory function and lead to respiratory failure in people living with Parkinson's.

1.4. Disease severity

The Hoehn and Yahr scale is the main screening test for Parkinson's severity, based on motor function only (Hoehn and Yahr, 1967). Figure 2 represents the five stages of the Hoehn and Yahr scale, and shows that the scale ranges from no signs, stage 0, to wheelchair bound or bedridden, stage 5. PLwP commonly suffer from both motor and non-motor symptoms (Jankovic, 2008). In this thesis, the classification of PLwP into people at early stages of Parkinson's (I-III in Hoehn and Yahr), and advanced stages (IV-V in Hoehn and Yahr) will be used.

1.5. Clinical features of Parkinson's: motor symptoms

Usually, diagnosis of Parkinson's is made if a patient presents with bradykinesia, accompanied by at least one of the following symptoms: muscle rigidity, resting tremor or balance impairments that are not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction (Gelb et al., 1999).

Bradykinesia means slowness of movement, and is responsible for the slowness of motor activities, shuffling gait, masked face, and absence of arm swing; it is often associated with akinesia (lack of movement) and hypokinesia (reduced amplitude of movement) (Jankovic, 2008). It is caused by decreased ability or failure of the basal ganglia to reinforce the motor cortex, leading to elongation in reaction time and slowness of movement (Berardelli et al., 2001).

Rigidity leads the individual to feel stiffness in joints and muscles, and may contribute to the discomfort and pain reported in PLwP. Cogwheel rigidity is clinically characterized by increased resistance to passive movement in the limbs (flexion, extension and rotation), even in low velocity stretching (Quinn, 1997). In

most cases, cogwheel rigidity is present, even in early stages of Parkinson's. PLwP may complain of pain as result of rigidity, specifically in the shoulders, trunk and neck, also called axial rigidity, and leading to postural abnormalities; those abnormalities include flexed neck, trunk, elbows and knees (Jankovic, 2008). Chest wall rigidity is the main cause for the weak respiratory muscles in PLwP (Torsney, 2017).

Resting tremor is the most common and recognized clinical feature in Parkinson's, at around 4-6 Hz (Jankovic, 2008). As its name implies, resting tremor disappears or decreases during movement. Also, resting tremor was found to disappear when sleeping and usually occurs in the distal part of the limb (hands and/or ankles) (Jankovic, 2008). Tremor in the hand usually occurs as a rapid alternation between supination and pronation and is described as "pill-rolling" (Jankovic, 2008). Additionally, resting tremor may occur in the lips, chin, jaw and legs (Jankovic, 2008).

The generic terms of balance and postural stability describe the dynamics of body posture required to prevent a fall (Winter, 1995). Balance requires maintenance of the body's centre of mass within the limits of the base of support during sitting or standing or controlling the body while moving to a new base of support while walking or running (Jankovic, 2008). Balance and postural instability usually occur in the late stages of Parkinson's, after the other main clinical features have appeared (Jankovic, 2008).

Freezing is a sudden and transient inability to move that usually lasts for less than 10 seconds (Jankovic, 2008). Freezing does not occur in all PLwP, reportedly experienced by around 47%, and is considered as a main risk of falls (Macht et al., 2007).

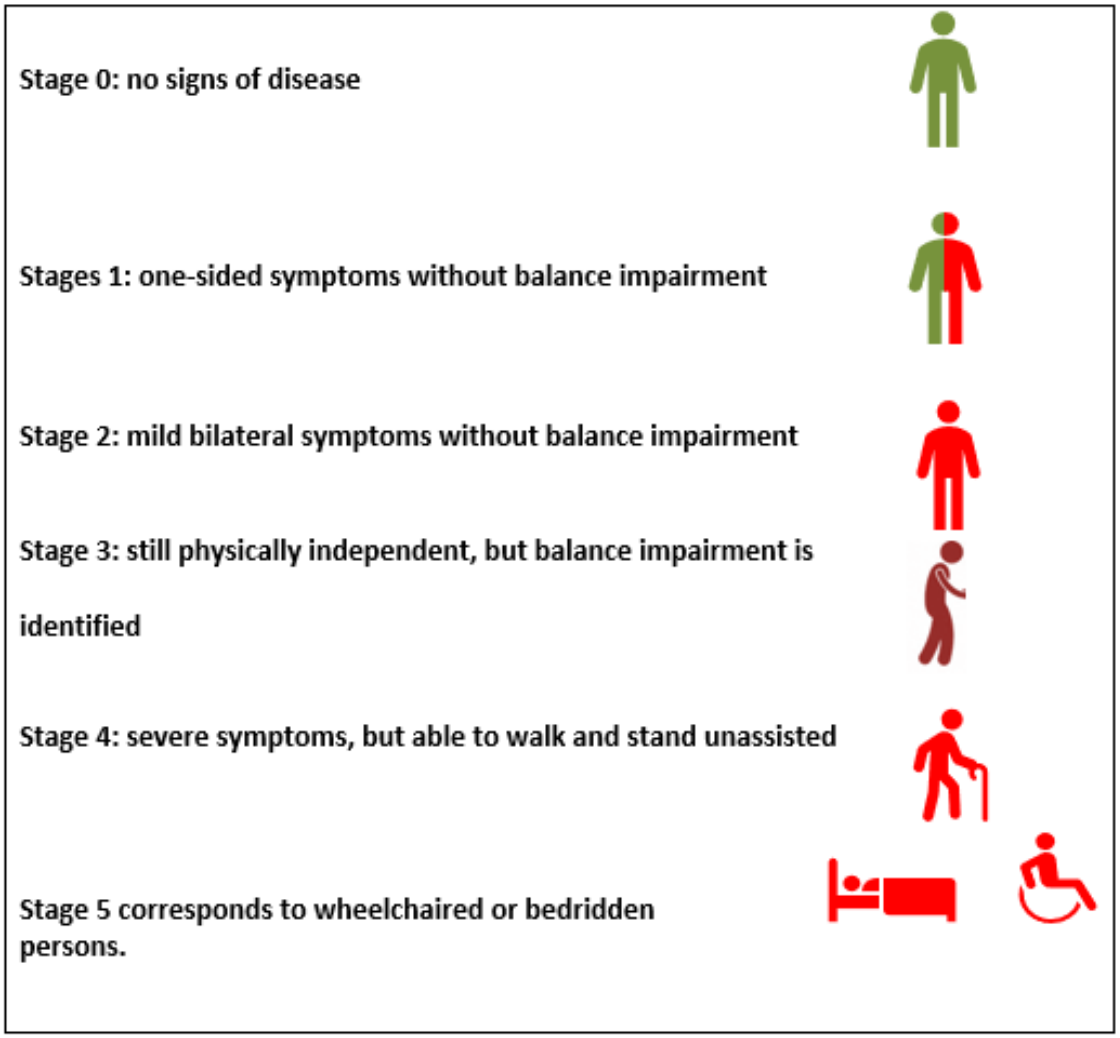


Figure 2: Stages of Hoehn and Yahr Scale

1.6. Clinical features of Parkinson's: non-motor symptoms

Non-motor symptoms appear throughout the course of Parkinson's, comprising a variety of symptoms, including respiratory deficits, neuropsychiatric symptoms, sleep disorders and cognitive impairments (Park and Stacy, 2009).

A review of pulmonary function highlighted the presence of abnormal pulmonary function associated with Parkinson's (O'Callaghan & Walker, 2018). These include: resting dyspnoea(shortness of breath), exertional dyspnoea, and daytime somnolence due to nocturnal hypoxia (Brown, 1994). The majority, however, remain asymptomatic due to the motor manifestations limiting their exercise tolerance (Brown, 1994). This might be due to the low levels of physical activity caused by motor symptoms, during which respiratory function is unchallenged and, consequently, respiratory complaints are not manifest (Polatli et al., 2001).

Dyspnoea is defined as an "unpleasant or uncomfortable awareness of breathing " (American Thoracic Society, 1999). Dyspnoea is a symptom that is usually attributed to impairment in the respiratory system, due to damage or stimulation of peripheral structures (lung parenchyma, upper airways, chest wall, respiratory muscles and vasculature) and central structures (brainstem ventilatory centres response to chemoreceptors in the carotid and aortic bodies) (Vijayan et al., 2020). The mechanisms that may lead to dyspnoea in PLwP is not yet fully known (Vijayan et al., 2020). However, given the widespread pathology of Parkinson's, a combination of effects of the disease on the respiratory system as a whole, sensory and perceptual changes, psychological factors, effects of the medications and/or other comorbidities, could contribute to the development of dyspnoea (Vijayan et al., 2020). As described earlier in this chapter, and according to the Braak hypothesis,

neurodegenerative processes in Parkinson's target the medulla in the brainstem which might affect the respiratory centres leading to the development of dyspnoea (Braak et al., 2011). Additionally, biomechanical factors (specifically diaphragmatic impairment, kyphoscoliosis and chest rigidity) might contribute to inability to expand the lungs in inhalation leading to the stimulation of the stretch receptors of the lungs and to the perception of dyspnoea. The decreased levels of dopamine affect the carotid bodies and subsequently contribute to the perception of dyspnoea in Parkinson's (Braak et al., 2011).

Neuropsychiatric symptoms include: depression; anxiety; fatigue; and psychosis, which includes visual hallucinations followed by auditory hallucinations (Park and Stacy, 2009). Psychosis is mainly caused by both disease progression and levodopa therapy (Poewe, 2003). Around 40% of PLwP are reported to experience depression (Cummings, 1992) and anxiety (Richard et al., 1996). Depression symptoms include lack of energy, sleep disorders, and poor concentration, as well as sadness, suicidal ideation and pessimism depression (Cummings, 1992), whereas anxiety symptoms include generalised anxiety, panic, social phobia, breathlessness, sweating, chest discomfort and restlessness (Richard et al., 1996). Respiratory impairments in PLwP are often mistakenly diagnosed as anxiety or depression (Torsney, 2017).

Sleep disorders affect 60% to 98% of PLwP, and include excessive daytime sleepiness, sleep attacks, early morning awakenings, and rapid eye movement sleep behaviour disorder (Stacy, 2002). Excessive daytime sleepiness was found to be three times more common in PLwP than in the healthy older population, and sleep attacks or sudden sleepiness, either with or without warning, are experienced by around 7% of PLwP (Abbott et al., 2005). Sleep apnoea and sleep disordered breathing, predominantly obstructive was reported in a study of 15 PLwP (Maria,

2003). However, it is not known if respiratory impairment is the main cause of sleeping impairment in Parkinson's.

Cognition impairments are common in PLwP, with a reported 30% diagnosed with dementia; that is, six times higher than the age-matched general population (Aarsland et al., 2001). In a multicentre study, 84% of PLwP showed a decline in cognitive function, and 48% met the diagnostic criteria for dementia (Hely et al., 2005). Cognitive impairment affects quality of life of PLwP and increases the health-economic requirements by increasing the need for nursing home care (Schrag et al., 2000b). Cognitive function is classified into four main domains: executive function, visuospatial impairment, attention, and memory. Executive function is a higher order function including planning, decision making, initiation, organizing, problem solving and evaluation (Lezak, 2004). It has been suggested that the decrease in dopamine level in Parkinson's leads to the disruption of communication between the basal ganglia and the frontostriatal circuits which, in turn, affect the frontal lobes and lead to deficits in higher level functioning (Lezak, 2004). Although PLwP have cognitive impairment because of the pathophysiology of Parkinson's disease itself, respiratory impairment (if found) might contribute to further impairment in cognitive function. This is evidenced in people with chronic obstructive respiratory disease (COPD) (Andrianopoulos, 2017) and acute respiratory distress syndrome (ARDS) (Sasannejad, 2019), but not yet investigated in PLwP.

Visuospatial impairment is the ability to receive, interpret, and apply meaning to shapes, angles and images and to be able to make sense of orientation of an object or image in space (Lezak, 2004). Visuospatial impairment has been reported in PLwP (Levin et al., 1991; Montse et al., 2001; Uc et al., 2005) and is associated with frontal-executive dysfunction in addition to deficit in temporal and parietal

cortices (Pereira et al., 2009). Attention is the ability to focus on an object or stimulus, to maintain concentration for an extended period of time and to resist distraction (Lezak, 2004). Attentional impairment in Parkinson's is associated with executive function impairment, increased risk of falls and gait problems (Allcock et al., 2009). Both visuospatial impairment and attention loss were found to be associated with physical activity level in PLwP (Maeshima, 1997). A decrease in physical activity level might lead over time to a reduction in lung volumes, and subsequently, development of atelectasis (Torsney, 2017).

Memory function is defined as assimilating, storing and retrieving information when needed (Lezak, 2004). PLwP have been found to have impairments in recalling past experience, people, events, objects and recognition of recently stimuli (Breen, 1993; Edelstyn et al., 2007; Edelstyn et al., 2010; Flowers et al., 1984; Higginson et al., 2005). Figure 3 represents the main motor and non-motor impairment in PLwP. Memory loss was found to be affected in people who have sleep disordered breathing and sleep apnoea (Lau, 2015), but was not assessed in PLwP.

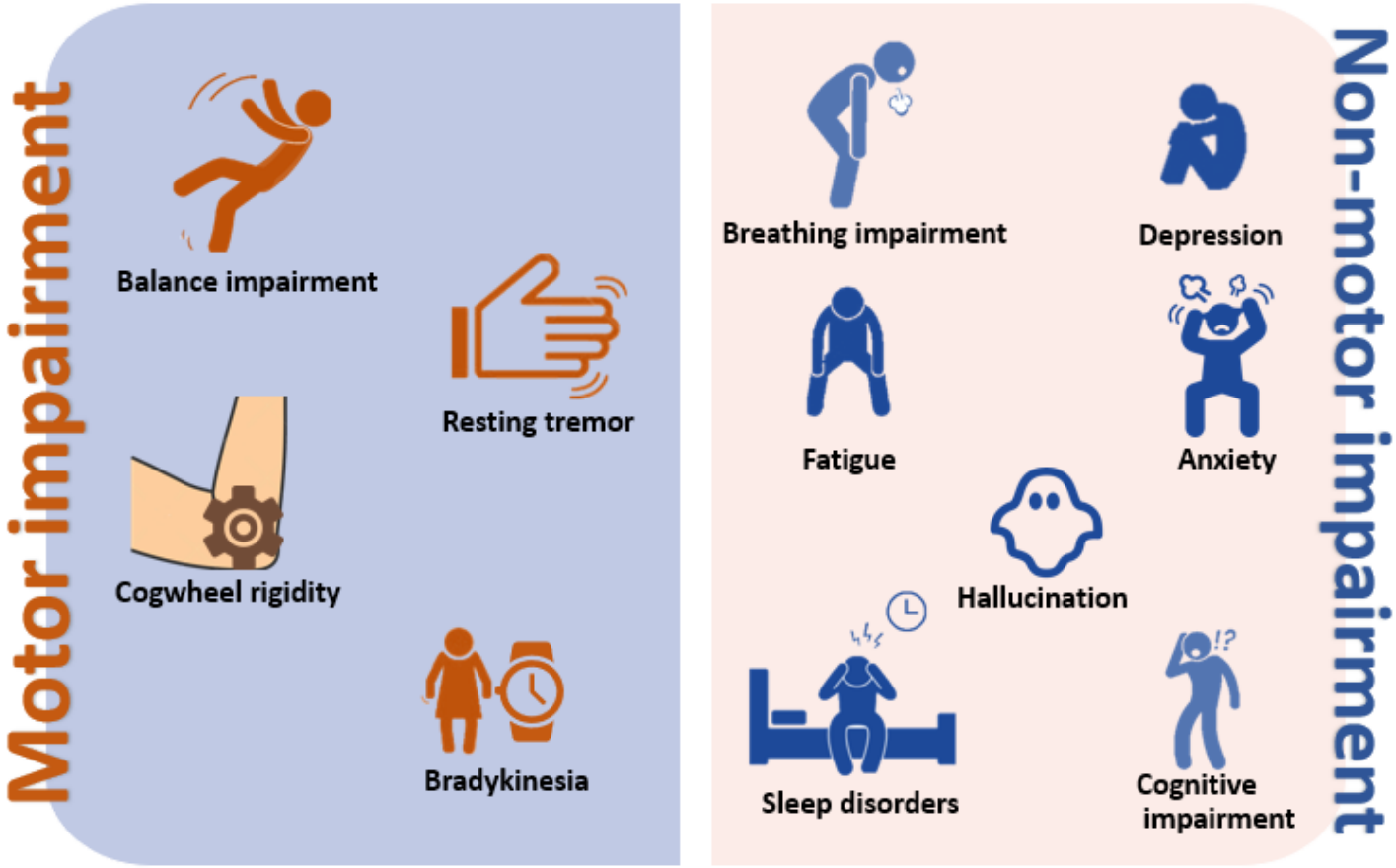


Figure 3: Main motor and non-motor impairment in people with Parkinson's.

1.7. Memory

This section seeks to explain memory classification and the terminology that is used in some chapters within the thesis. The simplest classification of memory is long-term memory (to save information for a long time) and short-term memory (the ability to temporarily save information; also called working memory) (Baddeley, 2007). Long-term memory is often divided into two further main types: declarative (or explicit) memory and implicit (or procedural) memory (Baddeley, 2007).

Implicit memory is the unconscious memory of skills and how to do things such as riding a bicycle or swimming (Baddeley, 2007). Declarative memory is memory of facts and events, and refers to memories that can be consciously recalled (Baddeley, 2007). It consists of information that is explicitly stored and retrieved (Baddeley, 2007).

Declarative memory can be further sub-divided into episodic memory and semantic memory. Semantic memory describes the acts and general knowledge about the world (Collins and Quillian, 1969), whereas episodic memory is defined as the memory of autobiographical events including times, places, people and emotions as a collection of past personal experiences that occurred in a specific time and place (Tulving and Donaldson, 1972). Tulving and Donaldson (1972) differentiated between “knowing”, which is more factual (semantic), and “remembering”, which is a feeling that is located in the past (also called time travelling). Figure 4 summarizes memory classification.

Another classification of memory is that of retrospective and prospective memory. Retrospective memory is remembering people, numbers, words, and events that happened or were faced in the past. Retrospective memory includes all other types of memory such as implicit or explicit, episodic and semantic memories (Baddeley, 2007). On the other hand, prospective memory is remembering something or remembering to do something after a delay, such as failing to mention or give something to a visitor that you were asked to pass on.

1.8. International Classification of Functioning, Disability and Health (ICF) model

The International Classification of Functioning (ICF) framework describes aspects of a person's health and health-related wellbeing at three levels: the individual body parts and functions; the individual as a whole (activity); and the individual in a social context (participation) (Cad, 2001). Within the ICF framework, each of these three levels encompasses different domains.

According to the ICF, body structures can be defined as the anatomical parts of the body, whereas body functions are defined as the physiologic functions of body systems (Cad, 2001). A problem in body function or structure, such as a significant loss, is interpreted as an impairment. For example, the ICF outlines that balance is an integrated function of the vestibular, visual, somatosensory as well as the musculoskeletal systems. Balance underlies a wide range of mobility activities that constitute normal daily life, including walking, and, therefore, impairment in balance is known to have negative effects on mobility activities (Vojciechowski et al., 2016).

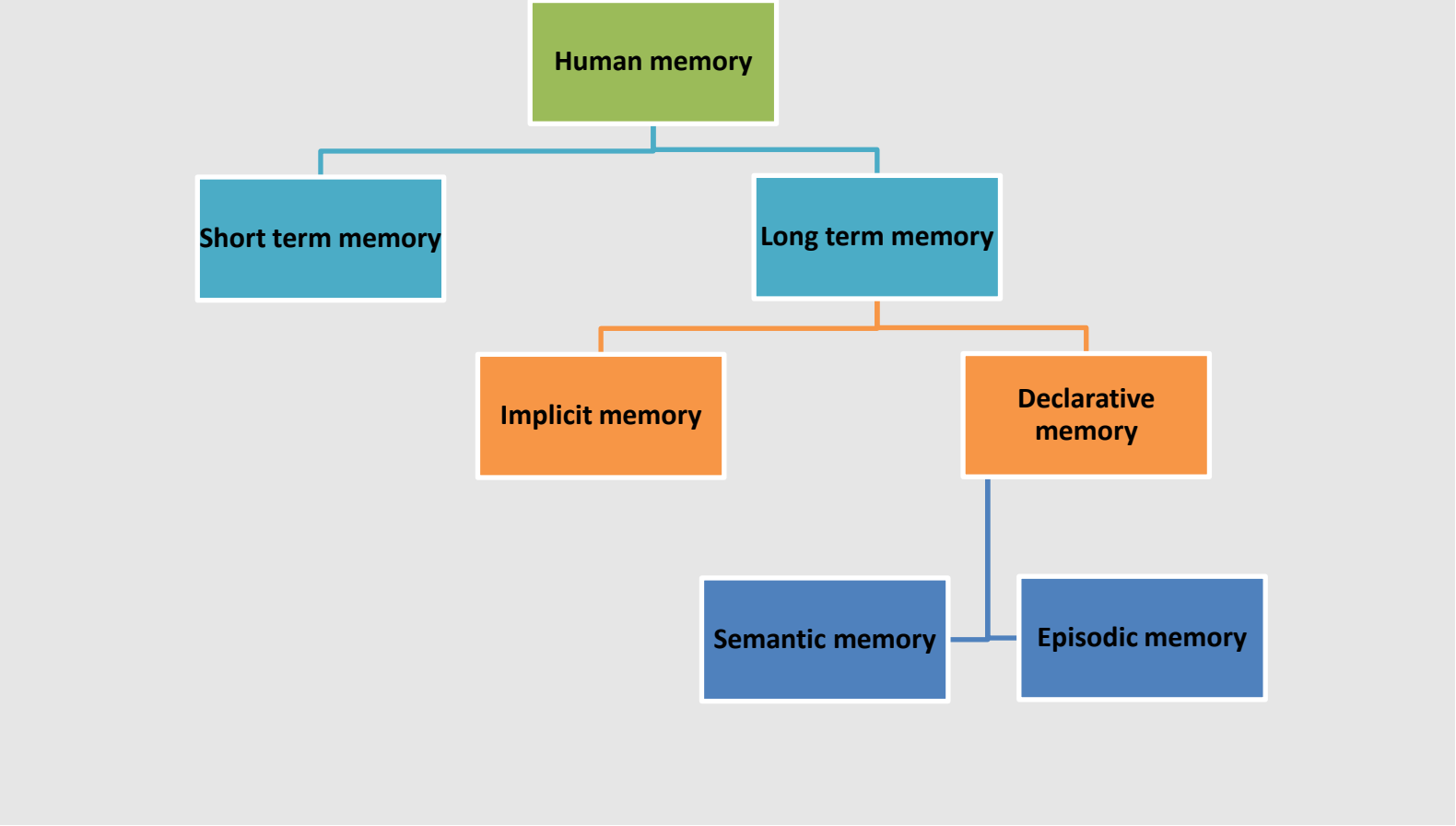


Figure 4: Classification of human memory

Activity forms the intermediate level of the ICF model and is a component of function that involves execution of a task or action by an individual (Cad, 2001). Among the most important and common day-to-day activities are tasks that involve mobility components. The World Health Organization (WHO) defines mobility as the "individual's ability to move about effectively in his/her surroundings" (Minaire, 1992). In a more general and comprehensive sense, mobility can be defined as the process of moving oneself and of changing body position or location (Cieza et al., 2009).

Participation forms the third and the last level of the ICF and can be viewed as the involvement in a life situation, and participation restrictions are problems that individuals may experience in involvement in life situations (Cad, 2001). Participation may be best presented by health-related quality of life measures (Power et al., 1999). Quality of life can be defined as the physical, social and psychological functioning of an individual as being influenced by a disease or therapy (Gotay and Wilson, 1998). It refers to the subject's appraisals of his or her current level of health, functioning, and satisfaction compared to what that person perceives to be ideal. In PLwP, the progressive loss of mobility may put them at risk of falls and lead to functional dependence, the aspects that may detract from health-related quality of life (Vojciechowski et al., 2016).

The ICF takes into account both the personal and environmental contexts that may impact on the functional performance of an activity. In PLwP, personal factors, including cognitive impairments and environmental factors, such as the physical environment and level of supervision required, may have an impact on the mobility tasks (Vojciechowski et al., 2016). Figure 5 shows how the different domains of the ICF in PLwP can be influenced by both individuals and environmental factors.

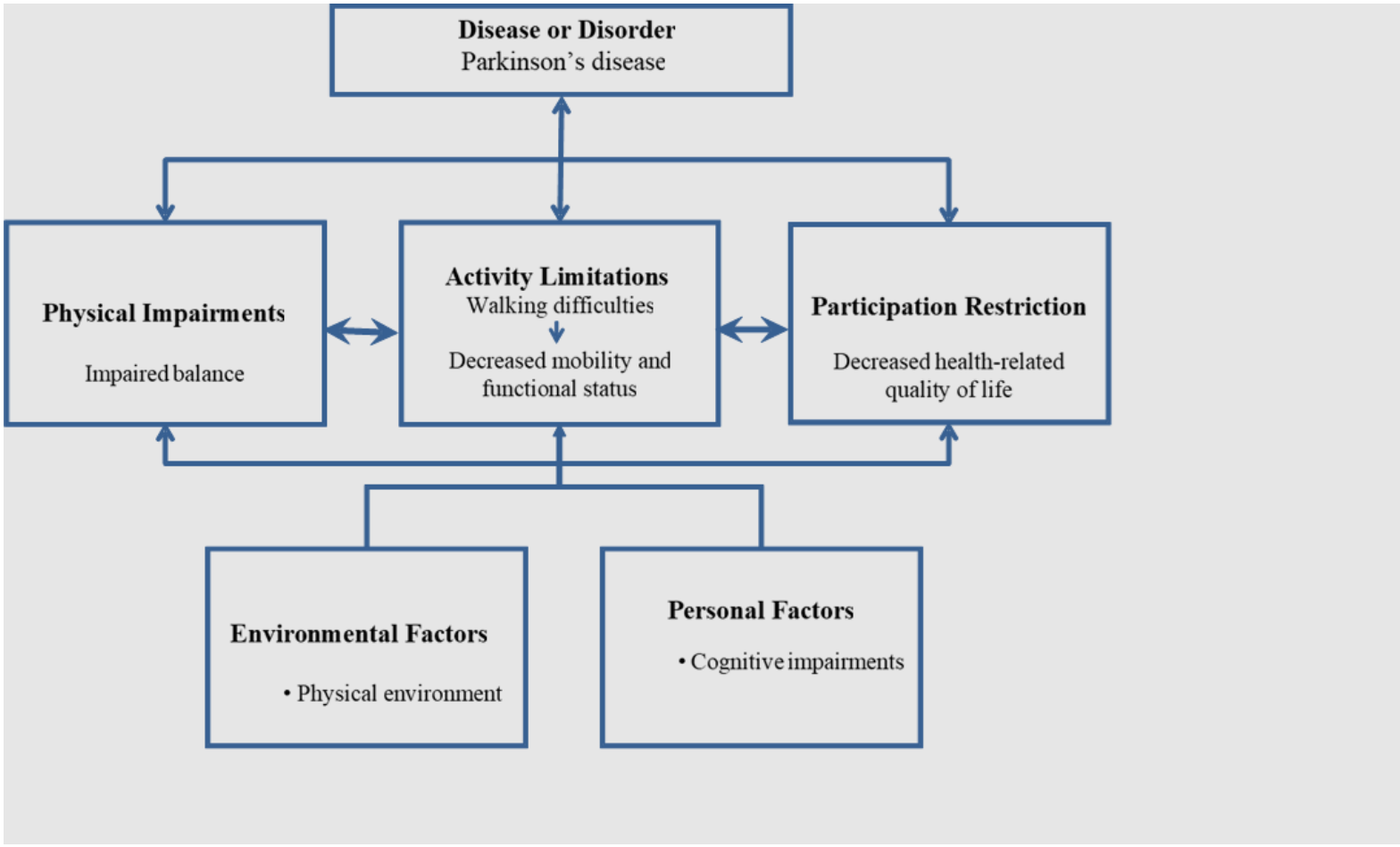


Figure 5: An example of the International Classification of Functioning, Disability and Health (ICF) model for people living with Parkinson's.

1.9. Pulmonary function in Parkinson's

Restrictive and obstructive pulmonary diseases are the main cause of mortality and morbidity in end-stages of Parkinson's (stages IV-V in Hoehn and Yahr) (Ebmeier et al., 1990). However, symptoms of pulmonary impairment do not appear in the early stages of Parkinson's (stages I-III in Hoehn and Yahr) due to the low levels of physical activity caused by motor symptoms, during which respiratory function is unchallenged and subsequently the symptoms do not appear (Polatli et al., 2001). Thus, respiratory impairment might act as a silent threat in the early stages of Parkinson's. A systematic review reported that little is known about respiratory function in neurodegenerative diseases including Parkinson's, and recommended researchers to investigate pulmonary function throughout disease progression, to identify when changes occur and therefore when physiotherapy interventions, for both preventative and restorative, should be implemented (Jones et al., 2016). Therefore, it is important to know whether PLwP have respiratory impairment in the early stages of the disease, and to investigate interventions that might help in improving or delaying respiratory impairment in Parkinson's, so it can be managed early, before symptoms appear.

Lung volumes may be altered in PLwP due to many factors. For example, PLwP have chest wall rigidity, which could lead to decrease in the ability of the lung to stretch and expand in inhalation, leading to decreased lung volumes. Additionally, the impairments in biomechanics of ventilation including diaphragmatic impairment and bucket handle movement impairment might further affect the ability to expand and recoil (Shill and Stacy, 2002). Furthermore, the decreased level of physical activity, might lead to decreased lung volumes and, over time, development of pneumonia and atelectasis (Torsney, 2017). Moreover, the pathophysiology of

Parkinson's itself might include impairment of the respiratory centres in the brainstem, leading to abnormal response to the hypoxemia and hypercapnia (Braak et al., 2011), and subsequently, inability to expand and recoil as needed. Thus, it is important to study lung volumes in PLwP.

The following sections contain a brief introduction to pulmonary function and cardiovascular response to exercise, in which important terminology is defined prior to the subsequent chapters.

1.10. Overview of pulmonary function

This section will describe the pulmonary function terminology and definitions that are used in some chapters within the thesis. Pulmonary function tests (PFTs) are a group of tests that measure how well human ventilation works, the primary purpose being to identify the severity of pulmonary impairment (Burrows, 1975). The PFT is mainly done using a spirometer, which is a device that measures the volume of air that moves in or out of the lungs (Burrows, 1975). Spirometry results include a range of measurements that are summarized in table 1.

Depending on the results of the PFT, pulmonary impairments are mainly divided into two categories: restrictive and obstructive pulmonary diseases (Burrows, 1975). Restrictive pulmonary disease, or restrictive pattern, is characterized by decreased lung volumes, increased work of breathing, and inadequate ventilation and oxygenation, and include pulmonary fibrosis, pneumonia and pulmonary oedema (Saxena, 2015). Obstructive pulmonary disease, or obstructive pattern, is generally characterized by inflamed and collapsible airways and obstruction to airflow; common obstructive diseases include asthma, bronchitis, and emphysema (Saxena, 2015).

In restrictive pulmonary disease, both forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are reduced; however, the FEV_1/FVC ratio is normal or increased (Quanjer et al., 1993). On the other hand, FEV_1 is decreased more than any decrease in FVC in obstructive pulmonary disease, i.e. a decrease in the FEV_1/FVC ratio (Quanjer et al., 1993). Table 2 summarizes spirometry interpretation for restrictive and obstructive patterns.

Table 1: Definitions of the main parameters retrieved during the pulmonary function test (PFT).

Spirometry test	**Abbreviation**	**Definition**
Tidal volume	TV	The volume of air inspired or expired with each normal breath.
Inspiratory reserve volume	IRV	The extra volume of air that can be inspired over and above the normal tidal volume when the person inspires with full force.
Expiratory reserve volume	ERV	The maximum extra volume of air that can be expired by forceful expiration after the end of a normal tidal expiration.
Residual volume	RV	The volume of air remaining in the lungs after the most forceful expiration.
Inspiratory capacity	IC	The amount of air a person can breathe in, beginning at the normal expiratory level and distending the lungs to the maximum amount. It equals the tidal volume plus the inspiratory reserve volume.
Vital capacity	VC	The maximum amount of air a person can expel from the lungs after first filling the lungs to their maximum extent and then expiring to the maximum extent. It equals the inspiratory reserve volume plus the tidal volume plus the expiratory reserve volume.
Forced vital capacity	FVC	The volume of air that can forcibly be expired after full inspiration.
Forced expiratory volume in 1 second	FEV_1	The volume of air that can forcibly be expired in one second, after full inspiration
Peak inspiratory flow	PIF	The maximal flow achieved during the maximal inspiration

Peak expiratory flow	PEF	The maximal flow achieved during the maximally forced expiration initiated at full inspiration.
Maximum voluntary ventilation	MVV	A measure of the maximum amount of air that can be inhaled and exhaled within one minute.

Table 2: Spirometry interpretation for restrictive and obstructive patterns.

Parameter	Obstructive pattern	Restrictive pattern
FVC	↔ or ↓	↓
FEV_1	↓	↓
FEV_1/FVC	↓	↔ or ↑
FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 second; ↓: decreased; ↑: increased; ↔: no change.		

1.11. Cardiovascular response to exercise

This section explains cardiovascular response terminology and definitions that are used in some chapters within the thesis. A cardiopulmonary exercise test (CPET), the golden standard measure of aerobic fitness, is a physical test that measures cardiovascular and respiratory ability to respond to external stress in a controlled clinical environment (Kisner et al., 2017). The CPET is done by challenging the cardiovascular and respiratory system, either by exercise on a treadmill or pedalling on a stationary cycle (Kisner et al., 2017). It is mainly used for fitness level assessment and as a diagnostic tool for coronary heart disease (Medicine, 1991). The CPET assesses cardiopulmonary response to physical stress by a gradual increase in resistance of the cycle ergometer or the speed or incline of the treadmill until the person reaches a maximal exercise capacity (Wasserman et al., 1987). Maximum exercise capacity is defined as “the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to extract oxygen from the blood” (Krikler, 1992). The main cardiopulmonary responses during the CPET are: increases in oxygen consumption (VO_2), heart rate (HR), blood pressure (BP), respiratory rate (RR) and respiratory exchange ratio (RER) (Krikler, 1992). Definitions of CPET measures are summarized in table 3.

Table 3: Definitions of the main measures derived while doing the cardiopulmonary exercise test (CPET).

CPET measure	Definition
Oxygen consumption (VO_2)	The amount of oxygen consumed by the tissues of the body, usually measured as the oxygen uptake in the lung.
Workload (W)	The speed and/or grade of the treadmill or the resistance on the bicycle ergometer that the person can achieve.
Heart rate (HR)	Number of heart beats per minute.
Respiratory rate (RR)	Number of breaths per minute
Systolic blood pressure (SBP)	Maximum arterial pressure during contraction of the left ventricle of the heart.
Respiratory exchange ratio (RER)	The ratio of carbon dioxide output/oxygen uptake.
Test duration	The maximum number of minutes that the patient can tolerate while doing the cardiopulmonary exercise test.

1.12. Respiratory impairment management guidelines for Parkinson's

The European Physiotherapy Guidelines for Parkinson's Disease (2018) and the National Institute for Health & Care Excellence (NICE) guidelines for Parkinson's disease (2019) included recommendations for respiratory muscle training, and management of ineffective cough using air stacking, mechanical insuflation-exsufflation, glossopharangeal breathing, and manually assisted cough. However, the guidelines did not include techniques to improve lung volumes, and did not include recommendations for management of respiratory impairment in the early stage of Parkinson's. Similarly, the British Thoracic Society / The Association of Chartered Physiotherapists in Respiratory Care (Bott, 2009) guidelines for spontaneously breathing patients focuses on neuromuscular disease but does not give detail for neurodegenerative conditions including Parkinson's. Thus, it is important to investigate if any other physiotherapy/ exercise interventions are going to improve respiratory function in PLwP.

1.13. Chapter summary

This chapter has presented the definition of Parkinson's, pathophysiology of the disease, prognosis, clinical features and the ICF model. Also, it explained the main terminology used in pulmonary function, cardiovascular response, and memory, which will be used in this thesis.

Additionally, this chapter presented factors in PLwP that might contribute in developing type 1 and type 2 respiratory failure, including: chest wall rigidity; ankylosis of costosternal and thoracovertebral joints; kyphoscoliotic posture; decreased physical activity level; atelectasis; aspiration pneumonia; and impaired respiratory drive. However, more information is needed about respiratory function in PLwP in terms of having restrictive or obstructive pulmonary pattern, and if any intervention is going to improve lung volumes at the early stages of Parkinson's.

Thus, the thesis will continue with the next chapter, which presents reviews of what is known about pulmonary function, cardiovascular response to exercise, and the effects of aerobic training on cardiopulmonary function in PLwP, and provides further context for the research and development of the research questions.

Chapter 2: Literature Review

2.1. Overview

In developing the research presented in this thesis, a systematic search of the literature was conducted, with narrative synthesis of findings, to identify the prevalence of cardiopulmonary impairments in Parkinson's, and determine the effects of aerobic interventions on pulmonary function and cardiovascular response to exercise.

This chapter is divided into six main sections. This first section provides an overview of the chapter. Sections 2.2 to 2.4 include reviews of the following literature:

- Pulmonary function in Parkinson's
- Cardiovascular response to exercise in Parkinson's
- Cardiopulmonary function and aerobic exercise in Parkinson's

Section five will include a summary of the three reviews and development of research questions. The last section will include specific objectives for the thesis.

2.2. Pulmonary function in Parkinson's

Although respiratory diseases are considered to be the main complaint in end-stages of Parkinson's (stages IV-V in Hoehn and Yahr) (Ebmeier et al., 1990), respiratory symptoms do not usually appear in the early stages of the disease (stages I-III in Hoehn and Yahr) (Polatli et al., 2001), acting as a silent threat. Thus, it is important to know if abnormal respiratory patterns (obstructive, restrictive or mixed pattern) exist in the early stages of Parkinson's. Subsequently, this review aims to review and summarise published literature on the prevalence of obstructive and restrictive pulmonary disease in Parkinson's.

2.2.1. Methodology

2.2.1.1. Purpose

The study objective was to review the published literature on prevalence of pulmonary function during the early stages of Parkinson's, and factors affecting pulmonary disease if found. To achieve this, the outcomes were defined as prevalence of abnormal pulmonary pattern as measured by the forced expiratory volume in one second (FEV_1) forced vital capacity (FVC) and FEV_1/FVC.

2.2.1.2. Design

A literature review with systematic search, quality assessment and narrative synthesis of relevant published literature.

2.2.1.3. Search strategy

A search was conducted through EBSCO using the following electronic databases: MEDLINE, AMED, and CINAHL Plus. The databases were searched for studies published between 1st January 1970 and 1st May 2020, with results of the searches managed using Endnote Version X7 (Clarivate Analytics, Philadelphia, USA). Keywords used in the search included "Parkinson's disease", "Parkinson's", "pulmonary function", "respiratory function", "spirometry" and "spirometer". Both retrospective and prospective observational studies were included. Papers were included if they reported pulmonary function tests (PFTs) in PLwP. Papers were excluded if they: examined PFT after interventions; were a pre-clinical study (animal model studies); were not written in English; or were a conference abstract.

2.2.1.4. Study selection

Following the search and subsequent removal of duplicates, titles and abstracts were screened independently by two researchers for relevance. Full texts of

relevant observational studies were then screened for eligibility against inclusion and exclusion criteria.

2.2.1.5. Data extraction

The following data were extracted from the included studies and recorded: age, sex, disease severity (by means of Hoehn and Yahr), sample size, pulmonary pattern (restrictive, obstructive, mixed obstructive and restrictive or normal pattern), and main results.

2.2.1.6. Risk of bias and quality of reporting

The quality of reporting of the studies was assessed by one person using the cross-sectional studies assessment items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement checklist (Von Elm et al., 2007); see table 4.

2.2.2. Results

In total, 205 citations were identified from the databases. Duplicates (n=36) were removed, and titles and abstracts of the remaining 169 citations were screened for inclusion/exclusions based on relevance. Then, full-text screening was conducted (n=33) according to the inclusion and exclusion criteria. Following exclusion of 155 citations, 14 articles were included in this review. None of the studies reported the ethnicity of the participants. Figure 6 represents search records and number of excluded and included articles. Results of the STROBE checklist for the included articles are presented in table 4.

Table 5 represents a summary of the main results of the 14 included studies, of which one reported movement of chest wall muscles and 13 reported pulmonary patterns on spirometry (restrictive or obstructive, or mixed of both patterns).

Table 4: Results of the adapted STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies.

	Checklist points	Included articles Author, year													
		Alonso et al., 1994	De Pandis et al, 2002	Guimarães et al., 2018	Hampson et al., 2017	Hovestadt et al., 1989	Monterio et al., 2014	Obenour et al., 1972	Owolabi et al., 2016	Polatli et al., 2001	Sabaté et al., 1996	Santos et al., 2019	Sathyaprabha et al., 2005	Tamaki et al., 2000	Wang et al, 2014
	(a) Indicate the study's design with a commonly used term in the title or the abstract	✓	×	✓	✓	✓	✓	×	✓	×	×	✓	×	✓	✓
	(b) Provide in the abstract an informative and balanced summary of what was done and what was found	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Background/ rationale	Explain the scientific background and rationale for the investigation being reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Objectives	State specific objectives, including any prespecified hypotheses	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Study design	Present key elements of study design early in the paper	✓	×	✓	✓	✓	✓	×	✓	✓	×	✓	✓	✓	✓
Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓	×	✓	×	×	✓	×	✓	×	✓	✓	✓	×	✓
Participants	(a) Give the eligibility criteria, and the sources and methods of selection of participants	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓

Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bias	Describe any efforts to address potential sources of bias	×	×	×	✓	×	✓	×	×	×	×	×	×	×	×
Study size	Explain how the study size was arrived at	×	×	×	×	×	×	×	×	✓	×	×	×	×	×
Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	×	×	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓
Statistical methods	(a) Describe all statistical methods, including those used to control for confounding	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓
	(d) Describe any sensitivity analyses	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Participants	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Descriptive data	(a) Give characteristics of study participants (e.g. demographic, clinical)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

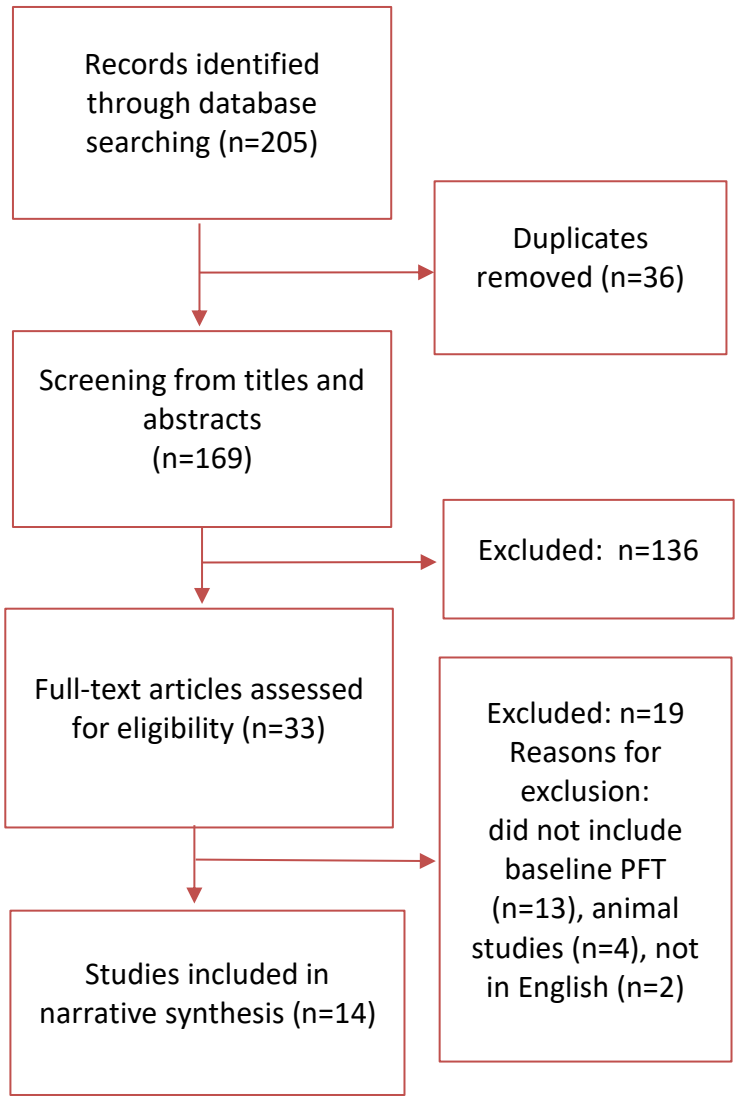


Figure 6: Flow-Chart of the search records. PFT: pulmonary function test.

Table 5: A summary of the main findings of studies included in the review of prevalence of pulmonary function in people with Parkinson's.

Author, year	**Sample size**	**Age mean (SD) - years**	**Male: female**	**Hoehn & Yahr stage**	**Pulmonary pattern**	**Main results**
Alonso et al., 1994	63	67.1 (0.9)	24:39	I-V	Mixed	Abnormal flow-volume loop in 49.2% of the sample. Lower FVC (p<0.05), and FEV_1 (p<0.001) than healthy controls.
De Pandis et al, 2002	12	67.7 (5.4)	4:12	>III (severe)	Restriction	Lower FVC (mean (SD)=76.83 (26.74), p<0.005) and FEV_1 (mean (SD)= 77.91 (28.88), p<0.05) in PLwP compared to healthy controls.
Guimarães et al., 2018	60	69 (5)	N/A	II-III	Mixed	Mixed pattern with low FEV_1/FVC (mean (SD)=63.25(18.60)).
Hampson et al., 2017	86	62.4 (8.7)	57:29	I-III	Normal	All spirometer values were within normal reference ranges of FEV_1 (mean (SD)=89.7(15.5)), FVC (mean (SD)=85.6 (14.9)), FEV_1/FVC (mean (SD)=79.6 (3.6)).
Hovestadt et al., 1989	31	64.6 (9.1)	16:15	>III (severe)	Obstruction	Upper airway obstruction when compared with healthy controls indicated by low PIF (p < 0.01) and PEF (p < 0.01).
Monterio et al., 2014	30	61.6 (10.7)	17:13	I-III	Obstruction	Lower FVC (mean (SD)=66.2(15.3) in PLwP vs. 90.2 (18.6) in controls, p<0.001)), FEV_1 (mean (SD)= 75.0 (16.0) in PLwP vs 90.2 (18.6) in controls, p<0.005)), and FEV_1/FVC (mean (SD)=84.4 (5.8) in PLwP vs.86.3 (27.5) in controls, p<0.04).
Obenour et al., 1972	31	67.4 (8.1)	18:13	N/A	Obstruction	Lower FEV_1 (mean (SD)=1.8 (0.7)) and FEV_1/FEV (mean (SD)= 60(11)) compared with healthy controls (p < 0.05).

Owolabi et al., 2016	78	63.3 (8.6)	60:18	N/A	Obstruction	Lower FEV_1 (mean=1.887), FVC (mean=2.48), and FEV_1/FVC (mean= 75.812) in PLwP than healthy controls (p<0.0001).
Polatli et al., 2001	21	62.5 (11.3)	10:11	I-III	Mixed	Lower FEV_1 (mean (SD)= 68.6 (19.7), P<0.03), FVC (mean (SD)= 83.42 (12.24), P<0.01), and MVV (mean (SD)= 52.83 (15.52), p<0.0001).
Sabaté et al., 1996	58	67.7 (1.0)	N/A	N/A	Mixed	Lower FVC, FEV_1 (mean (SD)= 88.7 (23.8), p<0.001) and FEV_1/FVC (mean (SD)= 86.3 (10.1), p<0.0001).
Santos et al., 2019	49	63 (8)	N/A	I-III	Mixed	Respiratory muscle strength and lung function are impaired from the early stages of Parkinson's. Bradykinesia and rigidity being the cardinal signs that correlate strongly with impairment of PFT values (p<0.001). FEV_1 (mean (SD) in H&Y stage 1= 2.4 (0.5), stage 2=2.2 (0.7), stage 3=1.7 (0.7)). FVC (mean (SD) in stage 1=85 (12), stage 2= 79 (18), stage 3=61 (22)).
Sathyaprabha et al., 2005	53	53.0 (10)	N/A	I and II	Restriction	Lower FVC (mean (SD)= 56.0 (14.5), p<0.001), FEV_1 (mean (SD)= 61.7 (16.5), p<0.001) in PLwP compared with healthy controls.
Tamaki et al., 2000	7	57.3 (14.5)	6:1	N/A	N/A	Thoraco-abdominal movement was associated with VC and FVC.
Wang et al, 2014	30	61.8 (4.2)	16:14	II-V	Mixed	Lower FVC (mean (SD)= 74.77 (13.92)), higher RV (mean (SD)= 122.66 (26.54), lower FEV_1 and lower FVC (mean (SD)= 56.67 (20.10) p<0.05.

FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; VC: vital capacity; MVV: maximum ventilatory volume; PEF: peak expiratory flow; PIF: peak inspiratory flow; RV: reserve volume; N/A: information not available.

Restrictive pulmonary pattern was reported in 28% to 94% in people in the early stages of Parkinson's (De Pandis et al., 2002; Sathyaprabha et al., 2005) while obstructive pulmonary pattern varied from 6% to 67% (Hovestadt et al., 1989; Monteiro et al., 2014; Obenour et al., 1972; Owolabi et al., 2016). Additionally, six studies reported mixed obstructive and restrictive pattern in PLwP during the early stages of the disease (Guimarães et al., 2018; Izquierdo-Alonso et al., 1994; Polatli et al., 2001; Sabaté et al., 1996; Santos et al., 2019; Wang et al., 2014). Eight studies included people in the early stages of Parkinson's (I-III in Hoehn and Yahr), two studies included severe stages, and four studies did not report Hoehn and Yahr stages in their publication (table 5).

In contrast, one study reported normal pulmonary function test values, with no restrictive or obstructive pattern (Hampson et al., 2017). Although this study included the largest sample size (n=96), inclusion was restricted to people with an FEV_1/FVC >75% of the predicted value, excluding people who already have obstructive pulmonary disease (Hampson et al., 2017). This could explain why the findings of this study were different from those reported by the other studies.

2.2.3. Discussion

This is the first review summarising literature on prevalence of pulmonary function in the early stages of Parkinson's (H&YI-III). The search included relevant studies from the last 40 years and involved independent screening by two reviewers. This review has shown that only a small number of studies have investigated impaired pulmonary function in the early stages of Parkinson's. these studies did not report ethnic backgrounds. Subsequently, the results could not be generalised to all ethnic populations, as they have not been included in these studies, and there may be differences in pulmonary patterns with other populations. There may be differences

in pulmonary patterns with different ethnicities (Wyss, 2018), due to gene expression, and the multiethnic nature (Wyss, 2018). Additionally, differences in management of Parkinson's in the early stages among different countries, and different physiotherapy, conservative and traditional treatment might cause differences in pulmonary function. However, no research was conducted on difference of pulmonary function among different ethnicities in PLwP, yet. Out of the 14 studies, 13 studies reported pulmonary pattern and the other study investigated chest wall muscle movement. Out of those 13 studies reporting pulmonary pattern, two reported restrictive pattern, four reported obstructive pattern, six reported mixed obstructive and restrictive patterns, and only one reported normal pattern.

This variation in results, in terms of obstructive, restrictive or mixed pattern, might be because of the difference in disease stages included in the studies and whether Levodopa was administered or whether smokers were included in the studies (De Pandis et al., 2002; Polatli et al., 2001; Sathyaprabha et al., 2005). For example, it has been reported that as the disease progresses to Hoehn and Yahr stages IV and V, the prevalence of restrictive patterns is higher than that in stages I–III (Izquierdo-Alonso et al., 1994; Santos et al., 2019). Even between stages I-III, the results of pulmonary function tests have been reported to be more severe in people who are in Hoehn and Yahr stage II than in stage I (Santos et al., 2019; Sathyaprabha et al., 2005). Similarly, obstructive pulmonary pattern has been found to have a higher prevalence in people with stage III than people in stage I and II (Polatli et al., 2001; Santos et al., 2019; Sathyaprabha et al., 2005).

The increase in severity and prevalence of restrictive and obstructive pulmonary patterns with progression of the disease could be explained by an increase in rigidity of chest wall muscles, which may result in kyphoscoliosis (Baille et al., 2016;

Santos et al., 2019); this may, in turn, lead to decrease in lung volume (Black and Hyatt, 1971; Sabaté et al., 1996). Furthermore, rigidity of chest wall muscles leads to decrease in the elasticity of the lungs' parenchyma and subsequently ability to expand the lungs. The chest muscle rigidity in Parkinson's is supported by an electromyographic study, which reported a decrease in respiratory muscle activity in Parkinson's during inspiration (Estenne et al., 1984).

The decrease in lung elasticity leads to decrease in the stretch during inspiration and recoil ability during expiration (Estenne et al., 1984). The decrease in lung stretching ability during inspiration may lead to a restrictive pattern, and the decrease of the recoiling ability during expiration may lead to an obstructive pattern (Estenne et al., 1984). It has been well known that the loss of alveolar wall elasticity leads to dynamic hyperinflation of the lungs, and subsequently increase in the residual volume and dead space, and decrease in the vital capacity (O'donnell et al., 2001).

PLwP who are being treated with Levodopa have shown improvements in pulmonary function tests post-medication compared with pre-medication (Polatli et al., 2001; Sathyaprabha et al., 2005; Wang et al., 2014), and a 41%-48% lower prevalence of obstructive pattern prevalence than in untreated Parkinson's (Obenour et al., 1972). This may be explained by the decrease in motor symptoms after taking the medication, and by improvement in aerobic fitness. Furthermore, taking the medication may result in decreased chest wall muscle rigidity and associated kyphoscoliosis, reducing their negative effect on lung elasticity and resultant impairment of pulmonary function (Obenour et al., 1972; Sathyaprabha et al., 2005; Stacy, 2002).

2.2.4. Conclusion and recommendations

Overall, it is too early to draw clear conclusions about lung function from these studies, and further studies are recommended with larger longitudinal samples to see the long-term respiratory manifestations, and with full respiratory file investigations, including spirometry, chest X-ray, exercise tolerance and clinical symptom investigations. Evaluation of pulmonary impairments is needed, as well as the investigation of interventions that could help to improve lung function in the early stages of the disease to decrease the impairment and to prevent the respiratory complications resulting from the abnormal patterns. Additionally, it is recommended to assess and report pulmonary function in PLwP with different ethnicities.

2.3. Cardiovascular response to exercise in Parkinson's

A number of studies (for example: Cruise et al., 2011; Dibble et al., 2009) have assessed the effects of exercise and physical activity on balance, mobility, quality of life and cognitive function in PLwP. However, there has been limited research on cardiovascular response to exercise in Parkinson's. This section includes a literature review that aimed to summarize cardiorespiratory response to exercise and factors that affect cardiorespiratory response in PLwP.

2.3.1. Methodology

2.3.1.1. Purpose and design

The study objective was to review the published literature on cardiovascular response to exercise during the early stages of Parkinson's, and factors affecting pulmonary disease, if found. To achieve this, the outcomes were defined as prevalence of high, low or similar cardiovascular response to exercise in PLwP compared with healthy people as measured by the VO_{2peak} or VO_{2max} (using the cardiopulmonary exercise test: CPET).

Study design: a review with quality assessment and narrative synthesis of relevant published literature.

2.3.1.2. Search strategy

A search was conducted through EBSCO using the following electronic databases: MEDLINE, AMED, and CINAHL Plus. The databases were searched for studies published between 1st January 1970 and 1st May 2020, with results of the searches managed using Endnote Version X7 (Clarivate Analytics, Philadelphia, USA). Keywords included “Parkinson’s disease”, “Parkinson’s”, “cardiovascular response”, “cardiopulmonary response”, “exercise stress test”, “exercise test”, cardiopulmonary exercise test” and “graded exercise test”. Papers were excluded if they: did not include CPET; examined CPET after interventions; were not written in English; or were conference abstracts. Papers were included if they: were cross-sectional in design; included CPET; included PLwP.

2.3.1.3. Study selection

Following the search and subsequent removal of duplicates, titles and abstracts were screened independently by two researchers for relevance. Full texts of relevant studies were then screened for eligibility against inclusion and exclusion criteria.

2.3.1.4. Data extraction

The following data were extracted from the included studies and recorded: age, sex, disease severity (by means of Hoehn and Yahr), sample size, protocol used for the CPET, and main results.

2.3.1.5. Risk of bias and quality of reporting

The quality of reporting of the studies was assessed by one person using the cross-sectional studies assessment items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement checklist (Von Elm et al., 2007); see table 6.

Table 6: Results of the adapted STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies.

	Checklist points	Included articles Author, year											
		Bryant et al, 2016	Canning et al, 1997	DiFrancisco-Donoghue et al, 2009	Haas et at, 2016	Kanegusuku et al, 2016	Mavrommati et al., 2017	Protas et al, 1996	Roberson et al., 2019	Speelman et al, 2012	Strano et al, 2016	Werner et al., 2006	Yahalom et al, 2014
	(a) Indicate the study's design with a commonly used term in the title or the abstract	✓	×	✓	✓	✓	✓	×	✓	×	×	✓	×
	(b) Provide in the abstract an informative and balanced summary of what was done and what was found	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Background/ rationale	Explain the scientific background and rationale for the investigation being reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Objectives	State specific objectives, including any prespecified hypotheses	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Study design	Present key elements of study design early in the paper	✓	×	✓	✓	✓	✓	×	✓	✓	×	✓	✓
Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓	×	✓	×	×	✓	×	✓	×	✓	✓	✓

Participants	(a) Give the eligibility criteria, and the sources and methods of selection of participants	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bias	Describe any efforts to address potential sources of bias	×	×	×	✓	×	✓	×	×	×	×	×	×
Study size	Explain how the study size was arrived at	×	×	×	×	×	×	×	×	✓	×	×	×
Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	×	×	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
Statistical methods	(a) Describe all statistical methods, including those used to control for confounding	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
	(d) Describe any sensitivity analyses	×	×	×	×	×	×	×	×	×	×	×	×
Participants	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Descriptive data	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	information on exposures and potential confounders													
Outcome data	Report numbers of outcome events or summary measures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Main results	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Key results	Summarise key results with reference to study objectives	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	×	×	✓	✓	×	✓	×	✓	×	×	×	×	
Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓	✓	✓	✓	×	✓	×	✓	×	×	×	×	
Generalisability	Discuss the generalisability (external validity) of the study results	×	×	×	×	×	×	×	×	×	×	×	×	
Funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

2.3.2. Results

In total, 351 citations were identified from the databases. Duplicates (n=121) were removed, and titles and abstracts of the remaining 230 citations were screened for inclusion based on relevance. Then, full-text screening was conducted (n=33) according to the inclusion and exclusion criteria. Following exclusion of 218 citations, 12 articles were included in this review. Figure 7 represents search records and number of excluded and included articles. Results of the STROBE checklist for the included articles are presented in table 6.

Nine studies have investigated the cardiovascular response to exercise using a maximal CPET (Bryant et al., 2016; Canning et al., 1997; DiFrancisco-Donoghue et al., 2009; Haas et at., 2016; Kanegusuku et al., 2016; Mavrommati et al., 2017; Roberson et al., 2019; Strano et al., 2016; Yahalom et al., 2014), and three studies assessed cardiovascular response to exercise at submaximal CPET (Protas et al., 1996; Speelman et al., 2012; Werner et al., 2006); see table 7.

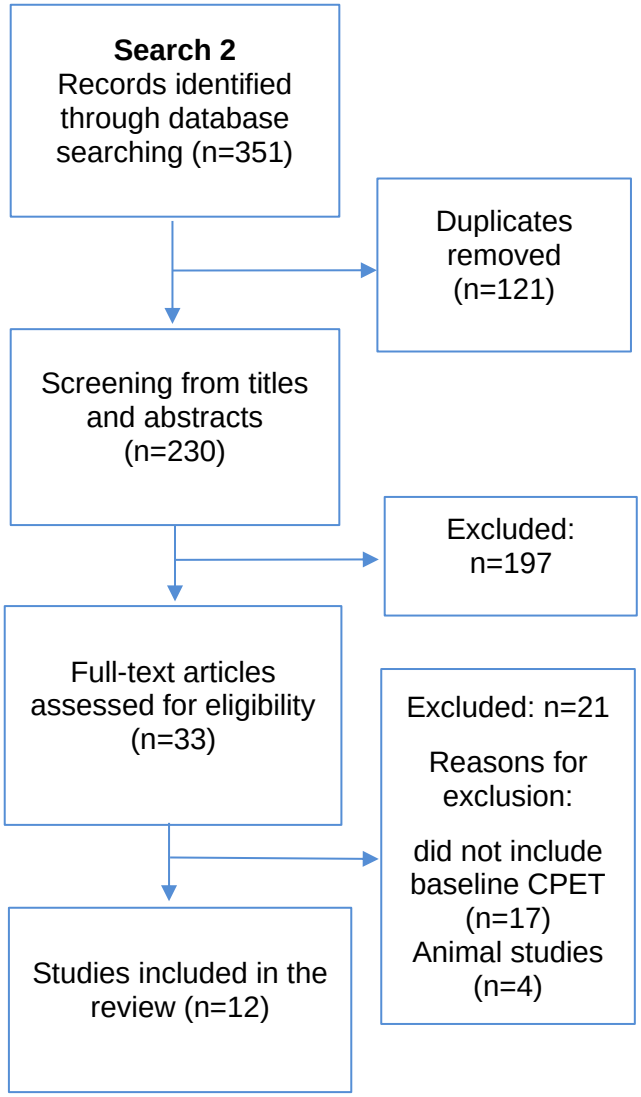


Figure 7: Flow-Chart of the search records. CPET: cardiopulmonary exercise test.

Table 7: Summary of papers related to cardiovascular response in Parkinson's.

Author	Sample size	Age mean (SD)	Male/ Female	Hoehn & Yahr	Protocol	Results
Bryant et al, 2016	45 PLwP	69.3(8.3)	34/11	II-III	CPET using the modified Bruce protocol (treadmill).	Around 60 % could not complete the test to the maximum intensity, reporting fatigue, shortness of breath, pain, difficulty walking, or arm fatigue.
Canning et al, 1997	16 PLwP	54.2(4.5)	13/3	I-III	CPET using Astrand-protocol (cycle).	In maximal exercise test, PLwP had similar peak VO_2 and workload to normal values.
DiFrancisco-Donoghue et al, 2009	14 PLwP	67.7(6.8)	14/0	I-III	CPET (Treadmill), Bruce protocol	Lower HR and BP but not lower VO_2 in PLwP than healthy controls in maximal CPET.
Haas et at, 2016	18 PLwP	65.1(6.2)	15/3	I-IV	CPET (cycle).	16 out of the 18 terminated the test because of leg fatigue and one participant because of knee pain.
Kanegusuku et al, 2016	48 PLwP	66(8)	35/13	I-III	CPET using ramp protocol (cycle).	In maximal intensity, PLwP showed lower HR, SBP and VO_2 than healthy controls.
Mavrommati et al., 2017	83 PLwP 55 healthy controls	67(8)	61/22	I-III	CPET (cycle)	Lower HR, VO_2 L/min, VCO_2 L/min and ventilation L/min in the PLwP group than healthy controls.
Protas et al, 1996	8 PLwP	61(10)	8/0	II-III	CPET (cycle)	Submaximal HR and VO_2 were higher in the PLwP group than healthy controls.

Roberson et al., 2019	14 PLwP 16 healthy controls	68.9(12.1)	N/A	I-III	CPET (cycle)	Lower HR, SBP and DBP in PLwP.
Speelman et al, 2012	546 PLwP	64(7.7)	360/186	I-III	CPET using Astrand-Rhyming (cycle).	Around 50% didn't complete the CPET. Height, weight and lower SBP were associated with the inability to sufficiently increase HR during the submaximal test.
Strano et al, 2016	18 PLwP	59.3(10.5)	12/6	I-II	CPET (cycle).	Peak VO_2 and maximum workload were lower than normal values.
Werner et al., 2006	16 PLwP	64.1(12.3)	10/6	NA	CPET using modified Bruce protocol (treadmill)	In submaximal exercise, no significant differences were found between the groups for HR or BP. At peak exercise, BP, but not HR, was significantly higher for the control group.
Yahalom et al, 2014	28 PLwP out of 16841 subjects	64.8(8.8)	24/4	Retrospective study	CPET using Bruce protocol (treadmill).	Similar maximal heart rate profile for those who developed Parkinson's compared to those who did not develop Parkinson's.
PLwP: people Living with Parkinson's; CPET: cardiopulmonary exercise test; HR: heart rate; SBP: systolic blood pressure; VO_2: oxygen consumption; BP: blood pressure.						

Contradictory cardiovascular responses to maximal exercise test in PLwP have been reported (Bryant et al., 2016; Canning et al., 1997; Kanegusuku et al., 2016; Mavrommati et al., 2017; Protas et al., 1996; Roberson et al., 2019; Speelman et al., 2012; Strano et al., 2016; Werner et al., 2006; Yahalom et al., 2014). Some authors (Kanegusuku et al., 2016; Mavrommati et al., 2017; Roberson et al., 2019; Speelman et al., 2012; Strano et al., 2016; Werner et al., 2006) reported lower maximum responses of oxygen uptake (VO_2), heart rate (HR) and systolic blood pressure (SBP) in the early stages of Parkinson's (Hoehn and Yahr stages I-III) in comparison with age-matched controls in response to cycle and treadmill exercise tests. One study (Canning et al., 1997) found no differences in maximum cardiovascular responses between people with early stages of Parkinson's (Hoehn & Yahr I-III) and healthy controls in response to the cycle exercise test, whilst another (DiFrancisco-Donoghue et al., 2009) reported lower heart rate and blood pressure, but not lower VO_2, in a maximal cycle CPET in the early stages of the disease (I-III in Hoehn and Yahr).

Achieving maximal responses may be difficult in PLwP because of the motor symptoms of the disease (Katzel et al., 2011). Thus, evaluation of the submaximal cardiopulmonary responses to exercise may bring added knowledge. Studies that assessed cardiovascular response to exercise using submaximal testing reported contradictory findings in PLwP. One study (Werner et al., 2006) reported similar submaximal responses to exercise at the same workload in PLwP and age-matched controls. Speelman et al. (2012) reported lower VO_2 in PLwP compared with age matched healthy controls in submaximal intensities. On the other hand, Protas et al. (1996) reported higher VO_2 at submaximal workloads in PLwP than healthy age-matched controls.

In order to understand if the cardiovascular response is a pre-motor symptom in Parkinson's disease, a retrospective cohort study was done, with 16841 PLwP (Yahalom et al., 2014). Those who developed Parkinson's disease (n=28) had a similar maximum heart rate profile to those who did not.

Termination of the CPET in PLwP seems to be related to factors other than cardiovascular disorders, including leg fatigue, arm fatigue, knee pain or shortness of breath (Bryant et al., 2016; Haas, 2016). In addition, height, weight and lower SBP have been associated with the inability to sufficiently increase heart rate during the submaximal CPET in PLwP (Speelman et al., 2012). None of the included studies reported information about ethnicities of the participants.

2.3.3. Discussion

This review revealed contradictory findings about cardiovascular response to exercise in PLwP, with some studies reporting higher, lower or similar response compared to healthy people. These contradictory findings might be due to the variations in the CPET protocol used, or whether a cycle or a treadmill test was used. The absence of information about cardiovascular response to exercise in PLwP with different ethnicities, means that the results could not be generalised on different populations (Farrell, 1987). Cardiovascular response to exercise depends on physical activity level (Farrell, 1987). Different perception exercise and physical activity has been reported among different ethnicities (Horne, 2013). Accordingly, it is recommended to conduct and report cardiovascular fitness research with different ethnicities.

Most studies that assessed maximal CPET reported higher cardiovascular response to exercise in PLwP compared with healthy controls. Only one study reported

normal cardiovascular response to exercise at maximal intensity (Canning et al,. 1997). However, participants included in the Canning et al. (1997) experiment were exercising regularly, and this may explain the contradictory results compared with the other studies. In contrast, another study reported lower cardiovascular response to exercise than the normal population (DiFrancisco-Donoghue et al,. 2009). However, both Cannning et al. (1997) and DiFrancisco-Donoghue et al. (2009) included only small sample sizes (n=16 and n=14, respectively) compared to the rest of the included studies, and the sample size was not based on an appropriate calculation.

The higher VO_2 suggests higher energy demand for the same workload in PLwP which may influence cardiovascular responses (Protas et al., 1996). However, both Werner et al. (2006) and Protas et al. (1996) included only males and small sample sizes (n=16 and n=8, respectively).

Results of the retrospective study (Yahalom et al., 2014) suggested that cardiovascular response is not a pre-motor symptom in Parkinson's and may be developed as a result of other factors. Subsequently, further investigations are needed to assess what factors might affect cardiovascular response to exercise in PLwP.

2.3.4. Conclusion and recommendations

In summary, studies that assessed cardiovascular response to exercise in Parkinson's have reported contradictory results, with some reporting lower and insufficient cardiovascular response to exercise and some reporting normal profiles. These variations might be related to the sample size, gender differences or CPET protocols used. Thus, there is a need to assess cardiovascular response to exercise

in PLwP in maximal and submaximal intensities. In addition, there is a need to investigate rehabilitation programs that could improve cardiovascular response. Additionally, it is recommended to assess and report cardiovascular fitness in PlwP with different ethnicities.

2.4. Effects of aerobic exercise on cardiopulmonary function in Parkinson's

Aerobic exercise refers to the use of oxygen to adequately meet energy demands during physical exercise (Kisner et al., 2017). In the general population, heart rate and respiratory rate increase during aerobic exercise in order to fulfil demands of the exercised skeletal muscles (Kisner et al., 2017). It has been found that regular aerobic exercise, such as walking, cycling or swimming, of 30 to 60 minutes three times per week could decrease blood pressure, improve oxygen consumption and decrease shortness of breath in the general population (Myers, 2003). However, these effects have not been widely explored in PLwP. Thus, this section aims to review and discuss the effects of aerobic exercise on cardiopulmonary function in PLwP.

2.4.1 Methodology

2.4.1.1. Purpose

The study objective was to review and discuss published literature on the effects of aerobic exercise on cardiopulmonary function and walking economy in PLwP. To achieve this, the primary outcomes were defined as pulmonary function test (PFT) variables including FEV_1 and FVC and FEV_1/FVC and cardiopulmonary exercise test (CPET) variables including oxygen uptake at maximal exertion ($VO_{2\,max}$) and

oxygen uptake at peak exertion ($VO_{2\ peak}$). Secondary outcome measures included maximum HR (HR_{max}) and peak HR (HR_{peak}), CPET duration, blood pressure pre- and post-CPET, and walking economy. The study aimed to conduct a meta-analysis for the primary outcome measures, where feasible. If conducting meta-analysis was not possible, the study aimed to conduct a narrative synthesis.

2.4.1.2. Design

The study was designed to provide a systematic review with quality assessment and narrative synthesis of relevant published literature.

2.4.1.3. Search strategy

A search was conducted through EBSCO using the following electronic databases: MEDLINE, AMED, and CINAHL Plus. The selected databases were chosen because of the likely availability of Parkinson's physiotherapy- and exercise-related articles in these databases. The databases were searched for studies published between 1st January 1970 and 1st January 2020, with results of the searches managed using Endnote Version X7 (Clarivate Analytics, Philadelphia, USA).

Keywords used were structured by using the PICO approach (population, intervention, comparison and outcome) (Schardt et al., 2007). Table 8 summarizes the combinations of keywords included in the search strategies using the PICO approach. PICO search terms were combined using Boolean operators ‘AND’ and ‘OR’. Study design was not restrictive due to the low number of records. Articles were included if they assessed cardiopulmonary function in PLwP after aerobic exercise programmes. Articles were excluded if: the intervention used did not include aerobic exercises; the outcome measures did not include CPET or PFT; they were not written in English language; or they were conference abstracts.

Population	Intervention	Comparison	Outcome measures
Parkinson's disease	Aerobic exercise	No intervention	Cardiovascular
Parkinson's	Exercise	Other exercise interventions	Cardiovascular response
	Physical activity		Pulmonary function
	Training		Respiratory function
			Cardiorespiratory function
			Walking economy

2.4.1.4. Study selection

Following the search and subsequent removal of duplicates, titles and abstracts were screened independently by two researchers for relevance. Full texts of relevant studies were then screened for eligibility against inclusion and exclusion criteria.

Table 8: Keywords used in the search strategy presented by the PICO approach

2.4.1.5. Data extraction

The following data were extracted from the included studies and recorded: age, sex, disease severity, and sample size. Exercise intervention mode, intensity, duration, and frequency were noted.

2.4.1.6. Risk of bias and quality of reporting

Quality assessment of the included studies regarding the effects of aerobic exercise on cardiopulmonary function were done using the PEDro Scale (PEDro scale items and description in Appendix 1) (de Morton, 2009; Maher et al., 2003). The PEDro scale has been found to be a valid and reliable tool for assessment of quality of interventional studies specifically related to physical therapy interventions (de Morton, 2009; Maher et al., 2003). It contains 11 items (studies are awarded

between 0–10 points), depending on the number of criteria the articles meet (the first item is not used to calculate the summary score).

Due to the nature of exercise interventions, no studies included blinding of subjects or investigators to the intervention allocation, and hence none could earn points on the PEDro Scale items 5 and 6. PEDro scores of four points or higher were classified as “high quality”, whereas studies with three points or less were “low quality” (Maher et al., 2003). PEDro scores for the studies were not used as a threshold for their inclusion or exclusion, but as a basis for best-evidence synthesis and to discuss the strengths and weaknesses of studies.

2.4.2. Results

The systematic search identified 329 citations, of which 132 were duplicates. Consequently, 197 citations were screened from titles and abstracts and 172 were considered not to be relevant. Of the 25 remaining studies, 16 were excluded because they did not include aerobic exercise or CPET or PFT, or they were animal model studies or single-case studies. Consequently, nine studies were included in the review: one was a non-randomised controlled pilot study and eight were randomised controlled trials. None of the included studies reported information about ethnicities of the participants. Figure 8 represents the findings of the search.

2.4.2.1. Results of quality assessment

Due to the nature of exercise interventions, no studies included blinding of subjects or investigators to the intervention allocation; therefore, no points were awarded on the PEDro Scale for items 5 and 6. Table 9 shows the PEDro quality assessment scores for the included studies. Scores ranged from 5 to 8.

To assess the feasibility of running a meta-analysis, data were extracted and summarized in table 10 and focused on: pulmonary function test variables; the protocols used for CPET; mode of the test: treadmill or cycle test; CPET test primary outcomes (VO_{2max} and VO_{2peak}); secondary outcomes including HR_{max}; HR_{peak}; CPET test duration; blood pressure (BP) pre- and post-CPET; and walking economy. None of the studies investigated the effects of aerobic exercise on pulmonary function; therefore, no data related to FEV_1, FVC, and FEV_1/FVC could be reported. Meta-analysis of data was not undertaken owing to the heterogeneity of the studies, specifically: inclusion/exclusion criteria, exercise test protocol, mode of exercise test (cycle or treadmill), exercise intensity (maximum or sub-maximum), physiological outcomes (HR, VO_{2peak}, VO_{2max}), and systolic or diastolic BP. Instead, a narrative review was conducted. Furthermore, it was not possible to calculate effect sizes from the data provided in the published papers. Authors were contacted by email to request the additional relevant data, but none responded.

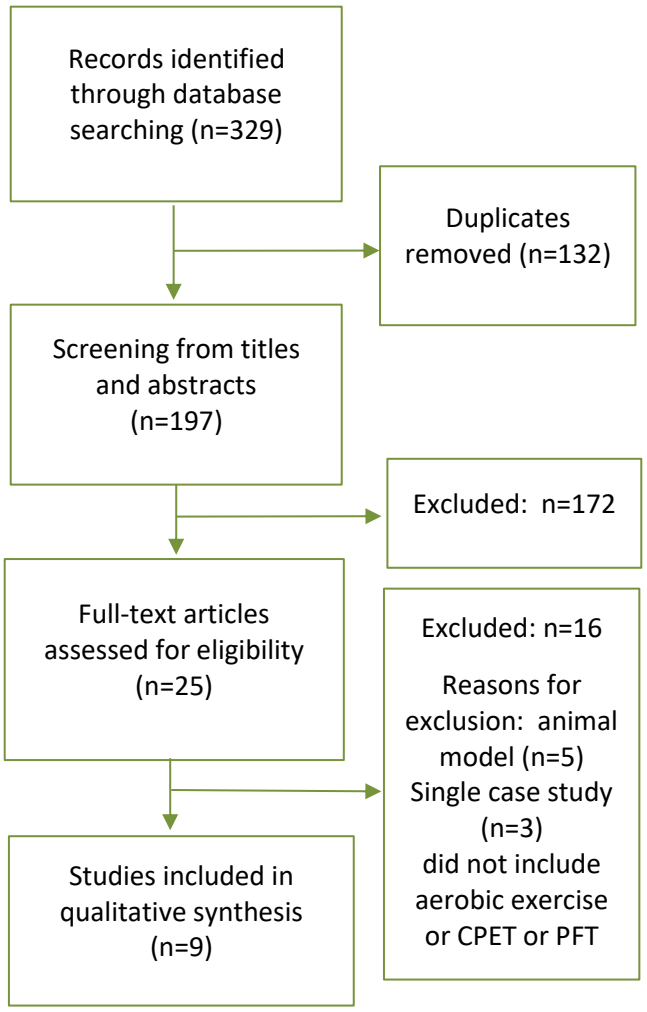


Figure 8: Flow-Chart of the search records. PFT: pulmonary function test; CPET: cardiopulmonary exercise test.

Table 9: PEDro scores for the studies that investigated the effects of aerobic training on cardiopulmonary function in people with Parkinson's.

	1. Eligibility criteria were specified	2. Subjects were randomly allocated to groups	3. Allocation was concealed	4. The groups were similar at baseline regarding prognostic indicators	5. There was blinding of all subjects	6. There was blinding of all therapists who administered the therapy	7. There was blinding of all assessors who measured at least one key outcome	8. Measures of at least one key outcome were obtained from more than 85% of the subjects	9. All subjects for whom outcome measures were available received the treatment or control condition as	10. The results of between-group statistical comparisons are reported for at least one key outcome	11. Point measures and measures of variability for at least one key outcome were reported	Total PEDro score
Bergen et al, 2002	1	0	0	1	0	0	0	1	1	1	1	5
Bridgewater and Sharpe, 1996	1	1	1	1	0	0	1	1	1	1	1	8
Burini et al, 2006	1	1	1	1	0	0	1	1	1	1	1	8
Corbianco et al, 2018	1	1	1	1	0	0	0	1	1	1	1	7
Fernández-del-Olmo et al, 2014	1	1	0	1	0	0	0	1	1	1	1	6

Mavrommati et al, 2017	1	1	1	1	0	0	1	1	1	1	1	8
Ridgel et al, 2016	1	1	1	1	0	0	1	1	1	1	1	8
Schenkman et al, 2012	1	1	1	1	0	0	1	1	1	1	1	8
Shulman et al, 2012	1	1	1	1	0	0	1	1	1	1	1	8

Table 10: Summary of studies that investigated the effects of aerobic training on cardiopulmonary function and walking economy in people with Parkinson's.

Author	Sample size	Mean (SD) age (years)	Male: Female	Study Design	Intervention	Outcome measures	Key findings
Bergen et al, 2002	4 G1 4 G2	56.8(6.5)	Not mentioned	Pilot non-randomised trial	G1: Cycling or treadmill walking for 3 times/week for 16 weeks. G2: Usual activity	CPET	Increased VO_{2peak} and achieved workload in the intervention group (from 19.5 to 24.5 ml.kg.min^{-1}). Decreased VO_{2peak} in the control group (from 15.9 to 14.1 ml.kg.min^{-1}).
Bridgewater and Sharpe, 1996	13 G1 13 G2	67.3(3.9)	9:4	RCT	G1: 12 weeks aerobic exercise (walking). G2: Usual physical activity level	CPET	Improvement in exercise test duration and HR in the exercise group • The exercise group had a minimum target heart rate of 82.92 ± 9.98 beats per minute (mean ± SE) and exercised at an intensity that produced a maximum HR of 121.27 ± 16.74 beats per minute (mean ± SE). • Significant group by session interactions between the exercise and control groups in mean CPET duration (F[2.75]=3.28, p=0.047).
Burini et al, 2006	13 G1 13 G2	65.2(6.5)	9:17	RCT	G1: Aerobic training 3 times/week for 7 weeks. G2: Qigong exercises 3 times/week for 7 weeks.	CPET	• G1: mean (SD) VO_{2peak} (ml.kg.min^{-1}) at baseline =1201.4(368), and 951 (337) after 7 weeks, within-group mean difference = 250 (t=2.3, *p*=0.04) • G2: mean (SD) VO_{2peak} (ml.kg.min^{-1}) at baseline =1064.7(229), and 1158(307) after 7 weeks, (mean difference=-94); within-group mean difference = -94 (t= 3, *p*=0.02)

							• Significant between-group difference for VO_{2peak} (F: 4.8, *p*=0.007).
Corbianco et al, 2018	10 G1 10 G2	58.8(3.9)	20:0	RCT	G1: treadmill training 20 minutes per day, 4 days/week for 4 weeks G2: Whole body vibration 20 minutes per day, 4 days/week for 4 weeks		$VO_{2\ peak}$ increased in both groups (ml.kg.min^{-1}): G1: baseline mean (SD) $\dot{V}O_{2peak}$ (13.46(4.96)), after 4 weeks (18.55(1.11)) G2: baseline mean (SD) VO_{2peak} (13.22(6.16)), after 4 weeks (20.70(1.16)) Between-group difference for VO_{2peak} non-significant
Fernández-del-Olmo et al, 2014	11 G1 11 G2	58.7(10)	13:9	RCT	G1: Treadmill training 3 times/week for 5 weeks. G2: Overground training 3 times/weeks for 5 weeks.	Overground walking economy	Treadmill training but not overground training reduced overground walking economy (*t*=5.61, *p* <0.001 for treadmill training). Mean difference (SD) within group (ml.kg.min^{-1}): • G1=15.54(3.24) • G2=19.40(4.78)
Mavrommati et al, 2017	36 G1 47 G2	67(8)	61:22	RCT	G2: Treadmill, cycle ergometer, cross-trainer or rowing ergometer 2 times/week for 24 weeks. G2: Usual activity	CPET	G2 obtained higher maximum values for HR, $VO_{2\ peak}$. • Mean (SD) VO_{2peak} (ml.kg.min^{-1}): G1 =1.66 (2.35), G2= 1.69 (2.57) • Mean (SD) $HR_{\ peak}$ (beats.min^{-1}): (G1=136 (114), G2=152 (108)) Significant difference between the two group for VO_{2peak} (p=0.008).
Ridgel et al, 2016	22 G1 22 G2	70.2(7.9)	19:5	RCT	G1: Combined intensive therapy including cycle resistance and aerobic exercises	CPET	No significant differences between both groups for cardiovascular variables (resting HR (*p*=0.59), $VO_{2\ max}$ (*p*=0.86)).

					3 times/week for 12 weeks. G2: Usual activity.		
Schenkman et al, 2012	39 G1 41 G2 41 G3	63.4(11.2)	76:45	RCT	G1: Supervised flexibility, balance and function, 3 days/week for 3 months. G2: Supervised aerobic exercise, 3 days/week for 16 months. G3: Control (home exercise), single supervised session and then 5–7 days/week for 16 months at home.	Walking economy	Walking economy was improved in the aerobic exercise group but not in the flexibility, balance and function group or the control group (mean difference= -1.2 ml.kg.min-1, 95% CI= -1.9 to -0.5).
Shulman et al, 2012	26 G1 26 G2 28 G3	65.8(10.7)	50:17	RCT	G1: Low-intensity treadmill training, 3 times/week for 3 months. G2: High-intensity treadmill training, 3 times/week for 3 months. G3: Stretching and resistance training, 3 times/week for 3 months.	CPET	Low-intensity treadmill intervention had the greatest effect in improving gait speed. Both treadmill interventions decreased maximum $VO_{2.}$ Mean difference (SD) between baseline and post training ($ml.kg.min^{-1}$): • Low intensity (1.54 (0.4)) • High intensity (1.53 (0.7)) Statistically significant with p=0.003

Aerobic training in PLwP has been reported to improve peak VO_2 (Bergen et al., 2002; Bridgewater and Sharpe, 1996; Burini et al., 2006), decrease breathlessness (Burini et al., 2006), increase maximum workload tolerated (Bergen et al., 2002) and increase test duration of the CPET (Bridgewater and Sharpe, 1996).

2.4.2.2. Frequency and duration of exercise

Frequency of exercise in the included studies ranged from 2 to 3 times per week, with varied exercise programme durations (Bergen et al., 2002; Bridgewater and Sharpe, 1996; Burini et al., 2006; Ridgel et al., 2016). For example, Bergen el al. (2002) investigated the effects of a 16-week exercise programme (n=4), whereas Bridgwater and Sharpe (1996), Ridgel et al. (2016) and Shulman et al. (2012) investigated the effects of 12-week exercise programmes (n=13, n=24 and n=67 respectively). Shorter programme durations of 7 weeks (Burini et al., 2006, n=26) and 6 weeks (Pelosin et al., 2009, n=10) have also been investigated. Although the duration of the aerobic exercise intervention varied in these studies, all of them reported improvement in exercise test outcomes, including HR and VO_2, except two studies.

2.4.2.3. Intensity of exercise

In order to investigate the effects of different intensity of the aerobic exercises, Shulman et al. (2013) assessed oxygen consumption and gait speed after high- and low-intensity treadmill training. The high intensity treadmill group started at a 40% to 50% of maximal heart rate and increased up to 70% to 80% of a maximal heart rate, whereas low intensity treadmill training started at 20% and increased up to 40-50% of maximal heart rate. Both high and low intensity treadmill training improved oxygen consumption (VO_2) similarly (1.54 ml/kg/min increase after low intensity and 1.53 ml/kg/min increase after high intensity treadmill training) (Shulman et al.,

2013). On the other hand, Ridgel et al. (2016) reported no change in VO_2 or any change in the cardiovascular response after aerobic training. However, his study included a combined aerobic-strengthening program and was not solely focused on aerobic training (Ridgel et al., 2016).

2.4.2.4. Walking economy and aerobic exercise

Walking economy is defined as the required energy to perform a sub-maximal walking intensity (Christiansen et al., 2009). It is measured by the rate of oxygen consumption per distance during walking (Christiansen et al., 2009). PLwP suffer from a high walking economy in comparison with a non-Parkinson's population (i.e., PLwP require higher energy for the same distance walked by age-matched healthy people) (Christiansen et al., 2009). Walking economy in PLwP was found to be affected by stride patterns, jerky movements and instability (Martinez-Martin, 1998). It was found that walking economy decreased after aerobic treadmill walking in PLwP (decrease in oxygen consumption around 1.3-1.21 mL/kg/ min) (Pelosin et al., 2009; Schenkman et al., 2012). However, these studies assessed treadmill walking economy but not overground walking economy (i.e., they assessed the energy required to walk on the treadmill, not on the ground). Only one study examined the effect of treadmill training and overground walking on overground walking economy in Parkinson's (Fernández-del-Olmo et al., 2014). To achieve this, 22 people with mild to moderate Parkinson's (Hoehn & Yahr scale stage I-II) were randomly grouped into an overground walking intervention group and a treadmill training group for five weeks. Both groups were to walk at their preferred speed. Results of the study indicated that treadmill training, but not overground training, reduced overground energy expenditure (15.54 ± 3.24 ml/kg/min versus 19.40 ± 4.78 ml/kg/min, respectively). Although this study used a small sample size (n=22), it is the only study that assessed overground walking economy in PLwP.

The increase in walking economy in Parkinson's leads to excess fatigue and, in turn, could affect independence and quality of life (Christiansen et al., 2009). Further studies are needed to investigate functional (overground) walking economy, since this might affect participation and overall quality of life in this population. Cardiopulmonary parameters in Parkinson's have not been extensively investigated. Moreover, there is a need to investigate whether non-motor impairments such as pulmonary impairment, including restrictive and obstructive patterns, and cardiovascular fitness are associated with walking economy in PLwP. There is a need to investigate the effectiveness of specific interventions aimed at improving cardiopulmonary function and walking economy in Parkinson's. Table 10 summarizes the main findings of the studies that investigated the effect of aerobic training on cardiopulmonary function and walking economy in PLwP.

2.4.3. Discussion

Only a small number of studies have investigated the effects of aerobic exercise on cardiopulmonary function in PLwP, and revealed that aerobic exercise could help in improving cardiac fitness (by means of CPET). The advantages of aerobic exercise as an intervention include: considered as a cheap intervention; widely accepted; and could be conducted as a self-management intervention with minimum supervision needed.

Most of the studies used similar intensities and frequencies recommended by the World Health Organization (WHO) (30–45 minutes of moderate intensity, three times per week) (World Health Organization, 2020). However, none of these studies investigated the effects of aerobic exercise on pulmonary function. Thus, future trials are recommended to investigate the effects of aerobic exercise on cardiac

fitness and pulmonary function in PLwP.

The decrease in walking economy in PLwP could lead to more fatigue and, subsequently, could affect quality of life (Christiansen et al., 2009). Only two studies (Fernández-del-Olmo et al., 2014; Schenkman et al., 2012) assessed walking economy in PLwP. Investigating walking economy could help in understanding if PLwP are in need to consume more energy to walk, and if different interventions could affect energy consumption. It is obvious that there is a lack of knowledge about the factors that might affect walking economy in PLwP. Further studies are needed to determine functional (overground) walking economy, because this might affect functional activity and overall quality of life in this population.

2.4.4. Strengths and Limitations of the Review

This review is the first review addressing the effects of aerobic exercise on cardiopulmonary function in PLwP. The search included studies from the last 40 years and involved screening by two reviewers. It was not feasible to do meta-analysis because of the heterogeneity of the data and the outcome measures, and protocols used in the included studies.

2.4.5. Conclusion

This review has addressed the effects of aerobic exercise training on cardiopulmonary function and walking economy in PLwP and revealed that aerobic exercise could help in improving cardiac fitness and walking economy. However, no studies have been conducted to investigate the effects of aerobic exercise on pulmonary function using spirometry in PLwP. Therefore, further research that may help to determine the effects of aerobic exercise on pulmonary function is

warranted.

2.5. Summary of the literature review

This chapter included three reviews that brought together findings from the published literature in order to achieve three goals:

1. **To review and discuss the published literature about prevalence and causes of pulmonary function impairments in PLwP.** It is clear that there is a limited knowledge base in the area of pulmonary function in Parkinson's. The review also reported different findings about the prevalence of obstructive and restrictive pulmonary patterns in PlwP in the earlier stages of the disease.

2. **To review and discuss the published literature about cardiopulmonary response to cardiopulmonary exercise test in PLwP.** This review revealed contradictory findings in cardiopulmonary response to exercise when measured by CPET, which included higher, lower or similar cardiovascular response to exercise between PLwP and age-matched healthy controls.

3. **To review and discuss the published literature reporting the effects of aerobic training on cardiopulmonary function in PLwP.** This review showed that there was an improvement in cardiopulmonary function in PLwP who participated in an exercise intervention, with key improvements reported in oxygen consumption, heart rate, respiratory rate and duration of exercise test. However, studies that investigated aerobic exercise effects on cardiovascular function did not include a pulmonary function test to assess the

effects on pulmonary function. Two studies investigated aerobic training effects on walking economy in Parkinson's, and showed that high walking economy was present in mild to moderate Parkinson's. These studies also showed a decrease in walking economy after aerobic interventions.

2.6. Next steps

Based on the findings of these three reviews, it seemed important to consider developing an exercise trial that could address pulmonary function, cardiopulmonary response to exercise (cardiac fitness), and to investigate if aerobic exercise has positive effects on cardiopulmonary fitness and pulmonary function in the early stages of Parkinson's. However, it is important to run a pilot study before running the larger trial, and investigate aspects of feasibility of such a clinical trial, that could help in answering these questions. The next three chapters (Chapters 3-5) report on a pilot and feasibility study, the EXoCARP trial (also referred to as Study 1 in the thesis), with Chapter 3 outlining aspects of methodology, Chapter 4 reporting the findings of the trial, and Chapter 5 providing a discussion of the results.

Chapter 3: Study 1: The effects of exercise on cardiorespiratory function in Parkinson's - Methodology

This chapter is about the methodology and methods of study 1, which aims to answer the below research question about the feasibility of conducting a future clinical trial of aerobic exercise to improve cardiorespiratory function in Parkinson's. The chapter starts with research questions and objectives, methodology and study design, methods, and end-up with description of the statistical analysis and qualitative data analysis used.

3.1. Research Questions

A number of questions have arisen from the previous chapter (the three reviews' findings):

1. Is asymptomatic pulmonary impairment / pulmonary pattern present in people in the early stages of Parkinson's?
2. Are PLwP suffering from abnormal cardiovascular response to exercise (cardiac fitness) in the early stages of Parkinson's (I-III in Hoehn and Yahr)?
3. What are the effects of aerobic exercise training on cardiopulmonary function in people in the early stages of Parkinson's?

To answer these questions, a study that assesses the effects of aerobic exercise on pulmonary function and cardiac fitness is needed. However, before running a large clinical trial, conducting a study on a smaller basis is needed to understand if it is feasible and practical to conduct the main study. A pilot study is a small-scale, preliminary study which aims to investigate whether crucial components of a main

study, such a randomised controlled trial (RCT), will be feasible (Sim and Wright, 2000). Accordingly, it is important to run a pilot and feasibility trial before running a larger trial that could help in answering these questions. Thus, the study aims to answer the key research question:

> Is it feasible and acceptable to run a trial that investigates the effects of aerobic exercise on pulmonary function and cardiovascular response in PLwP?

3.2. Specific objectives of the study

The primary purpose of this study was to pilot and establish feasibility of recruitment to, and delivery of, a clinical trial of an eight-week community-based and patient-led aerobic exercise programme compared with usual care to improve pulmonary function and cardiovascular response to exercise in PLwP. The research included a mixed methods pilot and feasibility study of an aerobic exercise programme compared with usual care, involving focus group interviews with trial participants to explore acceptability and feasibility of the exercise intervention and the outcome measures.

3.2.1 Primary objective of the research was:

The primary objective of the trial was to investigate the feasibility and acceptability to participants' of delivering a trial of a self-managed 8-week aerobic exercise programme versus usual care, in the community, for PLwP at Hoehn and Yahr stages I-III.

This study objective involved the following sub-objectives:

1a: assess if recruitment methods were effective, by calculating the recruitment rate, number of people who contacted the research team,

and number of people who were eligible to participate and ultimately gave informed consent.

1b: calculate the attrition rate from the number of participants recruited who subsequently dropped out.

1c: evaluate the screening tool and inclusion/exclusion criteria.

1d: evaluate feasibility, acceptability and practicalities of using the outcome measures.

1e: explore feasibility of delivering the exercise intervention.

1f: explore participants' experiences and the acceptability and suitability of the aerobic exercise intervention, the outcome measures and adherence to the intervention.

3.2.2. Secondary objective of the research:

1. To assess pulmonary function in people with mild to moderate Parkinson's. This objective helps to inform the next trial to target people who have abnormal pulmonary pattern (if found).

3.2.3. Criteria for assessing feasibility:

1a: Recruit 50 participants within a period of 20 months (from April 2019 to December 2020), achieving a recruitment rate of >5%.

1b: Attrition rate <15%.

1d: Gain data about the practicalities of using the outcome measures and devices, and conduct the assessment tests safely without adverse reactions for the participants (assessed by the ability to conduct the tests with all participants included, adverse reactions reported and participants' experience data gained from the focus groups).

1e: Deliver the interventions to the participant safely with the prescribed dose of exercise (monitored by participants' opinions and experiences about the intervention, the dose and adverse reactions - where found). Additionally, adherence to the exercise intervention monitored by the ability of participants to perform around 30 minutes of moderate aerobic exercise per day, three days per week, verified by the activity monitors and the daily exercise diaries.

A traffic light system was used to indicate the recommendations for the next trial according to the feasibility and acceptability results.

3.2.4. Criteria for assessing acceptability:

1c: Participants report that the outcome measures are comfortable and acceptable (monitored from the focus groups).

1d: Participants report that the aerobic exercise intervention is comfortable and acceptable (monitored from the focus groups).

3.3. Methodology

In order to achieve the study aims, the methodology involved a randomised, single-blinded mixed-methods feasibility study (The EXoCARP trial: **Ex**ercise effects **O**n **Ca**rdio-**R**espiratory function in **P**arkinson's), which included collection and analysis of both quantitative and qualitative data, as recommended by the Medical Research Council (MRC) guidance (Craig et al., 2008).

The RCT is considered a methodology that can decrease bias within comparative studies (Boutron et al., 2007), by means of decreasing the preferential allocation of individual participants to one group or the other (allocation bias). Additionally, to

further reduce researcher-based-bias, blinding is used to prevent the assessor knowing to which group the participant belongs (Sim and Wright, 2000).

A mixed-methods research design offers the ability to gain a larger image about experimental research in one research study (Albright et al., 2013). Incorporating qualitative data to gain more information about participants' experiences in a specific intervention or event can allow detailed understanding of what is happening in the study and offers deeper analysis beside the quantitative data (Waterfield, 2003). Additionally, it has been recommended previously that mixed-methods research could help in triangulating both quantitative and qualitative insights in a way that both sets of results complement each other with the flexibility to answer research questions more comprehensively (Albright et al., 2013). A combination of qualitative and quantitative methods has been used in social and behavioural sciences, within a research paradigm named as pragmatism, with mixed methodologies emerging that combine both quantitative and qualitative approaches (Tashakkori and Teddlie, 1998).

There are around 40 mixed-methods research designs (Tashakkori and Teddlie 2003). One of those designs is the mixed-methods sequential design. The mixed-methods sequential design is commonly used by health researchers and includes collecting first quantitative and then qualitative data in two consecutive phases within one study (Ivankova, 2006). In EXoCARP, the mixed-methods sequential design was chosen with quantitative data collection followed by qualitative data collection in order to achieve the study goals. For example, the study goals 1d and 1e necessitate the need to deliver the intervention and to run the assessment tests (for example the spirometer and CPET), then to collect data about participants' experiences and opinions towards the intervention and outcome measures used.

Thus, the mixed-methods sequential design was considered to be the most appropriate design to serve the study goals of this trial.

Research studies are categorised into explanatory, descriptive or exploratory studies (Elman, 2020). Explanatory research is about trying to find out if a specific hypothesis is correct i.e: attempts to clarify why and how a relationship, association or if relationships exist between two aspects of a situation or phenomenon (Elman, 2020). Descriptive research presents specific details of a situation, social setting, or relationship, and aims to describe what is prevalent regarding a group of people or phenomenon or a program / intervention (Elman, 2020). Exploratory research investigates the possibilities of undertaking a particular research study and may function to test feasibility of a more systematic study or develop methods for a subsequent trial (Elman, 2020). Accordingly, EXoCARP is a mixed-methods sequential exploratory study, as it explores the feasibility of conducting a subsequent larger trial.

Pilot studies are small-scale, preliminary studies which aim to assess whether components of a main study, such as an RCT will be feasible (Thabane et al., 2010; Van Teijlingen and Hundley, 2001). For example, they may be used in an attempt to predict an appropriate sample size for the full scale/larger study or to improve various aspects of the study design, interventions or outcome measures. This is because RCTs require time and money to be conducted, so it is crucial that the researchers have confidence in the key steps they will take when conducting large studies to avoid wasting time and resources (Van Teijlingen and Hundley, 2001).

Feasibility and acceptability were the main focus of this study. Feasibility aims to monitor, evaluate and study the methods used in a study (O'Cathain et al., 2015),

aiming for a potential more definitive study. Feasibility includes monitoring recruitment of participants to a trial, evaluation of sites and settings, evaluation of inclusion/exclusion criteria of a trial, evaluation of ability to conduct the intervention and outcome measures used in a trial (O'Cathain et al., 2015). Acceptability covers important additions such as ability to accommodate the intervention in participants' day-to-day life and perceptions of the intervention and outcome measures (Sekhon et al., 2017p.8).

To gain insights into participants' experiences related to the feasibility and acceptability objectives, a phenomenological approach was used, as it gives insight to and understanding of the human condition and experiences (Finlay and Ballinger, 2006). Therefore, in order to explore participants' experiences of the trial, a phenomenological approach was the most relevant approach to fulfil this objective. This was to explore, in particular: experiences of the intervention, including any challenges, barriers, or practical difficulties in adhering to it; experiences of and ability to wear the Actigraph; and experiences of and ability to do the assessment tests including the pulmonary function test and the cardiopulmonary exercise test. Overall, a mixed-methods randomised controlled trial that incorporates feasibility and acceptability will inform a subsequent larger clinical trial.

According to the Medical Research Council (MRC) guidance (MRC, 2006) for developing complex interventions, the process of development of a complex intervention may take a wide range of different forms. The MRC (2006) guidance recommends developing interventions systematically, using a carefully phased approach, starting with a series of pilot and feasibility studies targeting the key uncertainties in the design, recruitment, outcome measures and intervention, then moving on to an evaluation phase, implementation, and development. However, evaluation still needs to be undertaken at the end of each stage, with a final

evaluation process at the end of all stages. This framework highlights the importance of taking time to develop and implement complex interventions, in order to enable rigorous analysis in future larger trials. The four distinct phases that have been identified for the development and implementation of research include feasibility/piloting, evaluation,

implementation and development, presented in figure 9 below (Craig et al., 2008). According to the MRC framework, EXoCARP trial fits within the first phase (feasibility and piloting), as it includes testing feasibility of recruitment, the intervention, outcome measures and screening tools.

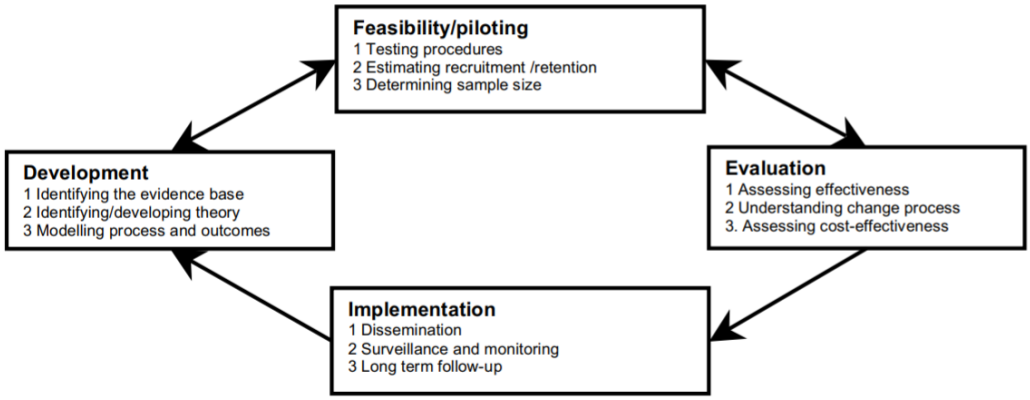


Figure 9: Key elements of the development and process of evaluating complex interventions, Reproduced with permission of the Medical Research Council (Craig et al., 2008).

3.4. Outline of overall study design

The chosen design was a mixed-methods, single blind, pilot and feasibility randomised controlled trial (RCT) with participants randomised to one of two groups: an aerobic exercise programme (intervention), or usual care (control, with usual care defined as participants' usual physical activity level). Focus groups were conducted with participants from the exercise group to explore their experiences of the intervention and outcome measures. Double blinding was not feasible in this

trial, because participants need to know if they will be doing the exercise intervention or to continue their usual physical activity level as it is.

Figure 10 represents the flow chart of the study.

3.5. Method

3.5.1. Research ethics approval

The research team had reviewed the trial protocol and the trial was registered in the ISRCTN registry (ISRCTN14167992; https://doi.org/10.1186/ISRCTN14167992). Ethical approval was received from Keele University Ethical Review Panel (ERP) (Appendix 2), approved 07/03/2019, Faculty of Medicine and Health Sciences Research Ethics Committee (FREC) ref: MH-180006; MHFI-0003.

During the early stages of the feasibility trial, one ethical amendment was required, relating to the randomization process. During the planning stages of the trial, randomization was stratified by age and sex; however, after conducting the first assessment session for the first participant (April 2019), we found that it would be more meaningful to randomize participants based on disease severity (Hoehn and Yahr score) and sex. Thus, approval for the amendment was received before continuing with further participants (Appendix 3).

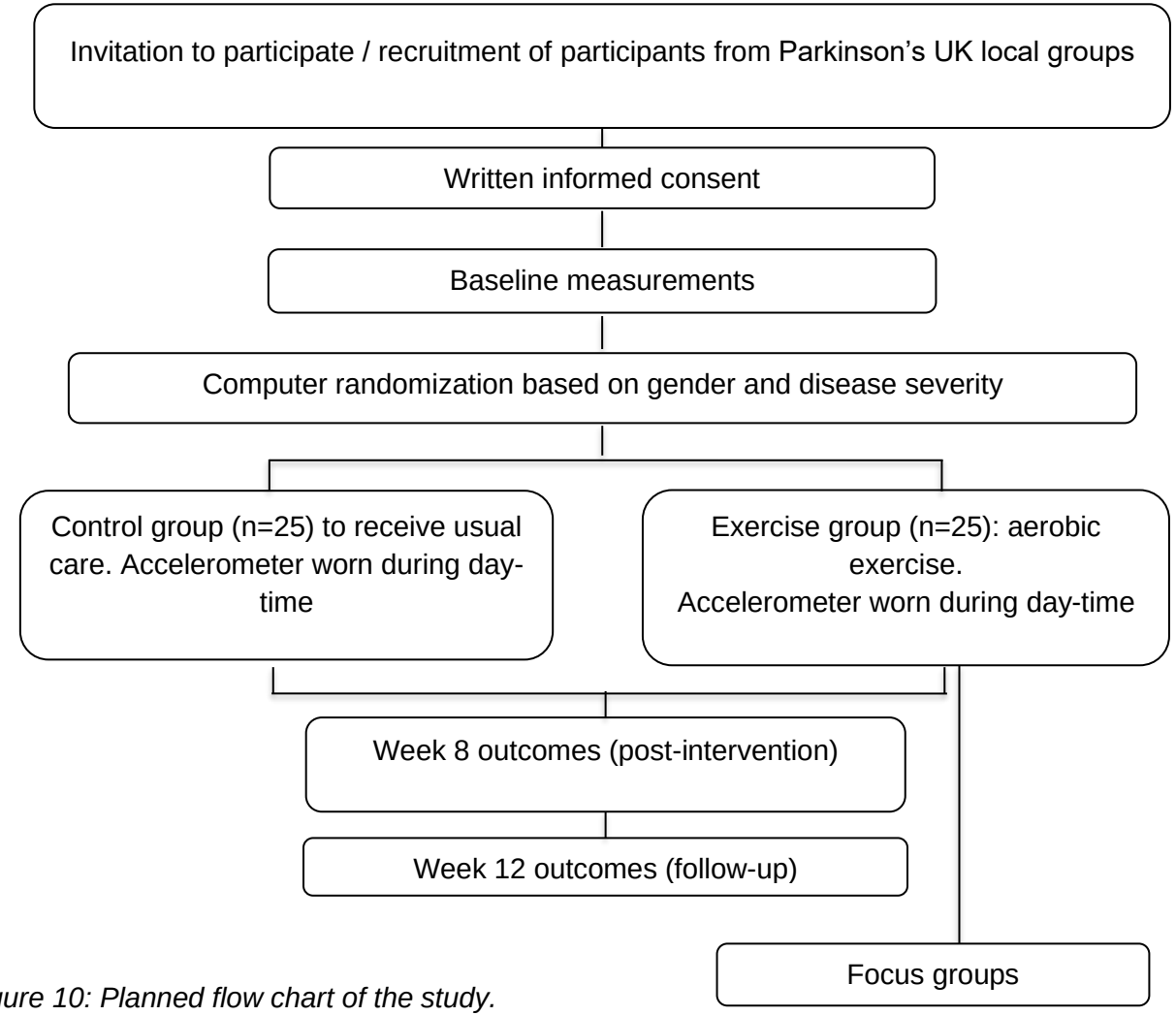


Figure 10: Planned flow chart of the study.

All participants were required to provide informed consent (Appendix 4). Participants were free to withdraw at any time without giving any reason. Although individuals were subjected to testing used in standard clinical practice, any testing is not without some risk. The clinical assessment was unlikely to cause undue stress to participants. All participants were fully informed of testing procedures before participation and made aware they could withdraw from the study without reason at any time. Individuals were carefully monitored during testing by the researcher (PhD student, an HCPC registered physiotherapist). The care and comfort of the participants were ensured at all times.

3.5.2. Patient and public involvement and engagement (PPIE)

During the trial planning phase, stakeholder meetings were undertaken to explore the interest and views of members of Parkinson's UK. Thus, PPIE meetings were conducted with community-based Parkinson's support groups in Stafford (n=32), Whitchurch ('Friends of Parkies') (n=26), Chester (n=12), Crewe (n=22), and Telford (n=26), at which an introduction to and overview of the proposed study were presented to group members. Members were asked for their feedback, suggestions, and comments on the proposed protocol. Participants' feedback was taken into consideration while developing the protocol. In particular, they were asked to comment on: the study's proposed requirement for participants to be able to get on and off a stationary bike; preference towards running on a treadmill compared to stationary cycling; ability to attend the assessment sessions at Keele University; and acceptability of wearing an accelerometer every day during the trial.

Group members reported that they would prefer the cycle test to the treadmill test and reported that they felt it would be more stable even if they had a harness for the treadmill. Also, most of them reported that they would feel uncomfortable wearing

the oxygen consumption face mask during an exercise test, with some reporting experiences of claustrophobia. Additionally, most of them confirmed that they would be able to get on and off a stationary cycle.

3.5.3. Study protocol

The study protocol was published in the IRCTN registry (ISRCTN14167992, https://doi.org/10.1186/ISRCTN14167992) under the title: Can exercise improve heart and lung function in people with Parkinson's? The EXoCARP study. The protocol is described within the below sections in this chapter. The SPIRIT checklist (Standard Protocol Items: Recommendations for Interventional Trials), was followed while writing the following sections to aim for a better quality of reporting. The SPIRIT checklist for the trial is represented below.

3.5.4. Population and sample size

3.5.4.1. Sample size

According to recommendations for pilot and feasibility studies (Browne, 1995; Lancaster et al., 2004), a sample size of at least 30 is needed. We aimed to recruit a maximum of 50 participants (25 per group) to allow for 10% attrition (drop-out) (Sim and Wright, 2005), and to provide a sufficiently large sample to estimate values (standard deviation) for the primary outcome measure, which will inform a subsequent sample size calculation for a larger controlled trial (Sim and Wright, 2005).

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Description	Addressed on page number
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__70_
Trial registration	Trial identifier and registry name. If not yet registered, name of intended registry	___70___
Introduction		
Rationale	Description of research question	___59__
Objectives	Specific objectives or hypotheses	__60-61_
Trial design	Description of trial design including type of trial, allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__62-66_
Study setting	Description of study settings	__74__
Eligibility criteria	Inclusion and exclusion criteria for participants.	__73-74_
Interventions	Interventions for each group	_92_
Outcomes	Primary, secondary, and other outcomes	_75-91_
Participant timeline	Time schedule of enrolment, interventions and assessment sessions. A schematic diagram is highly recommended	_68__
Sample size	Estimated number of participants needed to achieve study objectives	___70___
Recruitment	Strategies for achieving adequate participant enrolment to reach target sample size	__74--_
Allocation:		
Sequence generation	Method of generating the allocation sequence (eg, computer-generated random numbers)	__92__

Blinding (masking)	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts)	__92___
Statistical methods	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_100-101
Research ethics approval	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_67__
Protocol amendments	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__67___
Consent or assent	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_67_

Appendices

Informed consent materials	Model consent form and other related documentation given to participants and authorised surrogates	_276-277

3.5.4.2. Inclusion criteria:

- Adults over 18 years old, diagnosed with Parkinson's according to the UK Brain Bank Criteria (Appendix 5).
- Disease severity classified between I-III according to the Hoehn and Yahr scale (Appendix 6). People with Hoehn and Yahr score I-III are able to walk independently without assistance from others. Since participants were requested to do aerobic exercise, they needed to be walking independently during the study.
- Ability to stand and walk for at least 10 meters without assistance from another person. However, walking aids such as sticks were acceptable.
- Mini-Mental State Examination score (MMSE) >24 (Appendix 7). Participants with cognitive impairment were excluded because they need to understand instructions relating to the intervention and the assessment tests.

3.5.4.3. Exclusion Criteria

- Pre-existing diagnosis of lung disease, e.g. chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, emphysema, lung cancer.
- Current smoker.
- Participants with a history of heart disease that would present a risk of adverse cardiac event in response to the sub-maximal exercise tests (in accordance with the American Heart Association/ American College of Sport Medicine guidelines): such history includes myocardial infarction, congenital heart disease, heart attack, pacemaker/implantable cardiac defibrillator, heart valve disease or surgery within 3 months, unstable angina, uncontrolled arrhythmias, uncontrolled heart failure and angioplasty, as identified using the American Heart Association/ American College of Sport Medicine (AHA/ACSM) Health/Fitness Facility Pre-Participation Questionnaire (Appendix 8).

- Any other previously diagnosed musculoskeletal or neurological disorder that may prevent participation in physical activity.
- Inability to understand English language (for the purpose of understanding instructions and information related to the study, as no interpreter is available).

3.5.5. Recruitment

Participants were recruited from local Parkinson's UK groups. Permission was obtained from group leaders to approach group members. Then, an invitation letter (appendix 9), a participant information sheet (appendix 10), and a consent form (appendix 4) were sent to group members with Parkinson's by the group leader, by either email or post, according to preference. Those interested in the study were asked to contact the research team by email, telephone or letter, and were given opportunity to ask further questions about the study before deciding whether to participate or not. An appointment was made for them to attend their first assessment, which took place in the School of Allied Health Professions at Keele University, at which they were asked to sign the consent form and complete a health screening questionnaire (AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire – Appendix 8) to screen for eligibility/inclusion. Recruitment was not limited to a specific ethnicity, gender or age group (except being an adult).

3.5.6. Assessment sessions

Demographic and clinical data including age, sex, current medications, weight, height, years since Parkinson's diagnosis, Hoehn and Yahr stage, and dominant symptoms, were collected from those who consented to participate and were found to be eligible for inclusion. Baseline measurements (first assessment session) were recorded by the principal investigator (AA). Assessment included spirometry, CPET

and the questionnaires (PDQ-39, Barthel Index, Non-Motor Symptoms Questionnaire, Prospective-Retrospective Memory Questionnaire, and the Geriatric Depression Screening Questionnaire; *details about the outcome measures are in the following sections*). All participants (both groups) were given Actigraph accelerometers and asked to wear them for a period of eight weeks (further information about the accelerometer in the following sections).

On completion of baseline assessments, participants were randomly allocated to their groups. Participants in the control group were asked to behave as they usually do and not to change in their lifestyle.

The second assessment session was after eight weeks (end of intervention), at which accelerometer data was downloaded, and spirometer, CPET and the questionnaires were measured.

The third assessment session was after four weeks post intervention (follow-up), where spirometry and CPET were measured.

3.5.7. Outcome measures

3.5.7.1. Physiological measures

3.5.7.1.1. Pulmonary function test (PFT)

Pulmonary function test (PFT) is an evaluation of the respiratory function (Burrows, 1975). The primary goal of PFT is to investigate the severity of pulmonary impairment (Burrows, 1975). The gold standard for performing the PFT is spirometry (Burrows, 1975). The spirometry was assessed using a spirometer (CareFusion, Microlab, figure 11), and in accordance with the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines (Miller et al., 2005). The

best of three consecutive blows was used to obtain the FEV_1, FVC and FEV_1/FVC ratio (Miller et al., 2005).

Results were compared with norms from the Global Lung Initiative, to get the predicted percent values (Global Lung Initiative, 2012). The following instructions and procedures were followed:

Participant preparation (pre-test)

Before conducting the pulmonary function test, participants were asked not to smoke or to eat a large meat at least one hour prior to the test and not to wear clothes that would be restrictive to movement.

Position of the participant during the test

Participants were seated upright with back supported, feet flat on the floor using a chair with arm rests and without wheels. The participants put on a nose-clip and breathed through a rigid mouth-piece that was connected to the spirometer.

Performing and recording the test (according to the standardized European Respiratory Society/American Thoracic Society guideline) (Miller et al., 2005)

The assessor explained and demonstrated the test manoeuvre to the participants, and instructed the participants to place the disposable mouthpiece in their mouth and to put a nose-clip on the nose. The participants were encouraged to breath quietly to become accustomed to the apparatus and to attain a steady breathing pattern. At the end of expiration, the participants were encouraged to inhale maximally and rapidly to attain the total lung capacity (TLC). The participants were instructed to make maximal expiratory effort, blowing out as hard and as fully as possible until no further breath could be exhaled. Once fully exhaled of three manoeuvres.

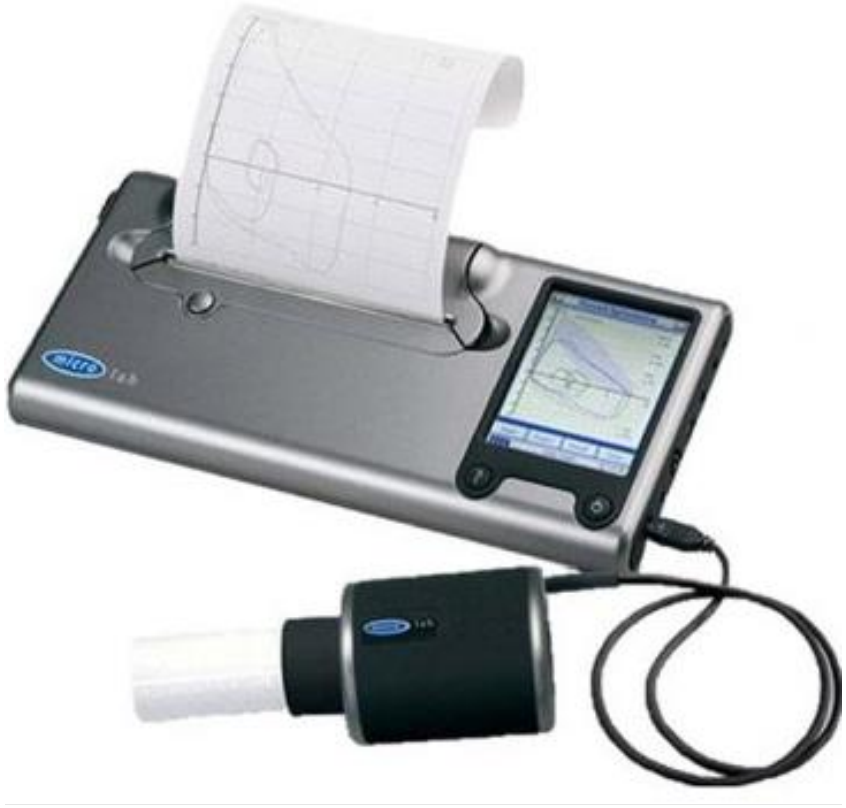


Figure 11: MicroLab Spirometer.

The participants were instructed to return to their normal breathing pattern and remove the mouthpiece and nose-clip and rest. The procedure was repeated for a minimum

Criteria for accepting the manoeuvres

Manoeuvres were rejected if: participants did not inspire to TLC initially; participants coughed during the first second of exhalation; mouthpiece was obstructed by tongue or teeth; participants started the expiratory effort poorly coordinated; there was an air leak at the mouthpiece; participants failed to expire fully to reserve volume (RV); or effort appeared submaximal.

Between-manoeuvre criteria

After three acceptable manoeuvres had been obtained, the following were applied:

- The two largest values of FVC must be within 0.150 L of each other.
- The two largest values of FEV_1 must be within 0.150 L of each other.

If both of these criteria were met, the test session was concluded. If both of these criteria were not met, the test was continued until:

- Both of the criteria were met with analysis of additional acceptable manoeuvres; or
- A total of eight tests had been performed (optional); or
- The participant could not or should not continue.

3.5.7.1.2. Cardio-Pulmonary Exercise Test (CPET)

Exercise work capacity was measured using incremental cycle ergometry. Tests were performed on an electrically braked cycle ergometer while monitored with

workload (resistance of the cycle ergometry), heart rate (measured by a Polar H10 (Polar, Kempele, Finland)), estimated peak oxygen consumption (VO_2 peak = 15 x (HR peak ÷ HR resting)) and rate of perceived exertion (RPE), measured by the Modified Borg Scale (Appendix 11). The Modified Borg scale allows individuals to subjectively rate their level of exertion during exercise or exercise testing by asking participants to rate the exertion level on a scale from 0 to 10, where 0 means resting state (no exertion at all) and 10 means maximum exertion (American College of Sports Medicine, 2010). The CPET was carried out in accordance with the standards and recommendation of the American College of Sport Medicine (ACSM) (American College of Sports Medicine, 2013). Written instructions along with a description of the evaluation were provided well in advance of the appointment so the participant could prepare adequately. Prior to the test, participants were instructed to: refrain from ingesting food, alcohol, or caffeine or using tobacco products within 3 hours of testing; be rested for the assessment, avoiding significant exertion or exercise on the day of the assessment; wear clothing that permits freedom of movement and includes walking or running shoes; be aware that the evaluation may be fatiguing and that they may wish to have someone accompany them to the assessment to drive home afterward; continue their medication regimen on their usual schedule so that the exercise responses are consistent with responses expected during exercise training; bring a list of their medications, including dosage and frequency of administration, to the assessment and should report the last actual dose taken; drink ample fluids over the 24-hour period preceding the test to ensure normal hydration before testing; and fill the AHA/ACSM Health/Fitness Facility Pre-Participation Questionnaire (Appendix 8).

The following was accomplished before starting the test

Prior to conducting the test, the assessor provided participants with the consent form and allowed time for the individual undergoing assessment to have all

questions adequately addressed before signing the form, maintained the room temperature between 68F and 72F (20C and 25C), re-explained the CPET to the participants to confirm that they understood it.

The CPET was done within the “on” state of the antiparkinsonian drugs (i.e.; approximately 45 minutes to one hour after taking the drug). The assessor calculated 70% of the age-predicted HR prior to conducting the test. For example, for a 50-year-old person, the estimated maximum age-related heart rate would be calculated as 220 - 50 years = 170 beats per minute (bpm).

The 70% levels would be:

70% level: 170 x 0.70 = 119 bpm

Thus, a 50-year old participant would complete the exercise test below 119 bpm.

Procedure of the CPET

The assessor recorded resting heart rate (HR) and blood pressure before the test after an initial resting period for at least 30 minutes. Then, a three-minute warm-up period of slow pedalling without resistance was conducted. After that, the test started with an individualized ramp protocol, to aim for a sub-maximum exercise capacity to be achieved within 8-12 minutes, with a target cadence of approximately 50-60 round per minute (rpm).

Predicted maximum workload and work rate (ramp rate) was calculated using the following formulae:

W_{max}= -115.756+(2.271*age) + (4.043*weight)

For example; if the participant was 70 years old and weighted 65 Kg, then the predicted maximum workload would be:

W_{max}= -115.756+(2.271*70) + (4.043*65) = 306.009 Watts

To aim for an exercise duration around 12 minutes, work rate would be:

W_{rate} = W_{max}/12= 306.009/12 = 25.5 Watts for an estimated 12-minute exercise test.

Therefore, 25 Watts could be selected, or otherwise the closest appropriate option offered by the software.

Finally, the test finished by doing a six-minute recovery period (slow pedalling without resistance).

Blood pressure, HR, perceived rate of exertion (Borg scale- Appendix 11), and VO_2 measurements were recorded throughout the test (each minute) and during the recovery period. Test duration and maximum workload achieved were recorded.

The exercise was stopped if any of the following occurred (American College of Sports Medicine, 2013)

- Onset of angina or angina-like symptoms.
- Significant drop in systolic blood pressure or a failure of the systolic blood pressure to rise with an increase in exercise intensity.
- Excessive rise in blood pressure.
- Signs of poor perfusion: light-headedness, confusion, poor muscle coordination, paleness, blue or gray skin color, nausea, or cold and clammy skin.
- Failure of heart rate to increase with increased exercise intensity.
- Subjects request to stop.
- Physical or verbal manifistations of severe fatigue.
- Failure of the testing equipment.

- HR raised above 70% of age-predicted HR.

3.5.7.2. Function and activity outcome measures

3.5.7.2.1. Physical activity level

Level of physical activity was measured objectively by using an Actigraph accelerometer (ActiGraph, Florida). The Actigraph (figure 12) is a triaxial accelerometer that detects human movement, levels of physical activity, and energy expenditure. Actigraph devices were found to have high construct validity when compared with self-reported physical activity measures in PLwP in terms of step count (r= 0.56, p = 0.003), and moderate to vigorous physical activity level (r=0.98, p=0.0003) (Mantri et al., 2019).

While the researcher was searching for the best activity monitor for this study, two main devices came out of the search for PLwP. These were: the Actigraph and the activPal. However, after contacting the activPal producer and attending a seminar for the developer, the researcher confirmed that the activPal was not able to pick up very slow movements, such as bradykinesia, and might include tremor as a physical activity. In contrast, Actigraph has separate formulae that are validated for PLwP to record bradykinesia and to avoid recording tremor as a movement (Pan et al., 2013). Thus, for this study, the Actigraph data was used as the main outcome for monitoring physical activity and adherence to the intervention.

Participants were given the Actigraph in the first assessment session and were asked to wear it, using the belt provided (Figure 12), around their waist during daytime except for showering or swimming. At the end of the intervention, at week 8, the devices were returned by the participants and data were downloaded using the Actilife software (ActiGraph, Florida).

Figure 12: The Actigraph activity monitor and wearing in around the waist.

Choosing the area “around the waist” for PLwP is recommended to: 1) avoid overestimation of movement due to wrist/ankle movement; and 2) to reduce tremor effects and counting tremor as a physical activity movement if worn around the wrist or ankle.

Moderate to vigorous physical activity (MVPA) and number of steps/day were retrieved from the Actigraph. The following were the cut-points used for different activity levels as defined by the Actigraph: 1.5 to 2.9 METs or 100 to 759 counts per minute (cpm) for light physical activity; 3 METs or 760–2,019 cpm for moderate physical activity; and ≥3 METs or ≥2,019 cpm for vigorous physical activities (Matthew, 2005; Pan et al., 2013; Troiano et al., 2008).

In order to know which activities are normal (usually conducted before the study), and which activities are extra (on top of a participant’s usual activity – as part of the intervention), participants were asked to complete a daily physical activity diary and to mark the extra amount of time spent on exercise on top of their usual physical activity level. While doing the Actigraph analysis, the researcher matched the time of the extra activities as reported by the diaries with the activities in the Actigraph results to identify usual and extra time of exercise in terms of intensities.

3.5.7.3. Subjective outcomes and questionnaires

3.5.7.3.1. Quality of life

Quality of life was assessed using the Parkinson’s Disease Quality of Life Questionnaire (PDQ-39). PDQ-39 has been found to have acceptable internal consistency ($\alpha = 0.51$ to 0.96) and to be reproducible ($r = 0.96$, $p < 0.001$) (Peto et al., 1998). The PDQ-39 was chosen for this study due to its items being specified to aspects of PLwP life, and how Parkinson’s affects the participant’s life. This was not

the case with other quality of life scales such as the European Quality of Life Scale (EQ-5D), or the Older People's Quality of Life Questionnaire (OPQOL).

The PDQ-39 (Appendix 12) is a widely used questionnaire with 39 questions measuring the effects of Parkinson's on quality of life, covering eight dimensions (Peto et al., 1998):

- Mobility
- Activities of daily living
- Emotional well-being
- Stigma
- Social support
- Cognitions
- Communication
- Bodily discomfort

Participants were asked to think about their health and general well-being and to consider how often in the last month they had experienced certain events (e.g. difficulty walking 100 yards). They were asked to indicate the frequency of each event by selecting one of 5 options on an adverbial rating Scale:

- Never
- Occasionally
- Sometimes
- Often
- Always or cannot do at all.

The PDQ-39 provides scores on an ordinal scale for each of the eight scales and a sum of them for the overall score. Both subscales and the overall scores were calculated for the PDQ-39 data. The lower the PDQ-39 scores, the better the quality of life.

3.5.7.3.2. Non-motor symptoms

The non-motor symptoms general screening was assessed using the Non-Motor Symptoms questionnaire (NMS). The NMS is the only tool that assesses non-motor symptoms for Parkinson's. The NMS (Appendix 13) is a single-page self-administered questionnaire that contains 30 items that generally screen non-motor symptoms (Romenets et al., 2012). The symptoms are listed in items, and the participants can answer with Yes or No on each item (nominal scale). The NMS questionnaire has been found to have high sensitivity and specificity (71.8% and 88.5% respectively) (Romenets et al., 2012).

3.5.7.3.3. Independence in activities of daily living

Independence in activities of daily living (ADL) was subjectively assessed using the Barthel Index (Appendix 14). The Barthel Index is widely used in geriatric populations, and has been found to have a high construct validity when compared with the PDQ-39 ($r = 0.64$, $P < 0.00$) tool to assess ADL in Parkinson's (Morley et al., 2012). The Barthel Index consists of 10 items that measure a person's daily functioning, particularly the activities of daily living (ADL) and mobility (Morley et al., 2012). The ADL assessed by the Barthel index include:

- Toileting
- Bathing
- Eating
- Dressing

- Continence
- Transfers
- Ambulation.

The scoring system depends on participants' answers on each item, on a score from 0 to 2:

- 0 = dependent
- 1 = needs some help, but can do something alone
- 2 = independent

Scores on the items are added to create a total score. The total possible score ranges from 0 – 20, with lower scores indicating increased dependency (Morley et al., 2012). For this study, the total score of the Barthel Index was calculated and treated as ordinal data. The ten-item version of the Barthel Index was chosen over the other versions (for example: the short form 5-item, and the long form 15-item versions) because it is the only version that has been assessed for validity in Parkinson's.

3.5.7.3.4. Memory

Memory was assessed using the Prospective-Retrospective Memory Questionnaire (PRMQ) (Appendix 15). The PRMQ is a 16-item questionnaire (eight items measuring prospective memory and eight items measuring retrospective memory) (Smith et al., 2000). Each participant was asked to rate the frequency of occurrence of each type of memory failure in their daily life on a 5-point ordinal scale (Smith et al., 2000). The answers were based on a five-point adverbial rating scale:

- Very Often
- Quite Often

- Sometimes
- Rarely
- Never

The PRMQ has been found to have high sensitivity (93%) and specificity of 71% in older population (Foley, 2007). The PRMQ is the only tool that assesses prospective and retrospective memory. The optimum cut-off point is 31 for the PRMQ total score, 16.5 (mean rating of 3.3 points) for the prospective memory subscale, and 18.5 (mean rating of 3.08) for the retrospective memory subscale (Hsu et al., 2014).

3.5.7.3.5. Depression

The Geriatric Depression Scale (GDS) (appendix 16) has been tested and used extensively with an older population. The GDS Long Form is a brief, 30-item questionnaire (long form) and 15-item questionnaire (short form), in which participants are asked to respond by answering ‘yes’ or ‘no’ to statements based on how they felt over the past week (Sheikh and Yesavage, 1986). In the short form, 10 items indicate the presence of depression when answered positively, while the rest (question numbers 1, 5, 7, 11, 13) indicate depression when answered negatively (Sheikh and Yesavage, 1986). Scores of 0–4 are considered normal, depending on age, education, and complaints; 5–8 indicate mild depression; 9–11 indicate moderate depression; and 12–15 indicate severe depression (Sheikh and Yesavage, 1986).

The GDS was found to have a 92% sensitivity and a 89% specificity when evaluated against diagnostic criteria (Lesher and Berryhill, 1994). The construct validity and test-retest reliability of the tool have been supported through both

clinical practice and research. In a validation study comparing the Long and Short Forms of the GDS for self-rating of symptoms of depression, both were successful in differentiating depressed from non-depressed adults with a high correlation ($r = 0.84$, $p < .001$) (Sheikh and Yesavage, 1986).

3.5.7.3.6. Physical activity survey

In addition to the Actigraph data, participants were asked to fill in a physical activity survey (Appendix 17). The survey asks about number of minutes spent in aerobic exercise per week, mode of exercise, dyspnoea during exercise, and smoking status.

Table 11 summarizes the outcome measures used in the trial.

3.5.8. Randomization and blinding

Participants were randomly allocated by computer to either an aerobic exercise program in addition to usual care, or to usual care, stratified according to Hoehn and Yahr stage and gender. Computerised block randomization was used, with a ratio of 1:1, and this was achieved using block randomization, with blocks of four and two. The outcome assessor (AA) was blind to group allocation. Following randomization, a second researcher (SH) provided the intervention or control group instructions for participants according to group allocation. After week 8 session, the assessor was asked to guess to which group each participant had been allocated, in order to assess for success of blinding.

Table 11: Outcome measures used in the trial

Domain	**Outcome measure**
Pulmonary function	Pulmonary function test (spirometry). FVC, FEV_1 and FEV_1/FVC were derived.
Cardiovascular response to exercise	Cycle-cardiopulmonary exercise test (CPET). The following were derived: • Predicted peak oxygen uptake ($VO_{2\ peak}$). • Heart rate (HR). • Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP). • Maximum workload (power of the cycle) achieved. • Test duration (how many minutes did the patient tolerate before stopping the test). • The AHA/ACSM Health/Fitness Facility Pre-Participation
Physical activity level	Actigraph data including: • Minutes spent in low, moderate, moderate to vigorous, vigorous and sedentary activities. • Steps per minute Daily physical activity diaries Physical Activity Survey
Quality of life	Parkinson's disease quality of life questionnaire (PDQ-39)
Depression	The Geriatric Depression Screening Questionnaire
Independence in activities of daily living	Barthel Index
Non-motor symptoms	Non-motor symptoms questionnaire
Memory	Prospective-Retrospective Memory Questionnaire

3.5.9. Intervention

Participants in the exercise group were asked to engage in an 8-week programme of aerobic exercise (e.g. outdoor walking in the community, walking on the treadmill, stationary cycling, rowing on a row machine, running) according to their preference. They were asked to maintain the aerobic exercise for at least 30 minutes per day, for at least three days per week, for the eight weeks. Participants were not supervised and only the activity monitors recorded their exercise level (refer to next section for more information about assessment of adherence). Moderate aerobic exercise intensity was defined as activities that make the person work hard enough to raise his/her heart rate and break into a sweat, but still be able to talk while doing it (American College of Sports Medicine, 2013). Behavioural change models were not considered during the development of the intervention of this trial. This is because the researcher wanted to explore the adherence to the intervention. If adherence to the intervention was found to be poor, then using a behavioural change model would be needed.

The intervention was selected based on aerobic exercise training studies that have consistently resulted in improvements in cardiorespiratory fitness and maximal oxygen uptake (VO_{2max}) in PLwP (Burini et al., 2006; Fernández-del-Olmo et al., 2014; Mavrommati et al., 2017; Ridgel et al., 2016; Schenkman et al., 2012; Shulman et al., 2013). The intervention in most of these studies has involved exercise durations of 30 to 40 minutes per session, for two to five days per week. The eight weeks intervention period was used according to the recommendations of the British Thoracic Society (BTS) guidelines, which state that at least eight weeks of aerobic exercise is needed in pulmonary rehabilitation to improve quality of life in respiratory patients (British Thoracic Society, 2001).

Behavioural change models have been recommended to be used in interventions targeting behavioural change, including exercise interventions, in PLwP (Glanz et al, 2010). The Health Belief Model (HBM), the Theory of Reasoned Action (TRA), the Theory of Planned Behaviour (TPB), the Trans-Theoretical Model (TTM) and the Social Cognitive Theory (SCT) are the main behavioural change models (Taylor et al., 2006).

The HBM includes objective demographic and other variables such as cues to action not included in the other models' specifications (Rosenstock et al., 1994). The model is based on the theory that a person's willingness to change their health behaviours is primarily due to their health perceptions. However, the HBM has a weak predictive power for changing the behaviour (Taylor et al., 2006). This is due to weaknesses in the predictive validity of the HBM's core psychological components (Armitage and Conner 2000; Harrison et al., 1992). Thus, it was not used in EXoCARP.

The TRA and the TPB are framed at higher levels of generalisation than the HBM (Ajzen, 1998). Both models share identical attitudinal and social norm related components (Fishbein and Ajzen, 1975). The TRA explains that an individual's decision to engage in a particular behaviour is based on the outcomes the individual expects will come as a result of performing the behaviour. The TPB explains that intentions are influenced by the attitude about the likelihood that the behaviour will have the expected outcome and the subjective evaluation of the risks and benefits of that outcome. The TRA and the TPB are statistically better specified than the HBM and the TTM, and they have more precisely defined components. This may enhance the efficiency and consistency of the use of both the TRA and TPB (Taylor et al., 2006). However, both the TRA and the TPB were found to change behaviour in non-health related research only as reported by a systematic review and a meta-

analysis (Taylor et al., 2006). Subsequently, both the TRA and the TPB were not suitable to be used in EXoCARP.

Noar and Zimmerman (2005) assessed the components of HBM, the TRA, the TPB, and the TTM in terms of structures appertaining to: attitudinal beliefs; self-efficacy and behavioural control beliefs; normative beliefs; risk related beliefs and emotional responses; and intention, commitment and planning. None of the models were considered to be specified enough to incorporate and interpret the significance of social, economic and environmental factors as predictors and determinants of health behaviour (Noar and Zimmerman, 2005); the components and psychological components they contain relate to cognitions and perceptions that are part of a person's response to their environments (Kippax and Crawford 1993). Although descriptions of the HBM include demographic and socioeconomic variables, a systematic review and a meta-analysis identified that, in practice, the HBM has not normally been used effectively to reflect responses to environments (Taylor et al., 2006). When these models are used, there might be failures to record information relevant to such factors (Taylor et al., 2006). This could lead to cost ineffectiveness for interventions aimed at changing the environmental and organisational determinants of health behaviour (Ferguson et al., 1996). Additionally, this might increase health inequalities (Taylor et al., 2006). Thus, the HBM, the TRA, the TPB, and the TTM were not suitable to be used in EXoCARP.

Bandura's (1986) Social Cognitive Theory (SCT) positions self-efficacy and outcome expectancies (related to situation and action) as the main determinants of behaviour. Outcome expectations depend on perception that some consequences are determined by the environment and are therefore divorced from personal control (Taylor et al., 2006). Additionally, outcome expectations are related to the belief that one's actions are instrumental to a particular outcome. Self-efficacy relates to

confidence in person's own ability to carry out a particular behaviour. Thus, the social cognitive theory predicts that behaviours are performed if a person perceives control over the outcome, few external barriers, and confidence in the person's own ability (Taylor et al., 2006). t has been reported that PLwP with high self-efficacy were more likely to engage in regular exercise (Ellis et al., 2011). Subsequently, the SCT might be the most suitable health behavioural change model to be used in trials such as exercise trials. However, considering that EXoCARP was a feasibility trial, and did not aim for behavioural change, it was not considered necessary at this stage to use these models.

Participant adherence

Participants were provided with an accelerometer to wear constantly during daytime unless bathing, showering or swimming. This was one way of monitoring adherence to the exercise intervention. Additionally, participants were asked to complete an activity diary (Appendix 18) of their exercise during the eight weeks period.

3.5.10. Participants' experiences of the study and the acceptability and feasibility of the intervention, outcome measures (focus groups)

Qualitative research is concerned with how people make sense of the world and experience events (Finlay and Ballinger, 2006). This cannot be extracted from quantitative research, but in mixed methods studies the combination of quantitative and qualitative data could provide a more holistic view on what is happening with the participants. In the case of this trial, it was beneficial to collect physiological outcomes, including pulmonary function and cardiac response, quantitatively. However, participants' feedback about their experiences of participating in the study, experiences and acceptability of the intervention and the use of Actigraph

monitors and other outcome measures and tests undertaken as part of the trial were explored to generate qualitative data.

3.5.11. Focus groups

In order to address research objectives 1c, 1d, 1e, and 1f, to explore the feasibility and acceptability of the trial, focus groups were undertaken (Sim and Snell, 1996; Tong et al., 2007). A focus group is a type of group discussion, which is managed by a moderator who encourages interactive conversation and collects opinions from the participants of the group, aiming for qualitative data that is related to a specific topic area (Sim and Snell, 1996). Additionally, it is recommended that an observer and field-note taker attends the focus groups to provide additional insights behind the interactions of participants and to reduce bias associated with a single investigator (Archibald, 2016).

The suitability of the focus group in exploring peoples' experiences, attitudes, views, feelings and motives about health has been reported (Thomas et al.
1992; Hyden & Bulow 2003). Focus groups were found to be a good tool for older people, as they tend not to provoke anxiety (Gray-Vickrey 1993). The advantage of using focus groups is that they do not discriminate against people who cannot read or write, or people with visual impairment (Kitzinger 1996). Additionally, focus groups can encourage participation from people who are shy to speak alone, or who might feel 'put on the spot' if interviewed alone (Kitzinger 1996). Furthermore, focus groups are helpful for people who feel they have nothing to say but may subsequently participate in a discussion initiated by others (Kitzinger 1996).

On the other hand, focus groups do have some disadvantages; for example, some people may feel uncomfortable discussing and expressing their views in front of others (Morgan 1988). However, the focus groups in this research were generally undertaken to discuss participants' experience of the trial and did not include discussions about personal topics. The choice of focus group over the interviews was considered because the aim was to explore the overall experience of the trial being common for all participants, and to explore any individual differences in those common experiences, which might be discussed more fully in a focus group during wider discussion. For example, someone's comments might trigger thoughts and words from someone else, which might not come out in an interview if the differences were not apparent.

Participants who completed the exercise intervention were asked to participate in one focus group, lasting up to no more than one and a half hours. Invitation to participate in the focus groups was not limited to a specific ethnic group, age group or gender. Two focus groups were conducted, with the aim of a minimum of three and a maximum of 12 participants in each group. The optimum number of participants per group is approximately eight (Morgan, 1997), but this was dependent on the number of participants able and willing to attend. The groups were run after at least four weeks post-intervention, to explore the participants' experiences and views of the intervention, and its perceived effects, including quality of life, and to identify and explore barriers to exercise. In the first focus group, participants sat around a table in a circle, so they could see each other and hear each other easily.

A focus group topic schedule that included both open and closed questions (Appendix 20) was used to serve as a guide to the topics covered during the

interview. The focus group interview schedule was developed in advance by the researcher and members of the supervisory team. Additionally, the focus group questions were discussed with two physiotherapists who have experience in research related to older adults. The process of developing the focus group questions involved a series of back-and-forth revisions between the researcher, the supervisory team and the two physiotherapists until producing the final version. Appendix 19 is the first draft of the focus group questions, and Appendix 20 is the final version of the focus group schedule which was used.

The questions were printed and distributed around to each participant. This acted as a reminder for them to keep focusing on the topic (Kroll et al., 2007). However, the second focus group was conducted online due to the Corona-Virus (COVID-19) pandemic governmental regulations to minimise the spread of the virus. Thus, the second focus group was conducted virtually (online) using the Google Meet platform.

All the focus groups were audio recorded. The first focus group was held in the School of Allied Health Professions at Keele University. The groups were moderated by the first investigator (AA). The moderator introduced the questions and ensured that all the participants in the group were sharing their experiences and feedback. An observer (SH) was also present to take notes of any non-verbal interaction between the participants.

3.5.12. Thematic analysis (qualitative data)

In preparing the data from the focus groups (process evaluation) for analysis, all the data captured on audio tapes were transcribed verbatim and checked for accuracy. This process of full transcription helps to strengthen the trustworthiness of the data

by avoiding the selective recording of information (Patton, 2002). Ensuring the truth value of the study, the accuracy of the transcripts was also confirmed by another member of the research team listening to the tapes and checking the transcript to verify its accuracy.

The data from the transcripts were analysed using thematic analysis. Thematic analysis is a flexible research tool, not related to a specific epistemological or theoretical approach (Braun and Clarke, 2006), aiming to discover meaning behind individual conditions and circumstances (Maguire and Delahunt, 2017). Thematic analysis was used in this study on the basis that it is a general and flexible approach to qualitative data analysis that can be used across a range of approaches to analysis, including phenomenological methodology. In retrospect, an approach that is more specifically geared to descriptive phenomenology, such as Colaizzi's, could have been used and might have generated a fuller sense of the phenomenon of interest from the participants' accounts (Morrow et al., 2015). However, Braun and Clarke's six-step method is broadly similar to Colaizzi's seven-step method, except in respect of the emphasis in the latter on bracketing and the idea of respondent validation, but that both methods are based on identifying themes in the data (Morrow et al., 2015). The thematic analysis in this study was inductive, aimed to identify meanings from the data based on the participants' answers and discussion (Braun and Clarke, 2006). Data were coded independently by two members of the research team, who then discussed codes, and independently identified themes. The data from the transcripts were analysed using the process described by Braun and Clarke (2006), outlined below:

- **Familiarisation with data**

Braun and Clarke (2006) recommend that researchers read the transcribed data at least one time before starting to code. This is because ideas might be shaped as the researcher becomes familiar with the data. However, researchers are also advised to document their initial thoughts, reflection, values and interests in the data (Lincoln and Guba, 1986). The researcher can return to these ideas in the subsequent phases of analysis (Lincoln and Guba, 1986).

- **Generating initial codes**

After the familiarisation phase, the researcher needs to start initial production of codes from the data (Braun and Clarke, 2006). Coding is defined as the process of reflecting and interacting with and thinking about data (Savage, 2000). Simply put, when the researcher starts coding, he or she focuses on specific characteristics of the data, and, while in this phase, may start to identify important sections of text and label them (King, 2004). King (2004) suggested that a "good code" is one that helps to fulfil richness of the phenomenon.

- **Searching for themes**

After all the data have been initially coded, the third phase started by collecting all codes that are relevant into themes according to the recommendations of Braun and Clarke (2006). Themes are defined as "an abstract entity that brings meaning identity to a recurrent experience and its variant manifestations" (DeSantis and Ugarriza, 2000). Themes are significant concepts that link important sections of the data together (DeSantis and Ugarriza, 2000). Themes were created using an inductive approach.

- **Reviewing the themes**

After identifying the themes, phase 4 started by refining themes. In this phase, researchers need to review the coded data extracts for each theme and to look at the overall pattern. King (2004) recommends that in this phase, researchers need to identify relevant text that has not already been coded, initiate codes for it, and link it to a relevant theme.

- **Defining and naming the themes**

In this phase, the researcher defines the area each theme covers and identifies how each individual theme “fits” with the overall story.

- **Producing the report**

The researcher starts the writing up phase and produces the report after final definitions of the themes. In this study, the researcher used examples, or quotations, to support the qualitative analysis as recommended by Braun and Clarke (2006).

While the researcher followed the above-mentioned steps, the data were coded using NVIVO, independently by two members of the research team, who then discussed codes, and independently identified themes. Transcripts were read several times over and interview recordings listened to again so that the full sense of the interview could be remembered as a whole. Themes and sub-themes were discussed and agreed within the research team, following an iterative process over a series of meetings.

3.5.13. Quality assurance of reporting qualitative data

In order to ensure quality of reporting, the consolidated criteria for reporting qualitative research (COREQ) checklist was used. The COREQ checklist was

developed to help researchers report high quality transparent data, and to improve the rigor, comprehensiveness and credibility of studies that include interviews or focus groups (Tong et al., 2007). The COREQ has 32 items asking about three key issues: 1) research team; 2) study design; and 3) data analysis and findings.

3.5.14. Trustworthiness

In qualitative research, the researcher is the instrument for analysis, which puts the responsibility on the researcher him- or herself to ensure rigour, transparency and trustworthiness of the results (Nowell et al., 2017). Researchers need to follow trustworthiness and quality assurance recommendations while conducting the research and while reporting it, in order to convince the reader that the study results are convenient (Lincoln and Guba, 1986). Lincoln and Guba (1985, p.234) defined trustworthiness as "*introducing the criteria of credibility, transferability, dependability, and conformability to parallel the conventional quantitative assessment criteria of validity and reliability*".

These criteria were followed in this study and are reported in each phase of the analysis in the results chapter (Chapter 4). Below are the main criteria with brief definitions for each one:

- **Credibility**: Credibility is the consistency between participants' views and answers with the researcher's representation (Tobin and Begley, 2004). In order to assure credibility in this study, a second researcher checked if the representation of data and findings were consistent with the data.
- **Transferability**: transferability refers to the generalizability of the information to other cases, in which the researcher is responsible to provide a detailed description of the analysis and method in order to help people who wish to transfer the finding to their own situation (Lincoln & Guba, 1985).

- **Dependability**: Tobin and Begley (2004) recommended that researchers need to ensure the research process is logical, traceable, and documented in order to achieve dependability. To ensure dependability of this study, all the processes were audited by the research supervisor.
- **Confirmability**: conformability is reached when the research findings are derived from the raw data (Tobin & Begley, 2004). In other words, results are confirmed while using quotes and evidences from the transcripts and, according to Guba and Lincoln (1989), conformability is achieved when credibility, transferability, and dependability are achieved.
- **Audit Trails**: audit trails were kept by the research supervisor to ensure evidence of the findings and conclusions, methodologies used while the analysis and transcribing the audio records, and rationale for the decisions were made.
- **Reflexivity**: reflexivity has to do with consideration and documentation of the researcher's opinions and biases (Nowell et al., 2017). In order to address reflexivity, consideration of the researcher's own biases was reported, because the researcher was the person who collected the data and analysed it in the study. Reflexivity about the focus group and the qualitative analysis are addressed in Chapter 4. Additionally, reflexivity about the main trial, PPIE meetings and the PhD as a whole journey are covered in chapter 7.

3.5.15. Statistical analysis (quantitative data)

Data from all measurements were analysed using SPSS (version 24) and Microsoft Excel (Microsoft Office 365). Data were assessed for normal distribution and equality of variances using Q-Q plots and histograms. As this was a feasibility study, no formal hypothesis tests were undertaken. All data analysis took place

using a database that had been copied after freezing the database, just before breaking the blinding of the assessor.

In accordance with the CONSORT (2010) guidelines, baseline demographics of the two groups were recorded. The number of eligible patients who contacted the research team was included, and the number of people who dropped out at each visit was recorded. Means and standard deviations (SD) were calculated for normally distributed continuous data, and medians and interquartile range for ordinal data and data that were not normally distributed.

As this was a feasibility study, no effectiveness analysis was conducted. However, any potential to change in CPET and PFT between the baseline and end of intervention session (8-week session) was assessed by mean difference or median difference and plotted in graphs. Assessing these differences could give an idea about the outcome measures and their potential for change, and if any changes are needed in terms of using the outcome measures to detect changes over time.

To assess if similar outcome measures would be needed for the next trial, Pearson's or Spearman's correlations were calculated. This has been done to avoid collecting data from many outcome measures if they were measuring the same target (for example: the Barthel Index and the activity of Daily living domain in PDQ-39 assess similar components). Bar-graphs were used to illustrate frequencies and proportions.

3.5.16. Adverse reactions and adverse events

An adverse reaction is defined as "*'A response to a drug / intervention which is noxious / unintended, and which occurs at doses normally used in man for the*

prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function", whereas an adverse event is defined as "*Medical occurrence temporally associated with the use of a medicinal product or intervention, but not necessarily causally related*" (World Health Organisation, 1972). Although the outcome measures used in this study are used in routine clinical practice (not in PLwP, but in the general population), the below are the expected adverse reactions that could happen while conducting the tests/intervention:

- Risk of fall and fatigue during the aerobic exercise.

During the CPET participants may experience adverse reactions in certain exceptional circumstances under intensive aerobic exercises, such as abnormal blood pressure, fainting, angina, and in rare instances, heart attack or stroke, which could lead to death. However, the intensity of the exercise anticipated in the study was restricted and limited by the fact that participants were PLwP (i.e: participants have done the CPET under the age predicted HR formulae, which could help in tailoring the intensity of cycling on individual basis).

3.5.17. Trial management

The supervisory team provided overall supervision of the study and ensured that it was conducted in accordance with the principles of Good Clinical Practice and the relevant regulations (Craig et al., 2012). Additionally, the assessor completed the Good Clinical Practice training (certified from the National Institute for Health Research in 2018) before staring any data collection. The supervisory team agreed the trial protocol and any protocol amendments and provided advice to the investigators on all aspects of the study. The supervisory team monitored the

progress of the study, including the recruitment, data completeness, analysis and ensured that there were no major deviations from the study protocol.

Chapter 4: Study 1 - Results

This chapter presents the results of the EXoCARP feasibility study with findings related to each of the study objectives.

4.1. Recruitment rate, attrition rate and included participants (objective 1a and 1b)

Overall, 37 people contacted the researcher from online advertisements through the Parkinson's UK website and through local Parkinson's groups. Out of these, six said Keele was too far away for them to travel, three made contact during the first COVID-19 lockdown period (March/April 2020) so we could not recruit them or collect data, three were not eligible according to the inclusion criteria due to having respiratory or chronic cardiac diseases, and one was scheduled to attend the first assessment session at the first day of campus closure due to COVID-19 regulations and consequently no data were collected from the participant.

Overall, 24 participants were eligible and consented and were included in the trial and completed the first assessment session, of which: one dropped out after the first assessment session due to a personal issue; another dropped out due to medical reasons (not Parkinson's related); seven were part-way through the trial but could not attend the second visit due to COVID-19 lockdown; and one could not attend the third assessment visit due to the COVID-19 lockdown. In summary, 24 participants completed the baseline assessments, 15 completed the outcome assessments at the end of the intervention period, and 14 completed the follow-up assessments. The information related to recruitment and attrition is summarised in the CONSORT diagram (Figure 13). Actual recruitment rate versus planned recruitment rate is represented in Figure 14.

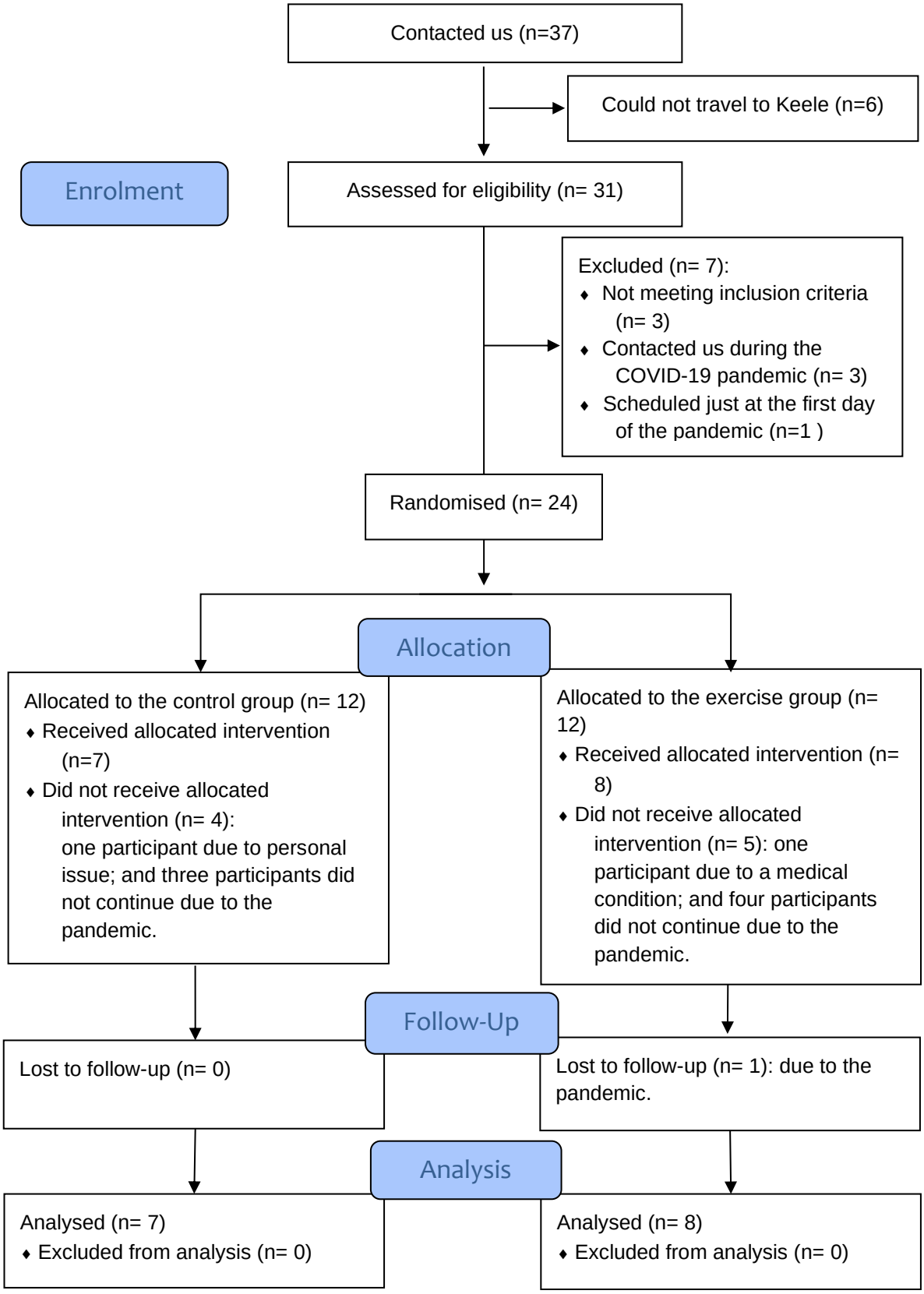
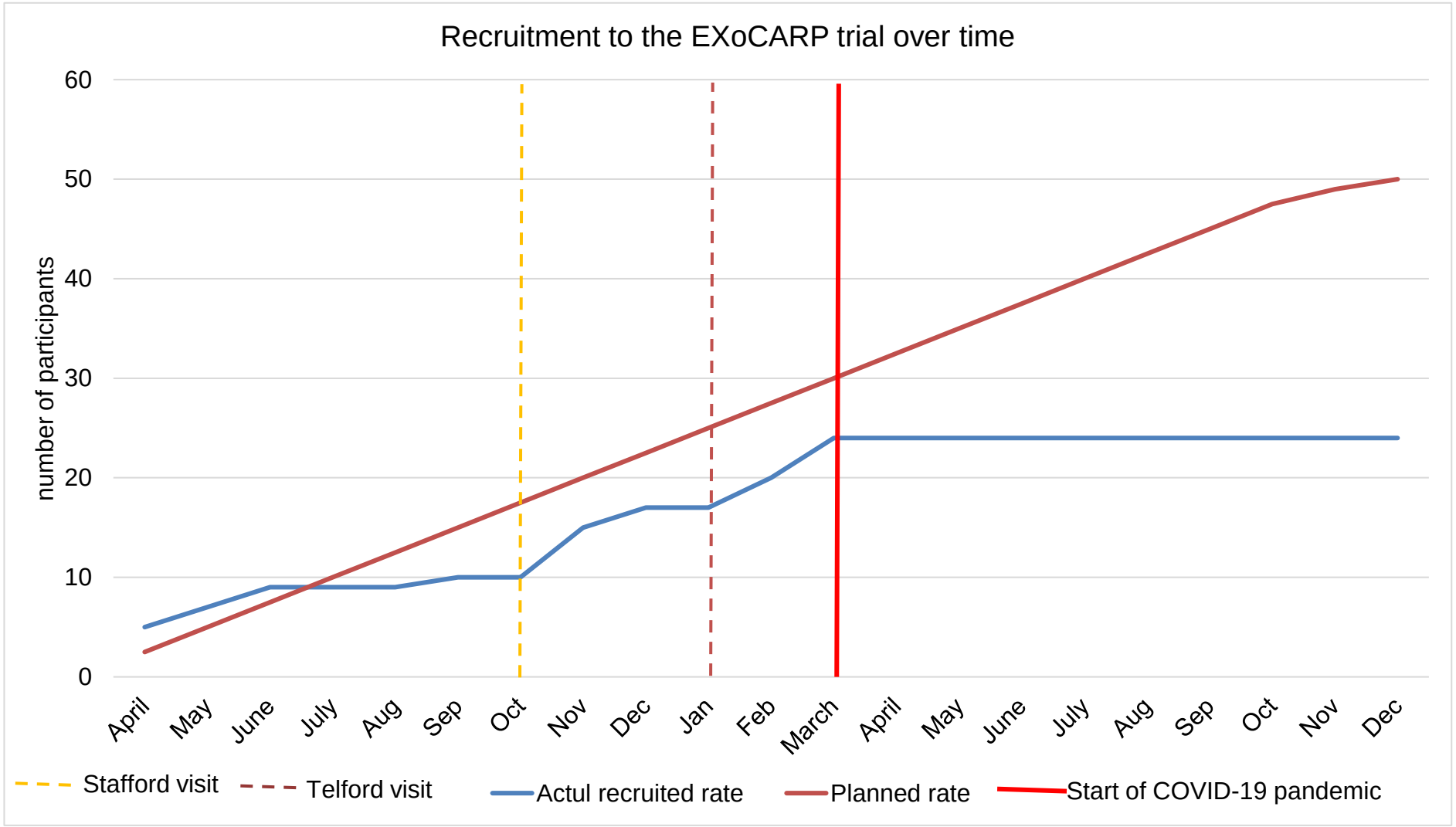


Figure 13: The CONSORT diagram for the trial.


Recruitment to the EXoCARP trial over time
number of participants
60
50
40
30
20
10
0
April
May
June
July
Aug
Sep
Oct
Nov
Dec
Jan
Feb
March
April
May
June
July
Aug
Sep
Oct
Nov
Dec
Stafford visit
Telford visit
Actul recruited rate
Planned rate
Start of COVID-19 pandemic

Recruitment rate (refers to the average number of participants recruited per month) was 1.92 participants per month (from mid-April 2019 until mid-March 2020). Figure 14 represents the actual recruitment rate compared with the planned rate (between the period April 2019 until December 2020). As figure 14 shows, there was a boost in recruitment after two visits to Parkinson's UK groups in Stafford (n=3) and Telford (n=5). The pattern shows that recruitment started similarly to what was planned, until the start of the COVID-19 pandemic that stopped continued recruitment due to the governmental regulation of social distancing, and suspension of face-to-face data collection at the university site to minimise the risk of infection of COVID-19 virus.

The proportion of participants recruited from the number of people who contacted the research team was 65% (24 out of 37 participants). Recruitment was 48% out of the targeted number (24 out of 50, from April 2019 to March 2020), and 80% out of the accepted sample size for pilot studies (24 out of 30). The achievement of the targeted number was not feasible due to the COVID-19 pandemic regulation in mid-March 2020, and inability to recruit until the rest of the planned period (data recruitment was originally planned to continue until December 2020). Attrition was 37% (9 out of the 24). Out of these, seven participants dropped out due to the COVID-19 pandemic (29%), and two dropped out due to other reasons as mentioned at the beginning of this section (8.3%).

4.2. Baseline characteristics of participants

The baseline characteristics for the groups are presented in table 12. The mean (SD) age for the two groups was similar (exercise group = 68.8 (11.1) years; control group = 65.55 (9.27) years). The proportion of males to females was similar in both groups with 75% males in each group. All participants who participated in the study

were Caucasian. There were slightly more people with higher H&Y scores in the exercise group (six participants with Hoehn and Yahr stage III in the exercise group) compared with four in the control group. This imbalance could be accounted for by the small sample size. Both groups were similar for mean (SD) years since diagnosis (exercise group = 6.17 (4.84) years; control group = 7.71 (7.53) years). Additionally, height and weight were similar in both groups (table 12).

A total of 17 participants (71% of the sample) experienced tremor as the dominant symptom, and the remaining 7 (29%) experienced rigidity as the dominant symptom.

Table 12: Baseline characteristics of the included participants.

		Exercise group (n=12)	**Control group (n=12)**	**All participants (n=24)**
Age (years)	Mean (SD)	68.8 (11.1)	65.55 (9.27)	67.25 (10.14)
Sex	Male (%) Female (%)	9 (75%) 3 (25%)	9 (75%) 3 (25%)	18 (75%) 6 (25%)
Height (cm)	Mean (SD)	173.38 (10.50)	174.08 (7.35)	173.73 (8.87)
Weight (Kg)	Mean (SD)	75.08 (17.24)	69.78 (12.82)	72.43 (15.10)
Mini mental state examination	Median (IQR)	29.5 (29, 30)	29 (29, 30)	29 (29, 30)
Years since diagnosis (years)	Mean (SD)	6.17 (4.84)	7.71 (7.53)	6.94 (6.24)
Hoehn and Yahr disease severity	Stage I (n) Stage 2 (n) Stage 3 (n)	3 3 6	5 3 4	8 6 10

4.3. Serious adverse reactions

Submaximal exercise is considered low risk for adverse reactions and events. Within this feasibility study, there were no adverse reactions to report, indicating that no participant reported pain or fatigue related to the intervention. However, three participants reported pain in the knee after running the CPET. Pain was temporary and was reported to be relieved after a period of rest.

There were two serious adverse events; however, neither of these was related to participation in the trial. One participant was investigated for an unrelated serious medical condition after the first assessment session and did not continue in the trial accordingly; another participant had a fall while on holiday, but that event was unrelated to the exercise intervention or tests.

4.4. Success of blinding

The blinded assessor correctly guessed the group randomization for seven participants (29.17%); table 13 represents the confidence level rated by the assessor when asked “How confident you are about in what group you think the participant was?”. The blinded assessor was not confident at all in five out of 16 cases (31%). The blinded assessor accurately guessed the allocation of participants only in four participants.

Table 13: Blinded assessor rating for group allocation.

Description	Assessors’ guess (number of participants)
Very confident	1
Confident	3
Somehow	4
Unsure	3
Not confident at all	5

4.5. Outcomes

4.5.1. Physiological measures

4.5.1.1. Pulmonary function test (PFT)

The PFT was conducted at the baseline session (n=24 participants), after 8 weeks (end of intervention, n=15 participants) and 4 weeks post intervention (12 weeks session, n=14 participants). The PFT was relatively a quick test (taking approximately 20 minutes to complete), with no adverse reactions reported or observed. When the PFT data were checked for normality using histograms and Q-Q plots, all PFT outcomes data were normally distributed, and mean (SD) was reported (table 14). Mean (SD) FEV_1 was 2.93 (0.83) L/min compared with a predicted value of 3.12 (0.67) L/min for healthy people of similar age, height, weight, sex, and ethnicity. Additionally, mean (SD) of FEV_1/FVC (%) was found to be 72.48 (7.21) % in the whole sample (n=24) (table 14).

Results of the independent *T*-test showed that disease severity was significantly higher (p=0.03), and baseline physical activity level was significantly lower (p= 0.003) in participants with abnormal pulmonary pattern (obstructive, restrictive and mixed patterns; n=13), than in participants with normal pulmonary pattern (n=11).

With regard to pulmonary pattern, 54% of the included 24 participants showed abnormal pulmonary pattern (11 participants with obstructive pulmonary pattern, one with restrictive pattern and one with mixed obstructive and restrictive pattern) (Figure 15). Effectiveness of the intervention was not assessed; however, changes in PFT outcomes overtime in both groups were calculated and reported in table 16 and figures 16 and 17. Differences in baseline characteristics between participants with abnormal pulmonary pattern vs participants with normal pulmonary pattern are reported in table 15.

Table 14: Baseline Pulmonary function test results for the whole sample (n=24) at baseline session, including predicted values for people with same age, gender, ethnic background, height and weight.

	FEV_1 (L/min)	**$FEV_{1\ Predicted}$ (L/min)**	**$FEV_{1\ Predicted}$% (%)**	**FVC (L/min)**	**$FVC_{Predicted}$ (L/min)**	**$FVC_{Predicted}$% (%)**	**FEV_1/FVC (%)**
Mean (SD)	2.93 (0.83)	3.12 (0.67)	93.67 (15.23)	4.03 (1.03)	3.97 (0.86)	101.37 (13.32)	72.48 (7.21)
Minimum	1.31	1.77	64.86	2.11	2.34	70.95	59.95
Maximum	4.51	4.17	122.11	6.10	5.35	138.91	87.04

Table 15: Differences in baseline characteristics between participants with abnormal pulmonary pattern (n=13) vs participants with normal pulmonary pattern (n=11).

	Age	**Sex**	**Years since diagnosis**	**Disease severity**	**Physical activity**
t	1.05	-0.92	0.80	3.34	1.00
p-value	0.08	0.37	0.54	0.003*	0.03*
*Differences between participants with abnormal and normal pulmonary patterns are significant if p-value>0.05					

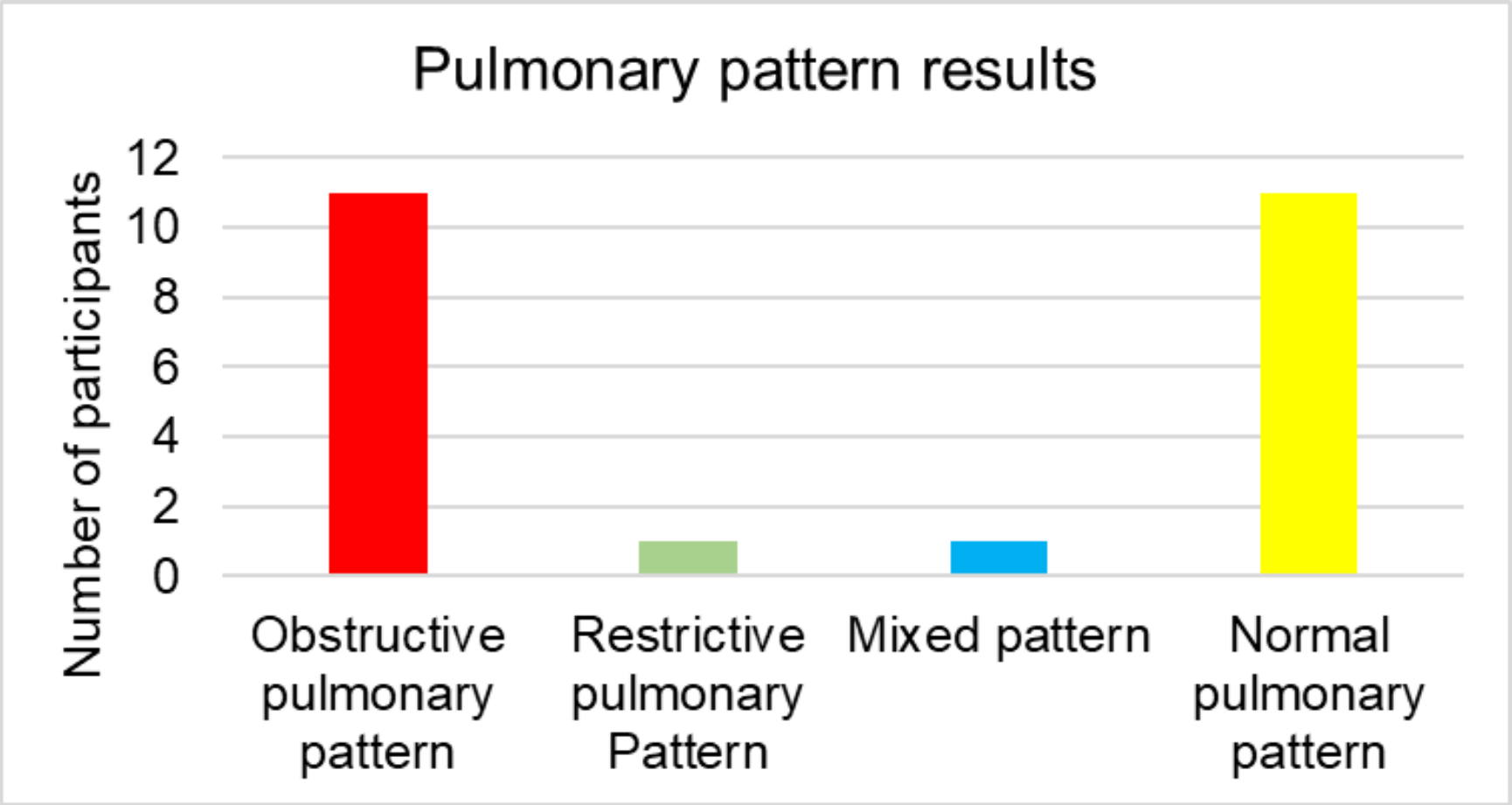


Figure 15: Bar chart representing pulmonary patterns for the included participants at baseline (n=24).

Table 16: Pulmonary function test for both groups at baseline (n=24), end of intervention (n=15), and the follow-up session (n=14).

		FEV_1 (L/min)			**FVC (L/min)**			**FEV_1/FVC (%)**		
		Baseline	**After 8 weeks**	**After 12 weeks**	**Baseline**	**After 8 weeks**	**After 12 weeks**	**Baseline**	**After 8 weeks**	**After 12 weeks**
Exercise group	**Mean (SD)**	2.83 (0.80)	3.12 (0.74)	3.13 (0.80)	3.86 (1.03)	4.13 (1.06)	4.27 (1.07)	73.02 (6.37)	75.86 (4.77)	73.33 (4.97)
	Change between baseline and 8 weeks*	0.29			0.27			2.84		
	Change between 8 weeks and 12 weeks*	0.01			0.14			-2.53		
Control group	**Mean (SD)**	3.03 (0.88)	2.82 (0.81)	2.92 (0.81)	4.20 (1.05)	3.86 (1.02)	4.02 (1.03)	71.94 (8.22)	73.38 (10.08)	73.13 (9.09)
	Change between baseline and 8 weeks*	-0.21			-0.34			1.44		
	Change between 8 weeks and 12 weeks*	0.1			0.16			-0.25		

* Calculated as the difference between the two means.

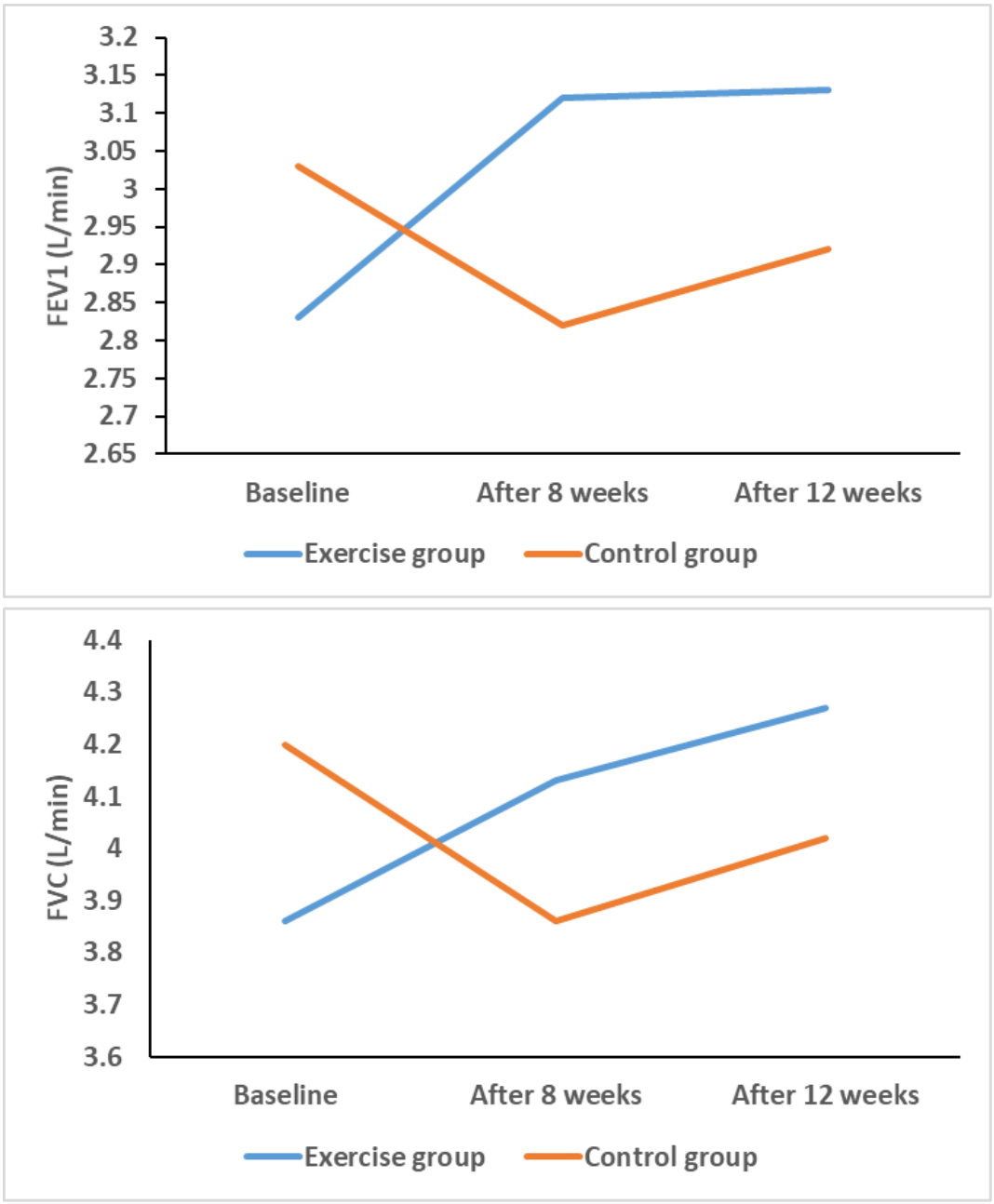


Figure 16: FEV1 AND FVC results in both the exercise and the control groups.

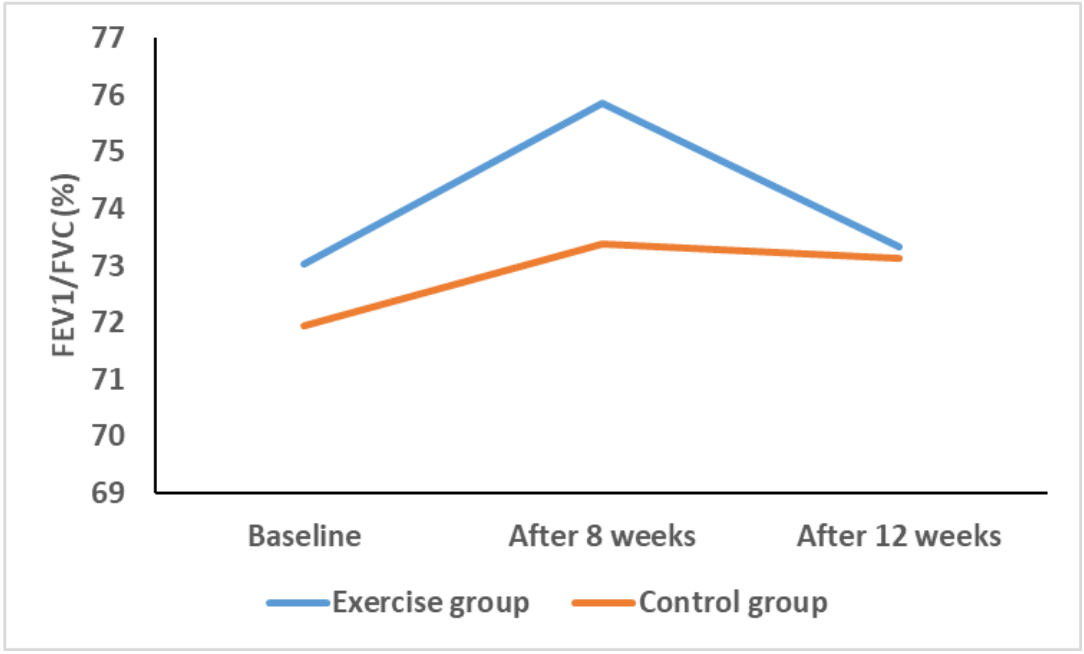


Figure 17: FEV1/FVC results in both the exercise and the control groups.

4.5.1.2 Cardiopulmonary Exercise test (CPET)

The CPET was conducted with 19 participants out of the 24 at the baseline session. This is because five participants presented with high blood pressure during the baseline session (blood pressure >140/90 mm Hg according to the AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire) and we could not run the test according to the safety guidance mentioned in chapter three. Twelve participants completed the CPET at the end of the intervention session and the follow up session. In 21 participants, the test was terminated early before the full duration of the test was completed due to achieving 70% of the age-predicted HR_{max}. In three participants, the test was terminated due to fatigue, indicated by Borg scores above 5. No adverse reactions were reported or observed.

As the data for CPET were not normally distributed, medians, IQRs and ranges were calculated and summarised in tables 17 and 18. Predicted median VO_{2Peak} was 20.22 ml.kg-1.min-1 in the whole sample, compared with 19.39 ml.kg1.min-1 predicted VO_{2Peak} for healthy people above 65 years old (Loe et al., 2016). Effectiveness of the intervention was not assessed; however, changes in CPET outcomes over time points in both groups are reported in table 19 and plotted in figures 18 and 19.

Table 17: Cardiopulmonary exercise test results for the whole sample at baseline (n=19).

	Predicted VO_{2Peak} ($ml.kg^{-1}.min^{-1}$)	**Resting HR (beats/min)**	**HR_{peak} (beats/min)**	**Resting SBP (mmHg)**	**Resting DBP (mmHg)**	**$Workload_{max}$ (kPa)**	**$Borg_{max}$ score**	**TD (min)**
Median (IQR)	20.22 (19.38, 20.96)	79.00 (72.00, 84.00)	107.00 (104.00, 111.00)	121.00 (107.00, 129.25)	70.00 (65.25, 76.50)	1.50 (1.25, 2.25)	3.00 (2.00, 4.00)	6.00 (4.00, 7.00)
Minimum	17.00	45.00	51.00	78.00	60.00	0.75	1.00	4.00
Maximum	28.36	92.00	124.00	182.00	93.00	4.00	5.00	9.00

VO_2: oxygen uptake; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; TD: test duration; IQR: inter quartile range.

Table 18:Predicted VO_2 peak for the included sample vs Predicted VO_{2Peak} for healthy people above 65 years old (Loe et al., 2016).

		Predicted VO_{2Peak} for the included sample ($ml.kg^{-1}.min^{-1}$)	**Predicted VO_{2Peak} for healthy people above 65 years old ($ml.kg^{-1}.min^{-1}$)**
Males	Median	20.23	40.20
Females	Median	19.39	31.10
VO_2: oxygen uptake			

Table 19: Cardiopulmonary exercise test results in both groups at baseline (n=19), end of intervention (n=12) and the follow-up session (n=12).

		Predicted VO_{2Peak} ($ml.kg^{-1}.min^{-1}$)			**HR_{peak} (beats/min)**			**Test duration (min)**		
		Baseline	**After 8 weeks**	**After 12 weeks**	**Baseline**	**After 8 weeks**	**After 12 weeks**	**Baseline**	**After 8 weeks**	**After 12 weeks**
Exercise group	**Median (IQR)**	20.06 (18.91, 20.62)	21.14 (18.80, 21.69)	19.75 (17.98, 20.64)	106.00 (96.75, 109.50)	105.00 (99.50, 112.00)	106.00 (102.50, 108.75)	5.75 (5.00, 7.13)	6.00 (5.75, 7.25)	6.50 (4.75, 10.00)
	Minimum	17.00	18.27	17.64	51.00	95.00	95.00	4.00	5.00	4.00
	Maximum	21.14	21.96	21.28	124.00	124.00	111.00	8.00	8.00	10.00
	Difference between week 8 and baseline*	1.08			-1.00			0.25		
	Difference between week 12 and week 8*	-1.39			0.00			0.50		
Control group	**Median (IQR)**	20.38 (19.34, 23.16)	20.65 (19.75, 26.57)	19.85 (18.48, 24.69)	108.00 (105.00, 115.00)	106.50 (104.75, 112.75)	108.50 (105.50, 114.25)	6.00 (4.00, 6.25)	6.00 (5.00, 7.25)	6.00 (4.00, 6.75)

	Minimum	17.93	18.10	18.30	104.00	104.00	104.00	4.00	5.00	4.00
	Maximum	28.36	31.05	26.03	120.00	118.00	118.00	9.00	8.00	9.00
	Difference between week 8 and baseline*	0.27			-1.50			0.00		
	Difference between week 12 and week 8*	-0.8			2.00			0.00		
VO_2: oxygen uptake; HR: heart rate; IQR: inter quartile range. *Calculated as the difference between the two means.										

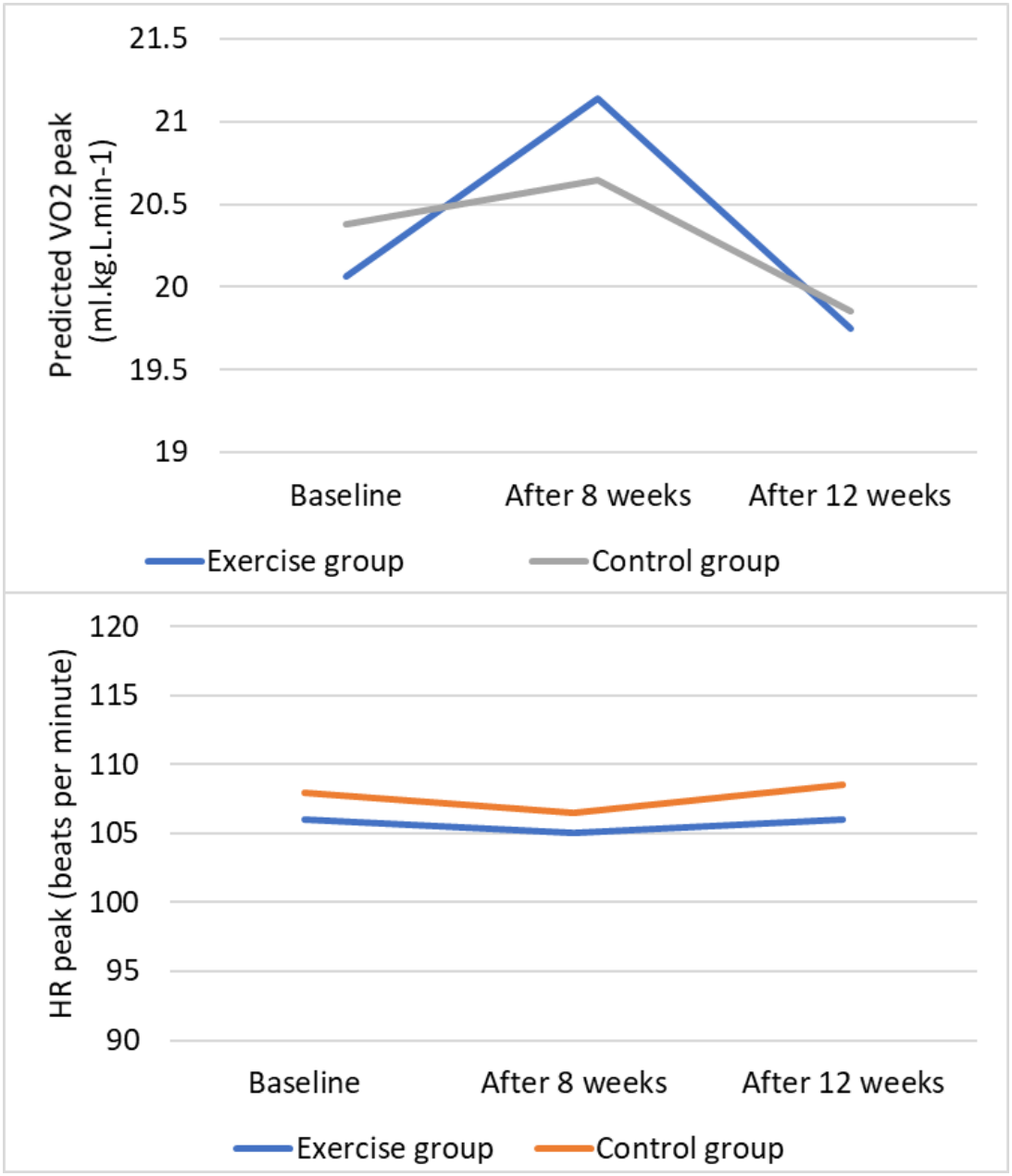


Figure 18: CPET changes in both groups in terms of VO_{2peak} and heart rate for both the exercise group and the control group.

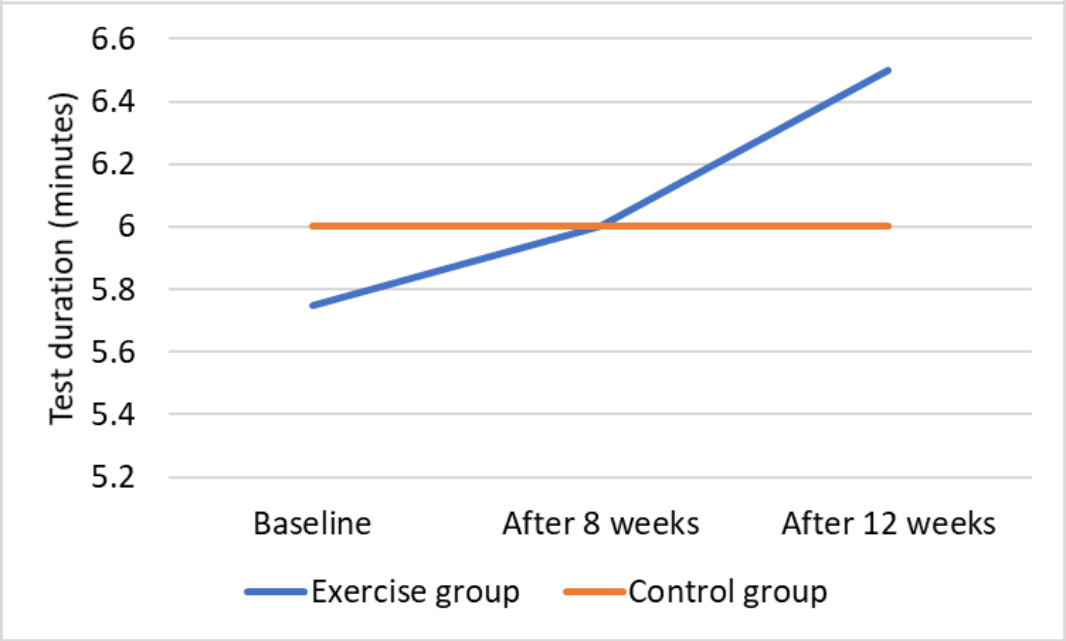


Figure 19: CPET changes in both groups in terms of test duration for both the exercise group and the control group.

4.5.2. Analysis of the physical activity diary form and Activity monitors data

All participants who were enrolled in the trial and completed the eight-week period (n=15) wore the activity monitors around their waists and completed the daily physical activities diaries. Mean (SD) of wearing days for the activity monitors was 42.5 (8.8) days out of a maximum of 56 days. Adherence rate of wearing the activity monitors was 75.95%.

All the physical activity data are reported as median (IQR) as they were not normally distributed. Table 20 represents the median (IQR) of minutes spent in exercise as reported by the physical activity diary and the Actigraph. From the daily diary sheets, participants in the exercise group reported doing 32.3 (28.9, 37.5) minutes of usual physical activity (without adding the extra amount of physical activity that they have been asked to do in the study) (figure 20A); of these minutes, only 3.7 (1.0, 8.9) were of MVPA intensity (figure 21A). The control group reported doing 21 (20, 51.3) minutes of usual physical activity (figure 18A), with only 3.0 (1.0, 3.0) minutes as MVPA intensity (figure 22A).

During the intervention phase of the study, participants in the exercise group increased time spent in MVPA up to 40.6 (22.3, 48.2) minutes per day, as recorded by the Actigraph (figure 21A). Of these minutes, 37.2 (27.1, 45.4) were the extra minutes that have been done on top of the 3.7 (1.0, 8.9) original minutes spent in MVPA as recorded by the Actigraph (figure 22B). Number of steps/day for each group is reported in Table 20 and figure 22B.

Table 20: Minutes spent in exercise as reported by the daily exercise diary and the Actigraph, including time spent in all intensities, and moderate to vigorous intensities specifically, as an extra minutes for the intervention, and as an original minutes without the intervention.

		Total minutes of usual exercise per day without the extra minutes of intervention as reported by the exercise diary (including all the intensities)	**Original MVPA per day (without the intervention extra minutes) by the Actigraph**	**Total minutes of exercise per day including the extra minutes of intervention as reported by the exercise diary (including all the intensities)**	**Extra minutes spent on MVPA as reported by the Actigraph**	**Steps per day by the Actigraph**
Exercise group	**Median (IQR)**	32.3 (28.9, 37.5)	3.7 (1.0, 8.9)	72.8 (56.1, 79.1)	37.2 (27.1, 45.4)	6021.6 (3522.7, 7001.0)
	Minimum	26.0	1.0	52.9	27.0	2073.7
	Maximum	39.2	12.5	89.3	52.4	10545.0
Control group	**Median (IQR)**	21 (20, 51.3)	3.0 (1.0, 3.0)	21 (20, 51.3)		5568.3 (2089.5, 7178.3)
	Minimum	20.0	0.0	20.0		454.1
	Maximum	61.0	4.1	61.0		15997.8

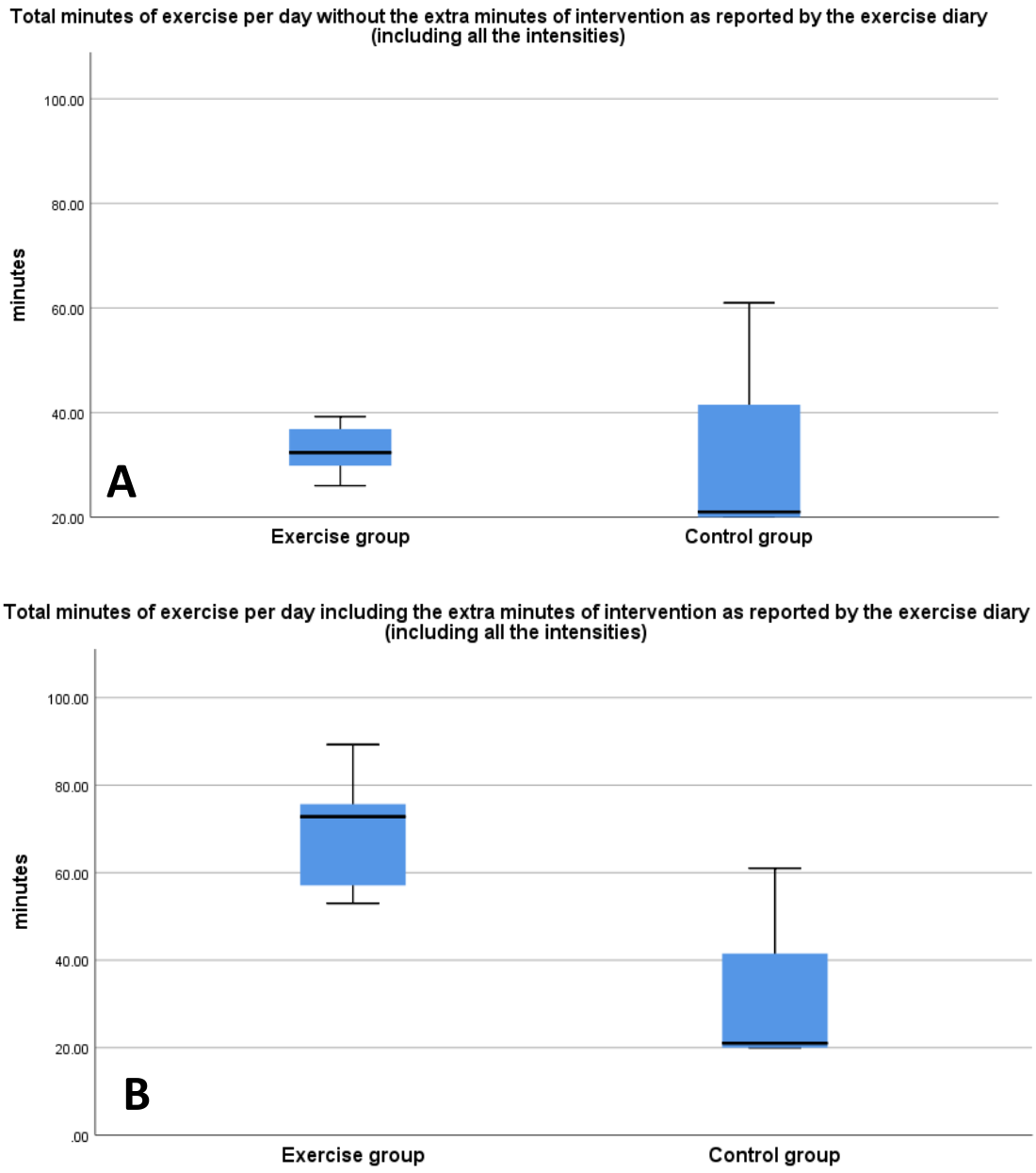


Figure 20: A) Boxplot representing the total minutes of exercise per day without the extra minutes of intervention as reported by the exercise diary (including all the intensities) in both groups; B) Boxplot representing the total minutes of exercise per day in both groups.

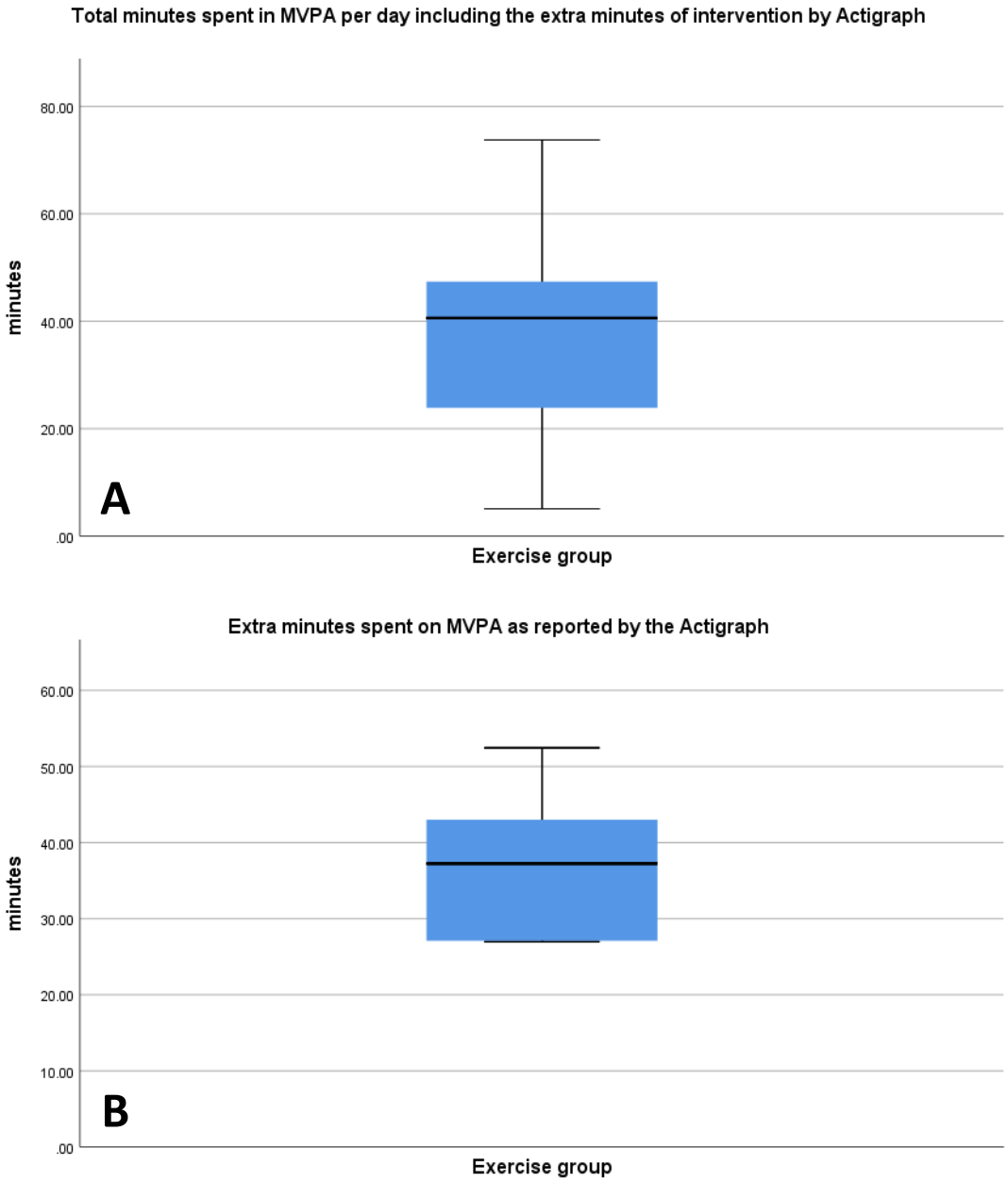


Figure 21: A) Boxplot representing the total minutes spent in MVPA per day including the extra minutes of intervention by Actigraph in the exercise group; B) boxplot representing the extra minutes spent on MVPA as reported by the Actigraph in the exercise group.

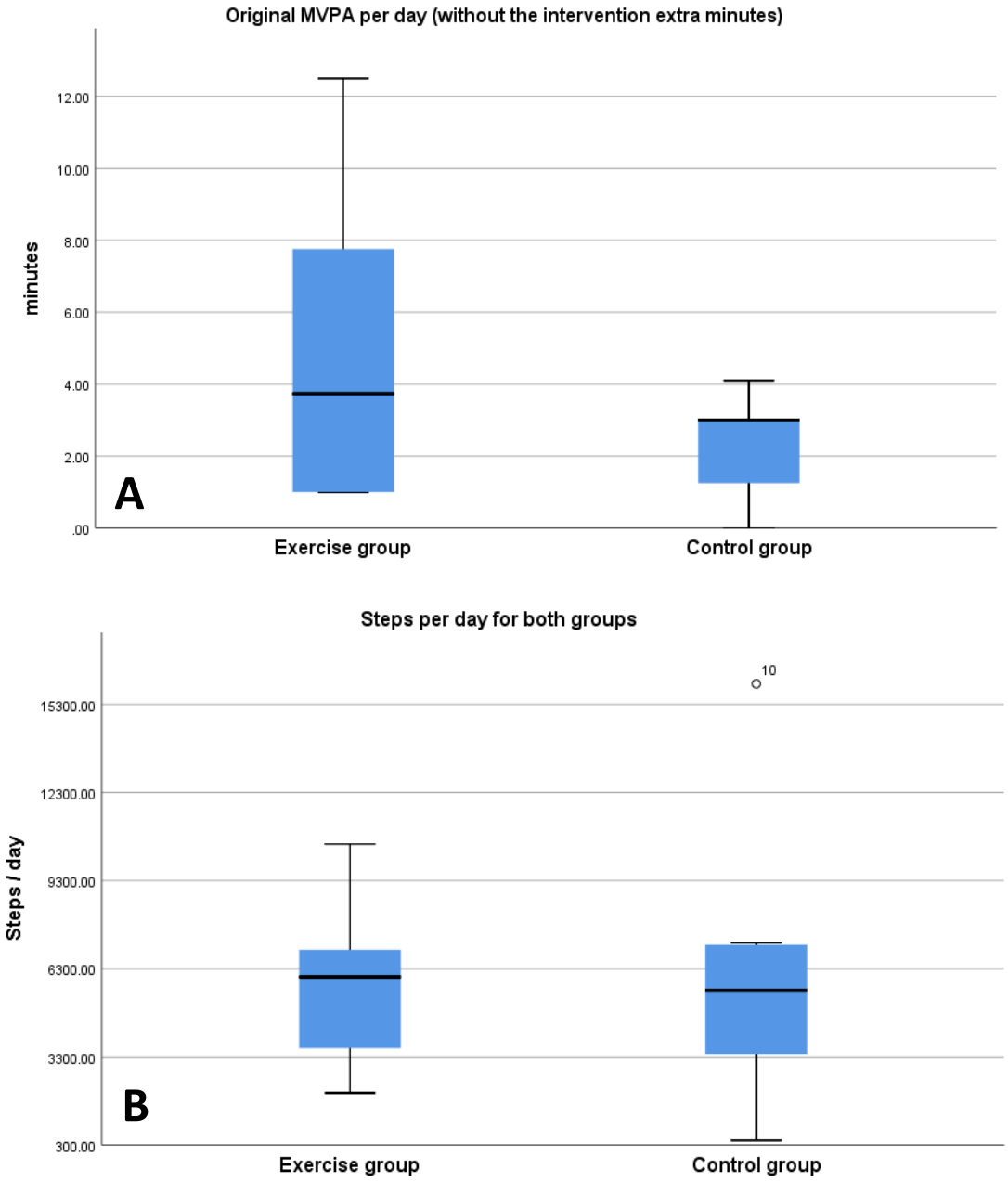


Figure 22: A) Boxplot representing the original MVPA per day (without the intervention extra minutes) by the Actigraph; B) boxplot representing steps per minute as reported by Actigraph for both groups.

4.5.3. Subjective outcomes and questionnaires

All of the questionnaires were completed at baseline (n=24) and at the end of intervention (n=15) by participants in both groups.

4.5.3.1. Quality of life

Participants in the exercise group increased their median (IQR) scores in the total PDQ-39 by 0.03 from baseline (0.27 (0.18, 0.37)) to end of intervention (0.30 (0.04, 0.34)). Those in the control group increased their median (IQR) scores by 0.07, from baseline (0.22 (0.07, 0.32)) to end of intervention (0.29 (0.09, 0.32)).

Results of the eight dimensions and the total score of the PDQ-39 are represented in Figures 23 - 27. The higher the PDQ-39 scores, the lower the quality of life. Lower scores (indication of better quality of life) were noticed in the exercise group in the following domains: ADL; emotion; stamina; social support; and bodily discomfort. In the control group, lower scores (indication of better quality of life) were noticed in the following domains: ADL; and stamina.

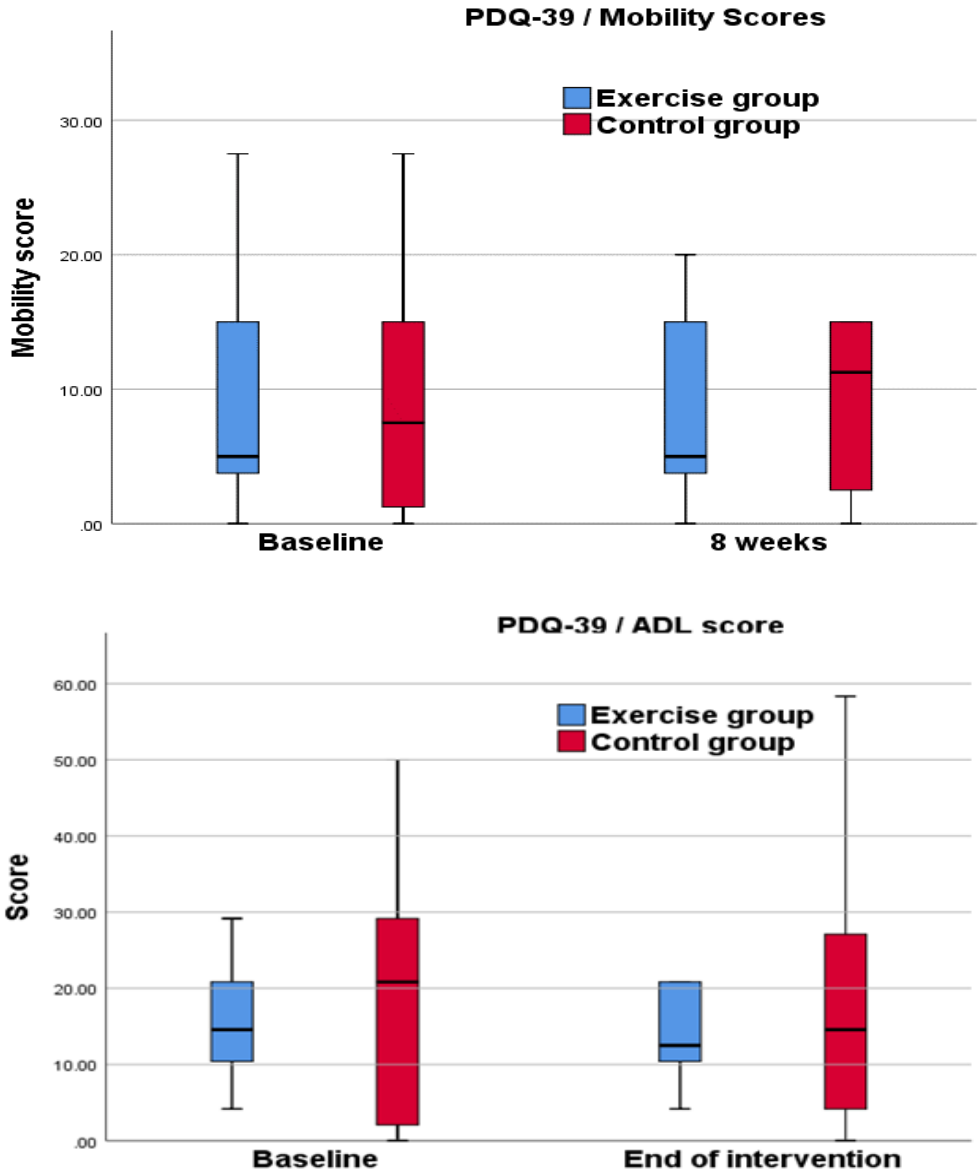


Figure 23: Parkinson's Disease Quality of Life Questionnaire results for: Mobility and Activity of Daily Life domains for both groups at baseline and at the end of intervention (after eight weeks).

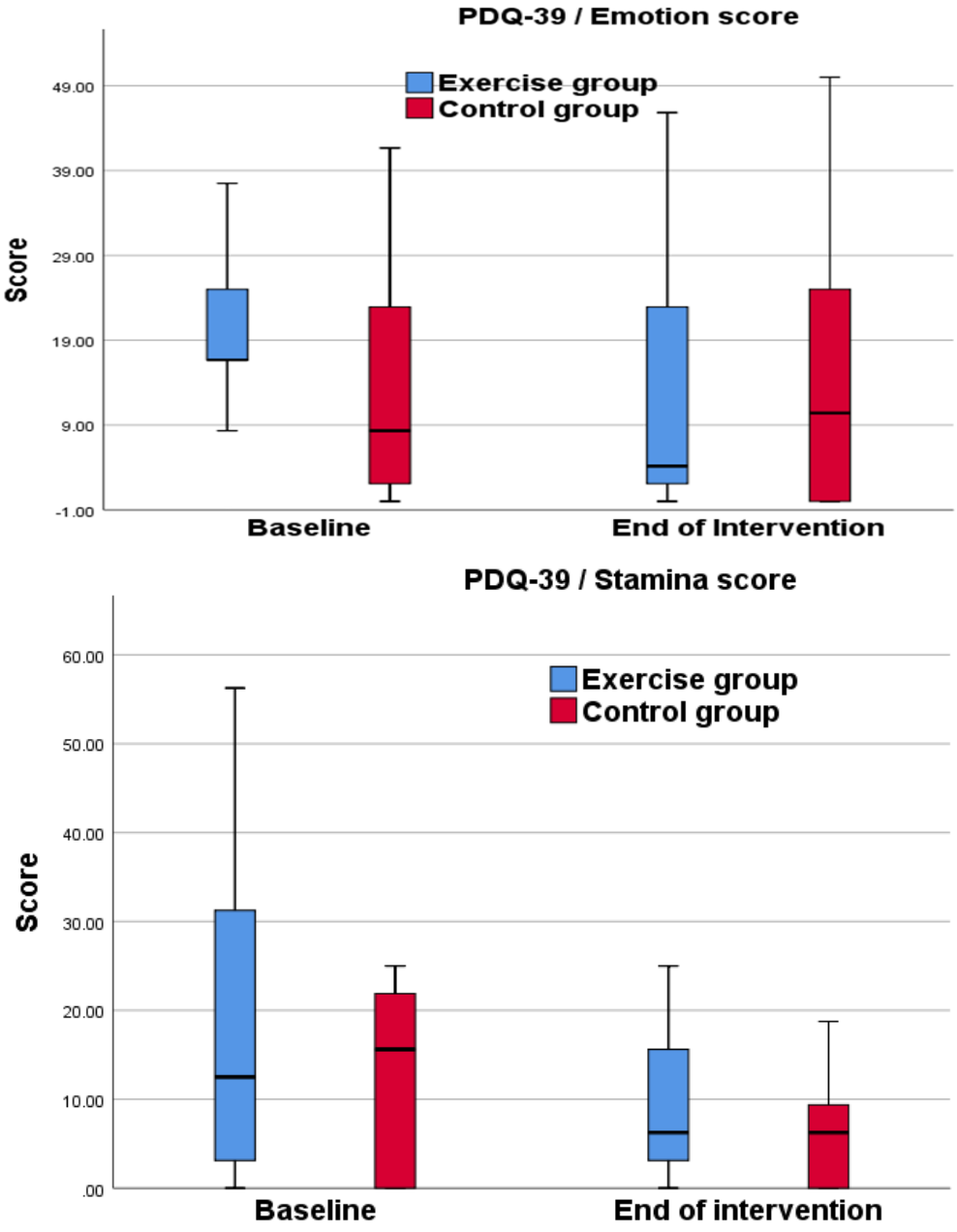


Figure 24: Parkinson's Disease Quality of Life Questionnaire results for: Emotion; and Stigma domains for both groups at baseline and at the end of intervention (after eight weeks).

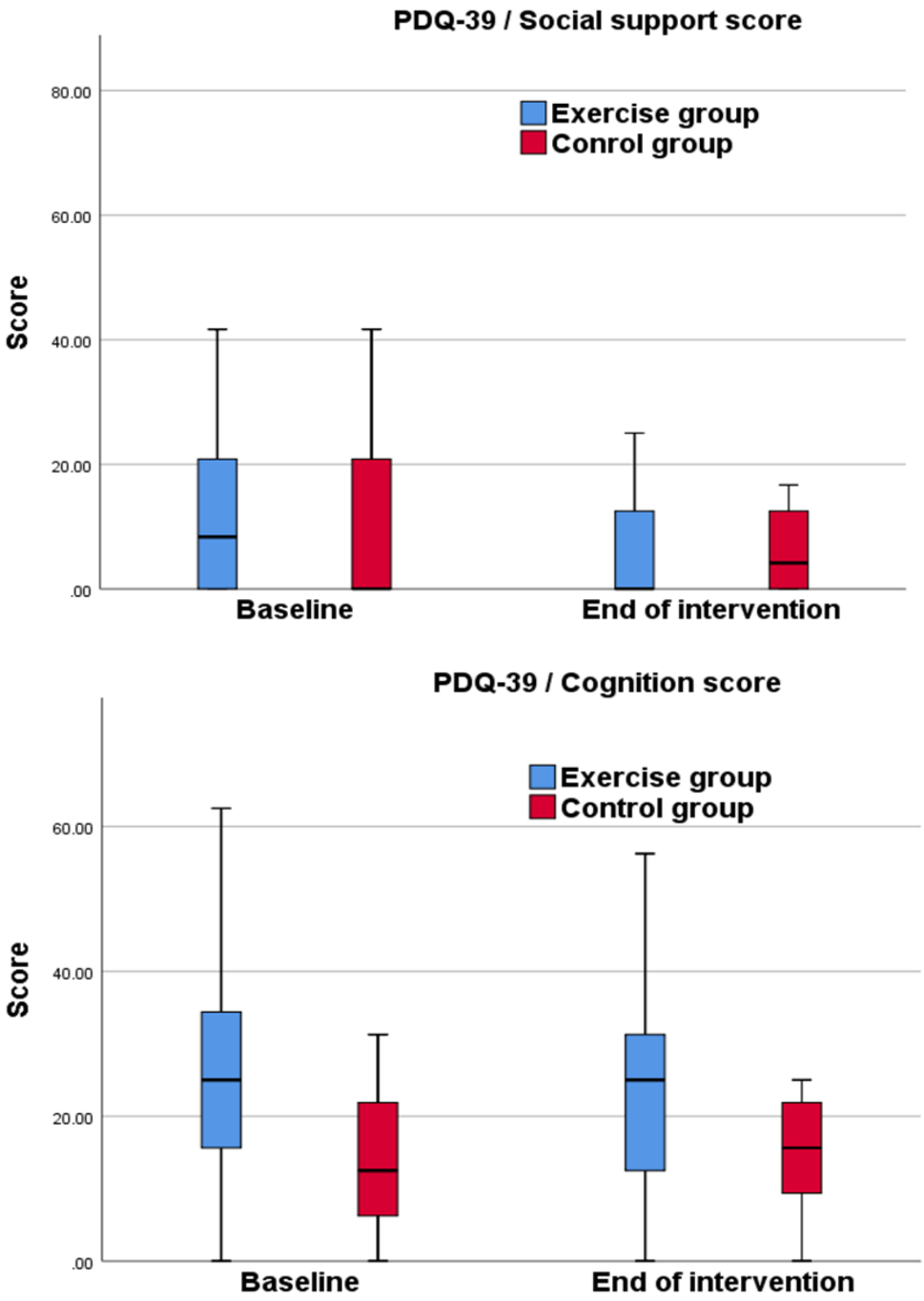


Figure 25: Parkinson's Disease Quality of Life Questionnaire results for: Stigma; Social support; and Cognition domains for both groups at baseline and at the end of intervention (after eight weeks).

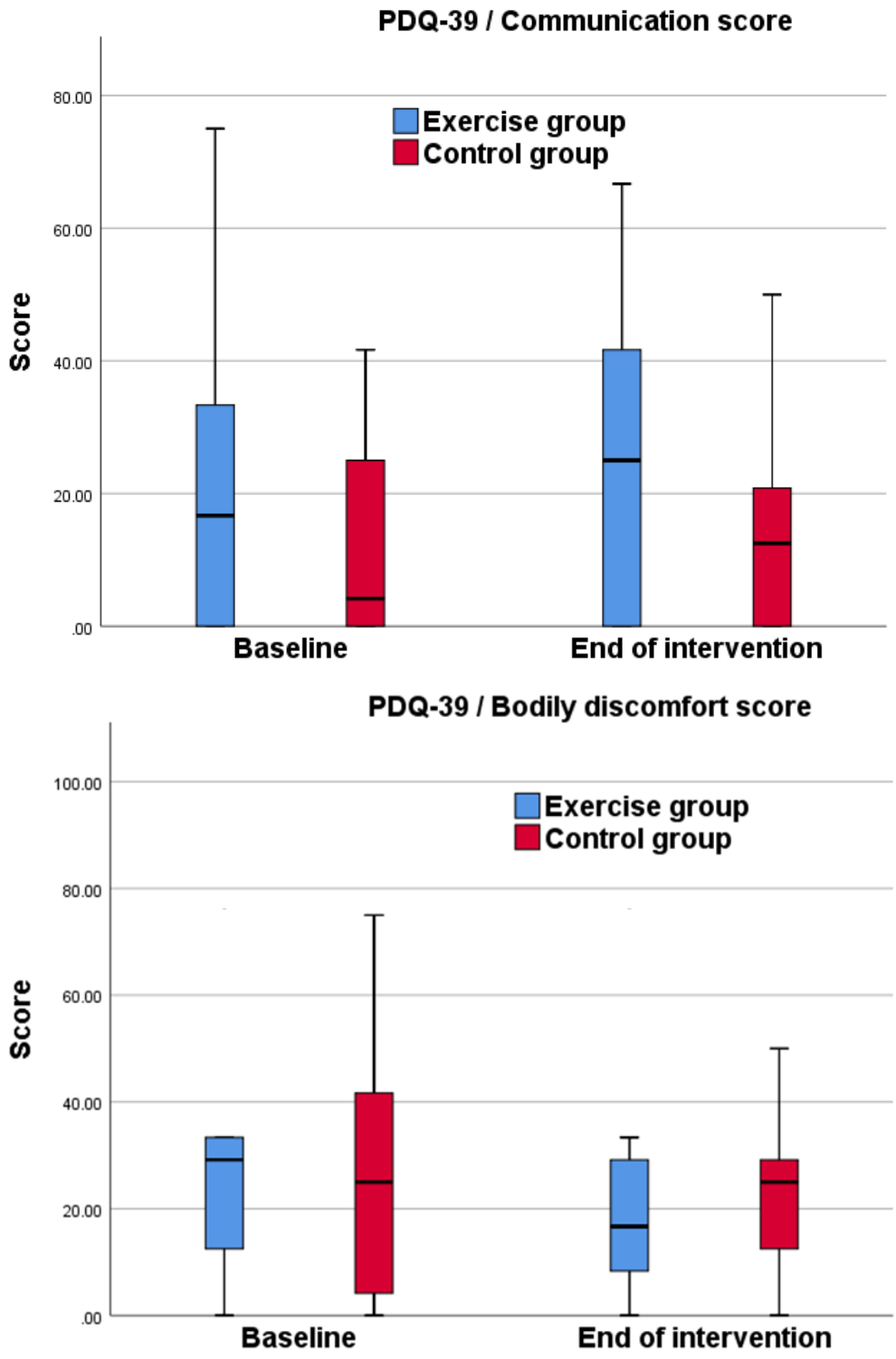


Figure 26: Parkinson's Disease Quality of Life Questionnaire results for: Communication; and Bodily discomfort domains for both groups at baseline and at the end of intervention (after eight weeks).

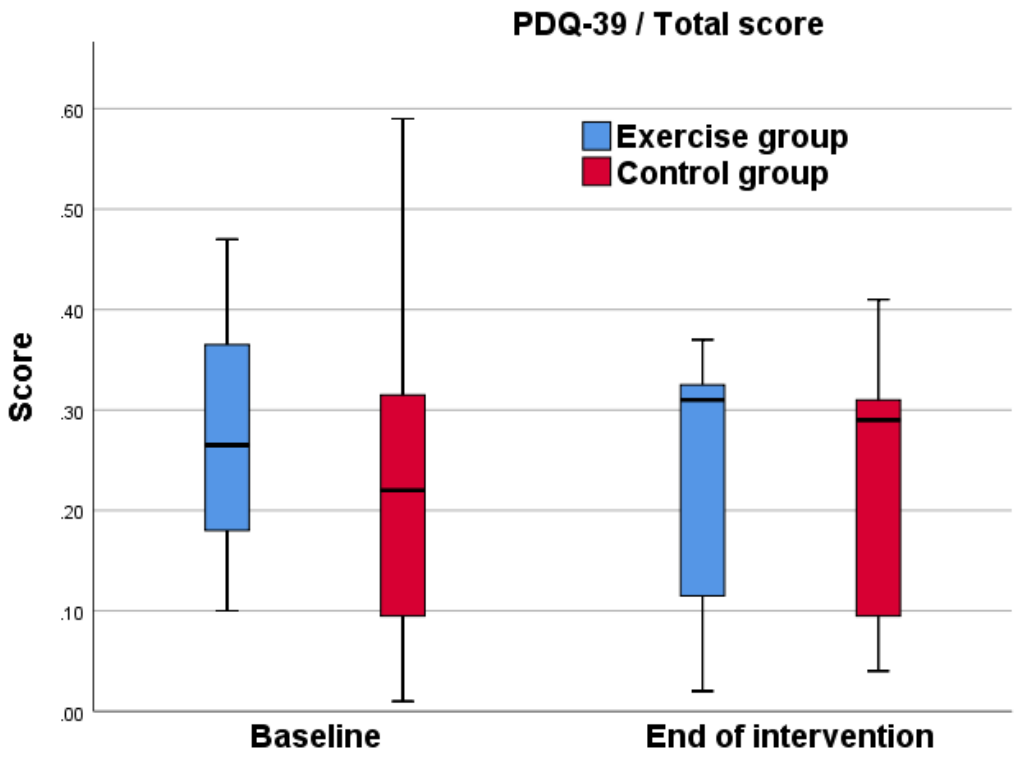


Figure 27: Parkinson's Disease Quality of Life Questionnaire results for the total score of the questionnaire for both groups at baseline and at the end of intervention (after eight weeks).

4.5.3.2 Non-motor symptoms

Median (IQR) total scores for the Non-Motor Symptoms Questionnaire (NMSQ) for the whole sample at baseline and at the end of intervention were the same (8), indicating mild symptoms (<10). However, the maximum score at baseline (18) and at end of intervention (17) indicate moderate symptoms.

Participants who were in the exercise group showed a decrease in their median score, from 8.50 at baseline to 7.00 at end of intervention, indicating improvement in non-motor symptoms. Similarly, participants in the control group showed a slight decrease in their median score, from 9.00 at baseline to 8.00 at end of intervention (figure 28).

4.5.3.3 Independence in activities of daily living

There were no changes in total scores of the Barthel Index for either group between the baseline and the end of intervention (exercise group median (IQR) = 19 (19,19.75) to 20 (19, 20); control group median (IQR) = 19 (19, 20) to 20 (19, 20)). Both groups showed high levels of independence (range 18-20) (Figure 29).

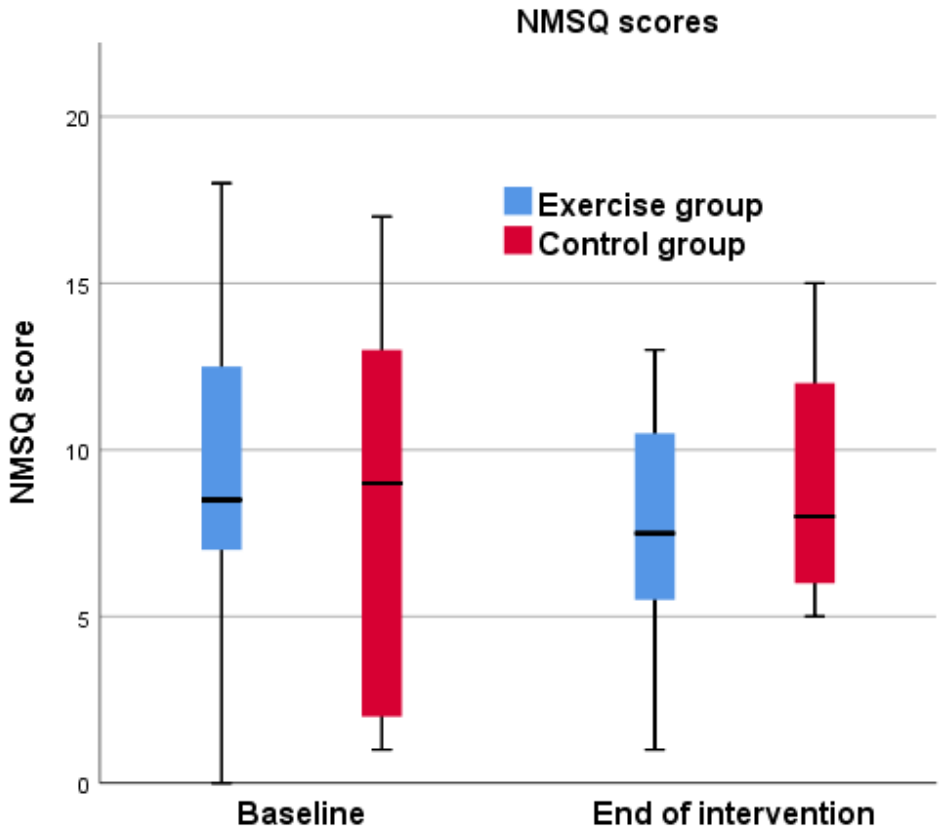


Figure 28:Results of the Non-Motor Symptoms Questionnaire (NMSQ) for both groups at baseline and at the end of intervention (after eight weeks).

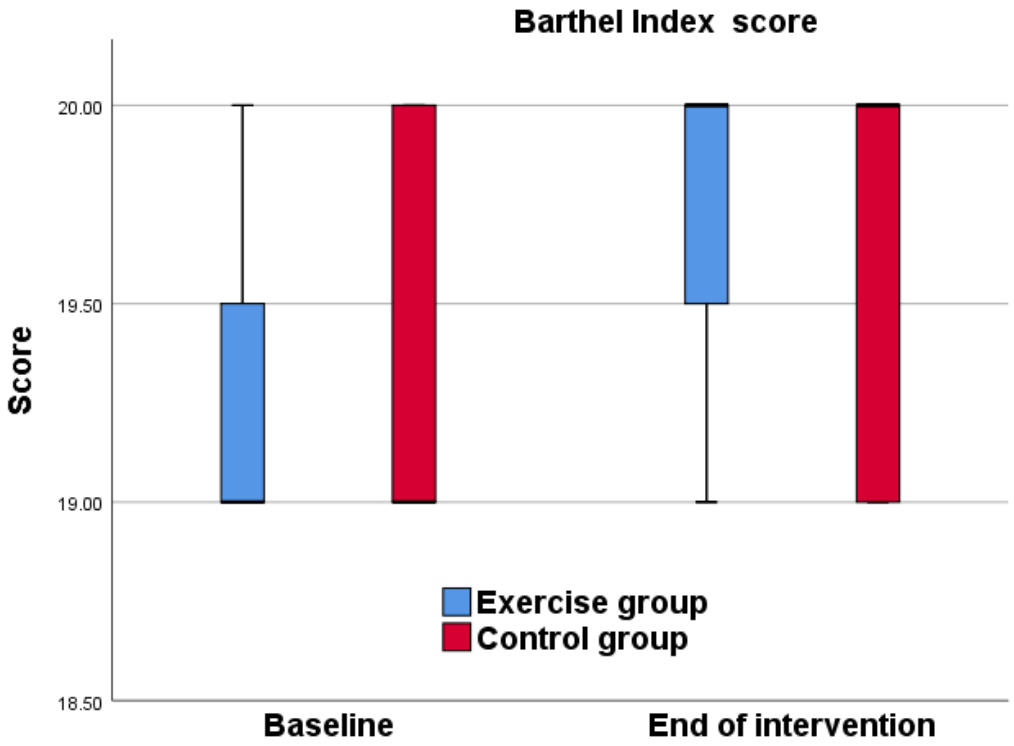


Figure 29: Barthel Index results for intervention and control groups at baseline and end of intervention (after eight weeks).

4.5.3.4. Memory

Median (IQR) prospective and retrospective memory questionnaire total scores increased for the exercise group by 3 points from baseline (25 (19.75, 38.75)) to end of intervention (28 (24.00, 46.00)), and for the control group by 5.5 points from baseline (28.5 (24.5, 38)) to end of intervention (34 (25.75, 47.75)). Similarly, the total PRMQ score increased in both groups from baseline to end of intervention (Figures 30 and 31). The higher the scores in PRMQ, the worse is the memory.

Median (IQR) prospective memory scores decreased in the exercise group by 2 points from baseline (15 (11, 20)) to end of intervention (13 (12, 24)), and retrospective memory increased by 3 points from baseline (12 (10, 19)) to end of intervention (15 (11, 25)). Median (IQR) prospective memory increased by 3 points in the control group from baseline (15 (14.25, 21.5)) to end of intervention (18 (14, 26.25)), and retrospective memory increased by 2.5 points from baseline (13 (10.25, 16.5)) to end of intervention (15.5 (12.25, 22, 25)).

4.5.3.5. Depression

Median (IQR) GDS scores showed almost no changes in the exercise group from baseline (3.0 (0.5, 4.0) to end of intervention eight weeks later (3.0 (0.0, 6.0)). Slight improvement (decrease in score) was noticed in the control group scores from baseline (1.5 (1.0, 3.5) to end of intervention (1.0 (0.0, 1.8)) (figure 32). Median scores for both groups were low (<4.00), indicating no depression.

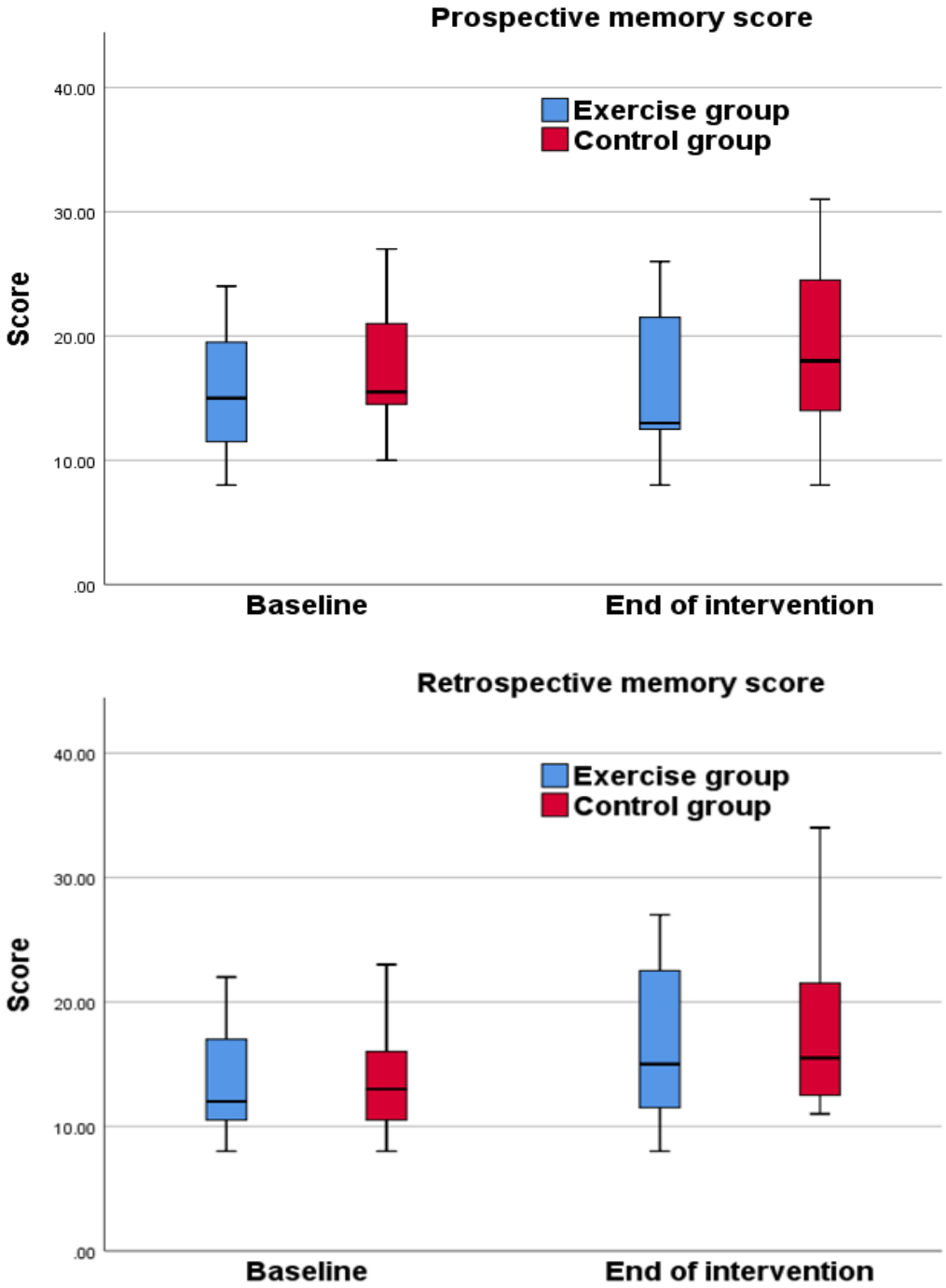


Figure 30: Prospective-Retrospective Memory Questionnaire results for both groups at baseline and at the end of intervention (after eight weeks).

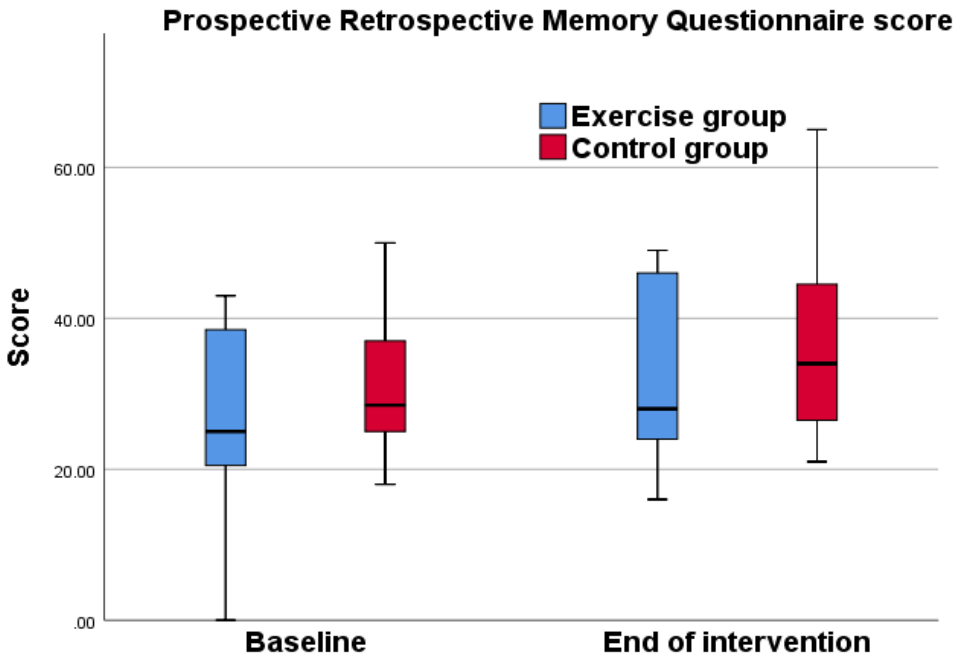


Figure 31: Total score of the Prospective-Retrospective Memory Questionnaire results for both groups at baseline and at the end of intervention (after eight weeks).

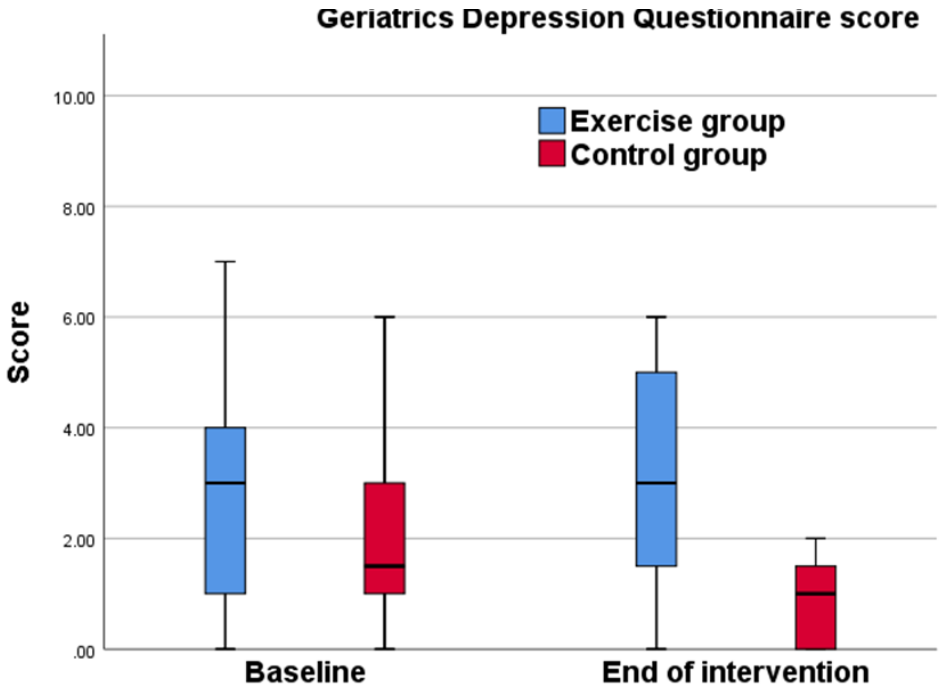


Figure 32: The Geriatrics Depression Scale scores for exercise and control groups at baseline and end of intervention (after eight weeks).

4.5.3.6. Baseline Physical activity (the Baseline Physical Activity Survey)

Baseline physical activity survey data showed that most participants (22 out of 24) were already doing aerobic exercise regularly, with a range of 0 to 65 minutes per day for 0 to 7 days per week (figure 28). Stationary cycling, outdoor cycling, walking, jogging, running outdoors, taekwondo, dancing, swimming, and treadmill walking were reported as aerobic exercise that was regularly done before the trial.

Nine participants (exercise group=4, control group=5) reported an average of 21-30 minutes of exercise per day, three times per week. One participant (control group) reported more than 60 minutes per day, three times per week, and one participant reported zero minutes of exercise per day (control group) (figures 33 and 34).

The baseline physical activity questionnaire revealed that 15 participants (exercise group=8, control group= 7) experienced dyspnoea while doing their regular exercise.

4.5.4. Correlational analysis between outcome measures

Spearman's correlational analysis did not show any significant correlation between the GDS and the emotion dimension of the PDQ-39 ($r=0.053$, $p=0.805$). A significant, moderate correlation was found between the Barthel Index and the ADL dimension of PDQ-39 ($r=-0.467$, $p=0.02$).

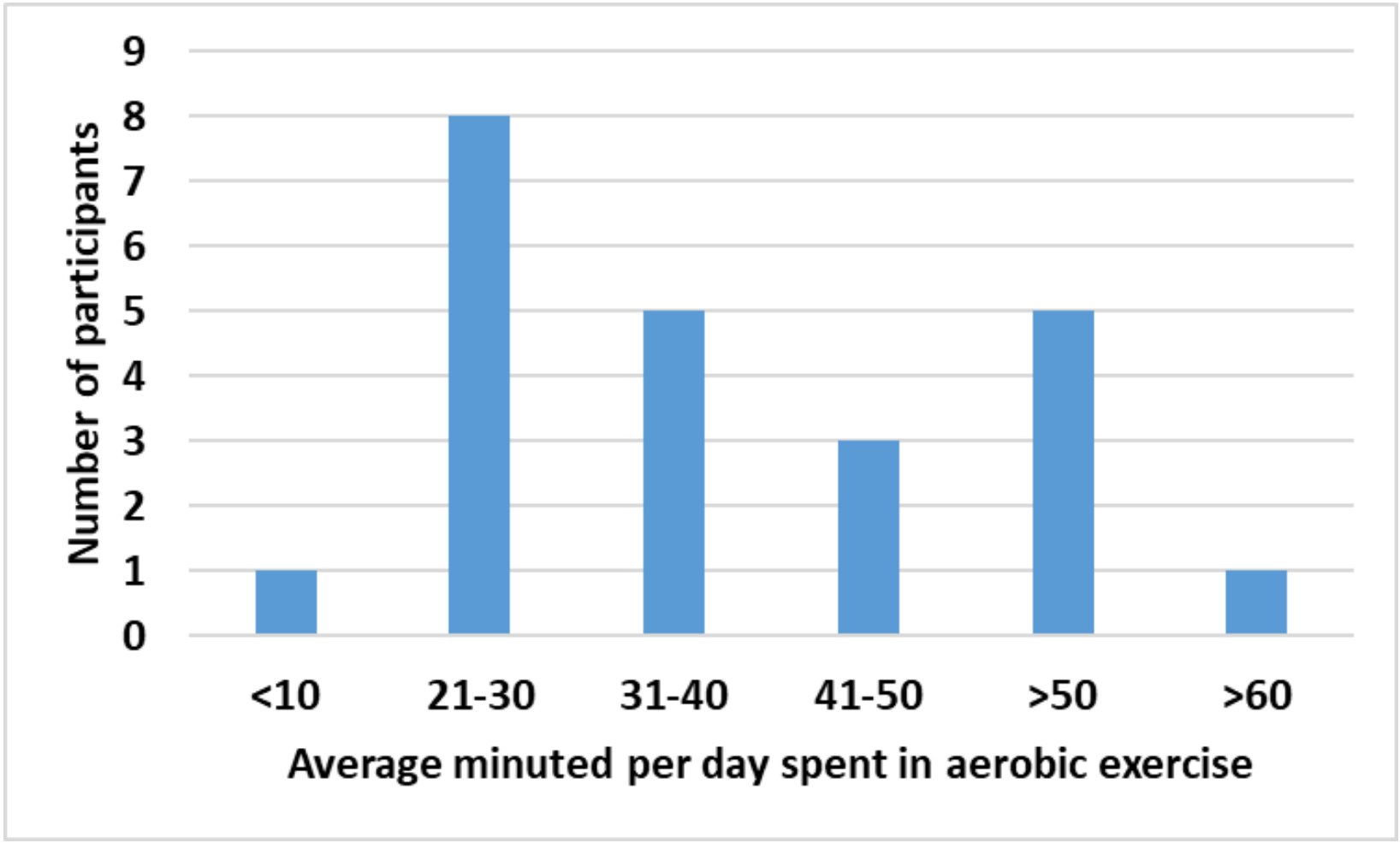


Figure 33: Average baseline minutes per day spent in aerobic exercise for the all participants as reported by the physical activity questionnaire.

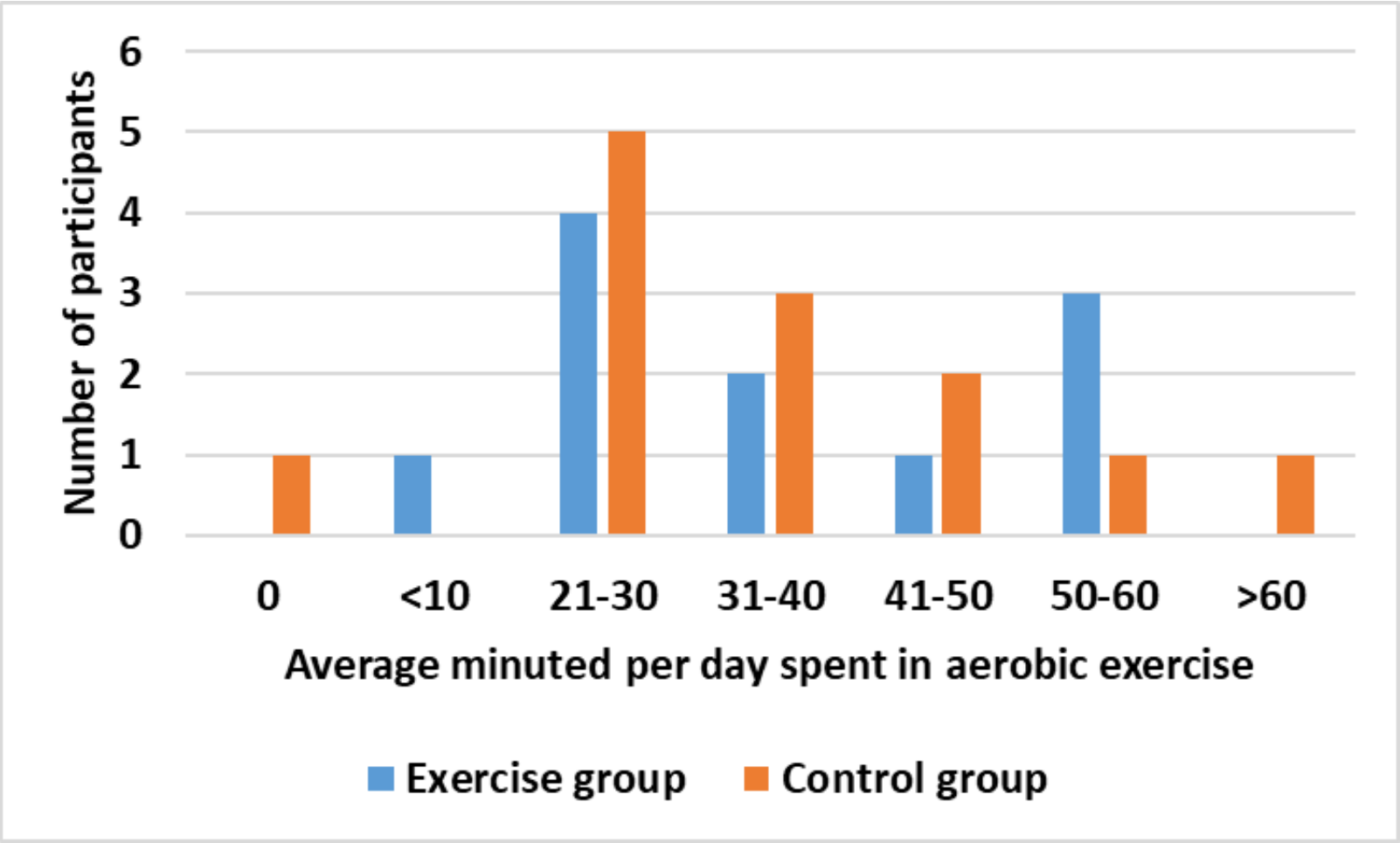


Figure 34: Average baseline minutes per day spent in aerobic exercise for the all participants as reported by the physical activity questionnaire, according to group.

4.6. Focus groups results

All 12 participants in the exercise group were invited to attend a focus group, and nine accepted the invitation. Two focus groups were held, with four participants (all male) in the first focus group and five participants (three female, two male) in the second. In total, 75% of participants in the exercise group attended a focus group. The first focus group was held in the School of Allied Health Professions at Keele University, and the second focus group was held online using Google Meet Platform due to COVID-19 pandemic governmental restriction on face-to-face data collection. The researcher (AA) was the interviewer, and the research supervisor (SH) attended the focus groups as a facilitator to collect any non-verbal data. Both the researcher and the facilitator were female. The COREQ checklist had been used while writing up the focus groups results to ensure the quality of reporting. The completed COREQ checklist is in appendix 21.

4.6.1. Results of the thematic analysis of the focus groups

4.6.1.1. Summary of themes

Themes were developed after coding. There were three main themes that developed and twelve sub-themes, which can be seen in table 21. These themes are related to the trial experience and are discussed with ideas supported by quotations from the focus groups. The themes were observed in one or both focus groups.

Table 21: Themes of the focus groups

Theme	**Sub-themes**
Exercise intervention experience	Dose of exercise Type of exercise (exercise mode) Perceived benefits Barriers / challenges
General experience about the assessment tools/data collection tools	Easy / difficult Comfort/ discomfort Preference of the test Problems with clothing Inconvenience Adherence to the actigraph
Advice for the next trial	Attraction of participants Multiple sites for data collection

4.6.1.2. Theme: Exercise intervention experience

Participants found it easy to perform the exercise programme throughout the trial period when asked about their general experience. Their answers were mainly around intensity and ability to adapt to intensity of exercise with time:

> *"I won't show off, but I thought it was easy!"* (P3 FG1)

> *"I thought it was easy as well*…" (P4 FG1)

> *"Well, my initial exercise was the stationary bike, so for me it was just easier."* (P1 FG1)

One participant reported difficulties at the beginning of the intervention and getting easier with time, and mixed his comment with conditioning to exercise over time;

"I must admit, it it always started off very easy but by the end of the er, session I was…I was fairly…tired! [light laugh]…I was trying to think of the word! It, as, as, as the sessions went on, it got easier." (P2 FG1)

4.6.1.2.1. Sub-theme: Dose of exercise

Frequency

When asked about frequency of exercise, participants' answers varied, with some of them adhering to the prescribed frequency, three times per week, because that was what was expected of them:

"Um…as to whether it was too much, I just fitted in three times because that's what they said we should do." (P1 FG1).

Some participants suggested that the exercise frequency should be more than three times per week, and that they were able to do more. Others reported that they were already doing more than the required frequency:

"I wonder whether three times a week is enough, and it should be four or five really. [all laughed]. It's doing something that is more than you otherwise have normally have done, to put a little bit of effort into your body." (P2 FG2).

"I go to the gym three times… on a Monday, Wednesday, Friday. I play badminton on a Tuesday night… and on a Thursday night I play basketball and five-a-side football…and then have a rest…[laugh]…Saturday and Sunday! Well, I go to the match as well." (P3 FG1).

Intensity

In terms of intensity, participants used different ways to monitor their exercise intensity, with some of them adhering to the instructions given by the researcher:

> *"I was just going to say the way you phrase it, to work up a sweat, to do more than otherwise you normally do, is good. It's making people exert themselves"* (P2 FG2).

Others used a machine monitored intensity, for example: HR measured by the cycle or the heart rate monitors:

> *"Well, for me, the bike just indicated, the little, the little heart appeared and I sort of thought I probably should do less…"* (P1 FG1).

> *"Well I have a heart monitor with a watch to look at, yes, and that is quite useful. Because you can tell whether you are putting in enough effort or not."* (P1 FG1).

Others adopted a pragmatic approach to intensity, increasing and decreasing the intensity either with no particular reason, or according to their physical ability and estimations:

> [Talking about the cycling] *"I think, probably into the second week or so, I thought 'Oh, I don't have to do the same speed all the time', so I started doing a bit faster and then a bit slower, but with no particular purpose behind it."* (P2 FG2).

"I was cycling…I, I, I have a bike in the house…so I sort of did it my own little way. Jon Bon Jovi was good to cycle to! If I did a slow one, I couldn't press the pedal so much, so I had something that was fairly…! So I did 5 minutes slow, then 5 minutes faster, and ten minutes faster still, then slowed it down and then slowed it down and…" (P2 FG1).

Some participants used distance walked outside as a measure of intensity, by means of increasing what distance that they used to perform before the trial:

"for me, its walking 200 yards rather than one." (P1 FG2).

"When I was walking, it was how long I walked for, not how fast I walked, so normally I, I tend to do my walking in 20-minute blocks, so I was extending that ... I am talking about distance more than speed" (P2 FG1).

Others did not specify intensity, but used longer durations rather:

"I was more, I've got, um, a particular route…which took exactly 20 minutes…so…um, so I found I had to extend it a little bit to fill the thirty minutes" (P4 FG1).

When asked about the preferred intensity prescription for future trials, participants agreed that it is very difficult to have one intensity prescribed for all cases, and this needs to be individualised:

"It is very difficult to sort of say "this is right for you, but it's not right for you". (P4 FG2).

"Parkinson's of course is a disease which is not sort of 'one size fits all'. It's a vague personal and individual thing, which makes it so very difficult even for the specialists, to say you've got it or you haven't." (P4 FG2).

Participants also preferred to have an individualised exercise prescription that has an objective measure, such as heart rate intensity prescription:

"I think that's perhaps less subjective if you do that [using the heart rate monitors to monitor the intensity of exercise in the next trial]*. I think asking somebody to, errrm, the way we did it this time was subjective, because what we think might be a fast pace for… isn't always, you just perceive it to be. Whereas, actually if you are taking a measurement, of the heart rate or something that's been this much more increased, um, it's more factual."* (P3 FG2).

"I was going to say I think having a specific measurement to work towards is better." (P1 FG2).

Duration

When asked about duration of the exercise intervention, how much they did perform and if that was suitable for them, participants reported varied answers, which ranged from 30 minutes to one hour and a half. However, the overall duration of

exercise did not necessarily include continuous high-intensity aerobic exercise. One participant reported exercising in the gym for an overall longer duration (90 minutes) than the intervention stipulated (30 minutes aerobic exercise), and some of those 90 minutes involved running fast, and some involved walking at a slower pace:

> *"So we…I mean, I was there for an hour and a half. But, obviously, I mean, what I was doing, if I was running fast, I'd slow it down to walking pace, just so, you know, you weren't too tired at the end of it."* (P3 FG1).

On the other hand, one participant followed the exercise intervention instructions and exercised for just an additional 30 minutes at the gym. Other comments related to "time" as a barrier are described in the following section.

4.6.1.2.2. Sub-theme: Type*/* mode of exercise

Participants reported performing different types of exercises, with walking and cycling being the most reported. Other types include taekwondo, badminton, basketball, football, boxing, swimming, dancing, tennis and gardening.

> *"I go to the gym three times…on a Monday, Wednesday, Friday. I play badminton on a Tuesday night…and on a Thursday night I play basketball and five-a-side football…and then have a rest…[laugh]…Saturday and Sunday! Well, I go to the match as well."* (P1 FG1).

> *"with this stationary bike, I just decided to try it out on your terms and, er, and see whether it makes a difference; and then I may be comparing it in terms of time. We started a boxing class now in Derby…I never thought of*

boxing in my life, but apparently, in the States, there's research that says boxing's good for you with Parkinson's. Okay, so I'll try that!" (P1 FG1).

4.6.1.2.3. Sub-theme: Barriers to exercise

Loss of balance was reported to be one of the main barriers to exercise:

"I cannot cycle the proper cycle, I never have, I've got no sense of balance whatsoever. So I can only cycle on the fixed one. That's the gym, or something like that." (P1 FG2).

"Well, in terms of balance. Um, to an extent stamina, which is getting better…but it, it's mainly my balance, and I, um, I, I, I was interested to see Billy Connelly on the television, saying that his wife has moved from New York to Florida because of these, the, the Parkinson's. I thought that was something to do with the heat…but it's not, it's to do with his balance when the weather gets bad." (P2 FG1).

Physical symptoms that are related to Parkinson's were mentioned as barriers such as fatigue, stamina, and overall progression of the disease. Additionally, participants reported that more effort was needed to do exercise if a person has Parkinson's:

"You have to put effort in, and effort sometimes is difficult to get into." (P1 FG2).

Breathing as a barrier to exercise was mentioned by participants. For example: breathing was reported to be an effort and one of the biggest problems experienced by one participant from focus group 2:

> *"errm, well again, do other people have difficulty with breathing? That was one of my first symptoms I think. And so that is an effort for me. But I do try to push myself. Breathing is the, one of the biggest problems of my Parkinson's."* (P5 FG2).

Additionally, participants 2 and 4 from focus group 2 reported that they were breathing too fast (increased their respiratory rate) and puffing while cycling or walking:

> *"There was sometimes, occasions that I was pedalling a little bit too fast on the bike, or was trying too much at the beginning that I struggled at the end of it, and sometimes I've overdone the walk, you go too far and you still have to go back again, and then the coming back became a little bit more difficult. Then I was puffing - Yes."* (P4 FG2).

> *"To be fair, I did breathe a bit faster while cycling."* (P2 FG2).

The time at which the medication should be taken was mentioned as a barrier to exercise by one participant, who explained the importance of matching the time of exercise to work within the dose-effective time. In other words, the participants tried to explain the need to do exercise within the "on" period of the medication, and to avoid the "off" periods in which motor symptoms return or get worse:

"I find that the timing of the exercise was important to me. It was easier in the morning, it was nearer to medication time, or in the right slot, in connection with medications. In the afternoon, exercise was no good, or not as beneficial I think as it was, and easy to do, as it was in the morning. That may differ with other people with their medication levels." (P4 FG2).

Mood and motivation to exercise were reported as barriers to performing exercise. For example, participant 1 from focus group 2 and participant 1 from focus group 1 reported the difficulty of finding self-motivation that could push them to start the exercise:

"Self-motivation is sometimes difficult to find." (P1 FG2).

"The motivation before you start…I find it more difficult." (P1 FG1).

Participants reported that motivation in terms of the internal drive is a barrier to performing exercise. For example, one participant reported that doing the exercise during the trial was because of the researcher and this motivation finished when finishing the trial. Another participant reported mood and described it as the "little inner devil" that need to be overcome:

"only my mind sometimes, you know [all laugh]…you have to overcome that little devil! ... yeah. I frequently say you see this little inner devil that tells us 'Oh why bother!'" (P4 FG2).

"I would say I was more motivated during the trial because I felt I was doing it for a reason, for you, whereas when the trial had finished I guess my concern was that I had to be self-motivated." (P3 FG2).

During the COVID-19 pandemic, participants reported that their motivation to perform exercise was affected due to the circumstances of lockdown and governmental restrictions for face-to-face meetings:

"I used to go to a class every week for balance and, called 'Strictly no falls', and of course that's had to stop because the village hall isn't available where we used to meet. All these things are sort of in limbo at the moment. It is difficult, because the … something organised does help with the motivation." (P1 FG2).

"during the lockdown, motivation sort of dwindled more than little." (P1 FG2).

Weather and temperature were mentioned as barriers to performing exercise as well. Rainy weather was reported to be affecting participants' exercise performance, by means of not to get wet, or affecting mood and motivation:

"if it is rainy, I don't go out. I don't like getting wet." (P3 FG2).

"I think personal inclination and the weather, I think the weather" (P2 FG2).

Fitting an extra 30-40 minutes of exercise was difficult for some participants and was mentioned as a barrier. For example, participant 1 in focus group 2 reported

that he was already doing exercise, and doing the extra 30 minutes of the trial exercise was difficult to fit in his diary. Additionally, participant 4 in focus group 1 confirmed that her main problem was fitting the 30 minutes in her diaries, more than any physical barrier:

> *"when I was doing it, I was already doing a lot of exercise and I found it difficult to even exercise the extra ones. I found it difficult to fit it in as well. There weren't enough days in the week, and there weren't enough hours in the day. I found it difficult but I managed it reasonably well. I am not doing so much now, I must admit.* (P1 FG2).

> *"It's, er, picking a gap, actually fitting it in was a problem for me, the extra half hour... Yeah. Physically it wasn't a problem…but just finding the time…"* (P4 FG1).

The second focus group was conducted online during the first COVID-19 lockdown period in the UK in the late Spring of 2020. Hence, some participants reflected on exercise being affected by the pandemic and the lockdown regulations that had been imposed by the government to reduce the rate of infection. Accordingly, the COVID-19 governmental regulation and the lockdown was reported as a barrier to exercise from the second focus group. For example, the governmental regulation prevented domestic help and this prevented participant 1 in focus group 2 from doing her usual exercise:

> *"During the lockdown my exercise was quite different because, previous to that, I had had quite a lot of domestic help. And during the lockdown period I had*

none…and I haven't gone back to doing all the exercises I did before." (P1 FG2).

Additionally, closure of Parkinson's UK exercise groups and sport centres during the pandemic affected participants' exercise. For instance, closure of swimming was reported:

"In my case I missed one particular thing. Because walking is no problem, or with an exercise bike, the cycling, is no problem. But another exercise that I would have liked to have undertaken is swimming, which obviously, with the situation, is not possible any more …" (P4 FG2).

4.6.1.2.4. Sub-theme: Perceived benefits

Participants generally felt that they were getting physical benefits from incorporating the exercise intervention into their lives. They reported that they felt able to move better; for example, walking more in terms of distance, cycling more in terms of time, having better flexibility and muscle strength, and less tremor:

"I just generally, generally felt better, as you know I couldn't quantify whether…I mean, I was walking more, I was cycling…I, I, I have a bike in the house…so I sort of did it my own little way." (P2 FG1).

"I think I also find that, depending on the exercise, because it's a resting tremor, when I'm exercising it doesn't, it doesn't, it goes away, not completely, but it reduces that symptom, so obviously that for me is a benefit." (P3 FG2).

"I think, in terms of maintenance of your muscle, avoiding atrophy of your muscle ... I think definitely, making sure we use our muscles, to make sure they keep their strength up … and also flexibility" (P2 FG2).

When they have been asked about any perceived breathing or respiratory related benefits, one participant reported that she felt her breathing pattern was better and wheezing was reduced:

"I was probably…Because I took longer…erm…I don't know! It's hard to say…erm…yeah…erm…my lungs felt clear, if you like, and I could breathe easier…" (P5 FG2).

"over the first two or three weeks, I was wheezing by the time, I don't know if you noticed, but, erm, I couldn't [demonstrated forced exhalation]*…It was better by the time I got through to week eight. But it was…I'm not as fit as everybody else."* (P5 FG2).

Other benefits included self-confidence, satisfaction and feeling better as a person:

"I would say we did, I did personally, it made me do something more than I would otherwise have done." (P2 FG2).

"There's a satisfaction in knowing you have done the exercise. Very much our satisfaction, you feel you're helping yourself. And I think that does motivate me to keep going when you feel benefit" (P1 FG2).

4.6.1.3. Theme: General experience about the assessment tools/data collection tools

Within this theme there were sub-themes of 'easy / difficult', 'comfort / discomfort', preference of the test', problems with clothing', 'inconvenience', and adherence to the Actigraph.

4.6.1.3.1. Sub-theme: Easy / difficult

CPET

In general, the cardiopulmonary exercise test was considered to be an easy test for participants to perform, and some felt that they could have exceeded the level of effort required, for example by cycling at a faster pace:

"I could have done…I could have gone faster than…" (P3 FG1).

Pulmonary function test

Spirometry, or pulmonary function test, was acceptable for the participants, and they found it easy to do, or they were familiar with it from previous tests or from language therapy sessions:

"I was used to do those because I had asthma for many years, which I haven't got any longer. It has gone away. So I was the accustomed to using those tubes and breath tests. So, that wasn't, didn't trouble for me at all." (P1 FG2).

"I do, um, speech and language therapy as well, and that's all about breathing so, it was, er, it came easy really." (P1 FG1).

However, for two participants, conducting the test was not easy for them, and they described it as being "*a bit of an effort"* (P5 FG2), or simply "*difficult".*

It was very hard to perform for another participant, who reported that in the first session it was harder. Also, he reported that the standardized motivational words that are used in the test were a nightmare for him:

"I was just thinking, my, my problem wasn't doing the test, it was surviving the test! ... you kept saying 'Keep going! Keep going! Keep going!' and I'd run out of breath and I was wheezing! 'Keep going! Keep going!' - and I just couldn't keep going, you know! It was better towards the end, so that was, it was a mark of my improvement!... But, but for the first two or three weeks, I, I used to have nightmares about this voice saying 'Keep going! Keep going!' [all laugh]" (P2 FG1).

Accordingly, the researcher asked him if saying these words was distressing for him, and he reported that it was not:

"Oh! It wasn't distressing! I just, you know, this thing through my head kept saying 'I wish she'd say something other than 'Keep going!', and you're like 'Stop!' [all laugh] But I did find that, out of all the things, those last few seconds of that exercise the hardest…And I felt better as time went on…" (P2 FG1).

Questionnaires

Participants reported that being asked to complete the questionnaires was acceptable, and the questionnaires themselves were acceptable and inoffensive:

> *"there was nothing in it was offensive, so no they were fine."* (P2 FG2).

Some participants were familiar with these questionnaires from having participated in other trials, or just from having been asked to complete many questionnaires as part of the routine assessment processes for someone with Parkinson's:

> *"I always felt that it was a part and parcel of tests with Parkinson's…every time you go to one of these things you get 1, 2, 3, 4, 5, ..."* (P2 FG1).

One participant reported that paper-based questionnaires that required a pen to complete them were difficult and suggested that the less handwriting the better for him, due to the Parkinson's affecting his handwriting:

> *"My only comment is it's good to have as little hand-written space as possible, because with Parkinson's the handwriting goes."* (P1 FG1).

4.6.1.3.2. Sub-theme: Comfort / discomfort

In general, participants reported that wearing the activity monitor around their waist was uncomfortable, and some of them reported that they would prefer to wear a physical activity monitor on their wrist or ankle:

"The belt, to wear it wasn't uncomfortable, but to exercise and keep it in place, get dressed with it on, undress with it on, and things like that. Running 24/7 as much as we can. I just found it awkward, I would prefer a wrist monitor. I mean, we have Fitbits these days, we're used to those. I just found the chest one awkward." (P2 FG2).

"well, I agree with [P2 FG2], I think around the waist is not ideal for me either. Although I wear my trousers with a belt, you know the additional one there, if it can be sorted differently probably would be better." (P4 FG2).

4.6.1.3.3. Sub-theme: Preference of the test

When asked if they would have preferred to use a treadmill rather than the cycle for the CPET, most participants reported that they would prefer the cycle test due to balance issue, even if a harness was used with the treadmill. However, they reported that the cycle saddle that was used for the cycle test was not comfortable for them:

"no problem on the bike except for the saddle." (P4 FG2).

"The bike's easier... Well, because of people who've got problems with walking erm… With balance – yes!" (P3 FG1).

"The harness, you wouldn't, erm, I mean, how can I put it…I , I , I get security by having my walking stick on the ground. If I was holding it up in the air, it would be like Mary Poppins, I wouldn't have the same sort of

stability, you know. It's getting some stability myself rather than, I just don't think I'd have the security when the harness, in my head. I might be wrong, but in my head, I don't think I'll have the same security." (P2 FG1).

4.6.1.3.4. Sub-theme: Problems with clothing

One male participant was quite happy about wearing the activity monitor under the clothes during the day:

"It didn't bother me during the day at all." (P4 FG1).

However, for another female participant, wearing it was an issue while wearing tight dresses:

"it wasn't so much uncomfortable for me, it was more, errrrm, if I was wearing a particular type of dress, and it was quite tight fitting, it was noticeable!" [All laughed]. (P3 FG2).

4.6.1.3.5. Sub-theme: Inconvenience

After explaining to participants during the focus group that wearing the device around the waist provides more accurate data for us than wearing it around the ankle or the wrist, in terms of detecting movements and steps, excluding tremor from the analysis, and including bradykinesia if the participant has this symptom, they accepted this explanation and understood the reasoning. However, they felt that this needed to be explained at the beginning of the trial so that participants understood the reasons for being asked to wear a waist monitor:

"I think it is feasible but as (P1 FG2) said you have to explain it far more, why it has to be on the waist" (P2 FG2).

"Yeah, I think errm, it was a bit inconvenient. But had you explained that, had it gone on the arm or the leg, would maybe give a false reading, er, I would have understood a lot more. (P3 FG2).

4.6.1.3.6. Sub-theme: Adherence to the Actigraph

The participants reported that they did try to wear the monitor according to the protocol every day, and developed strategies to remind them to put it on after their morning shower, by placing it in a position that was accessible and visible, such as beside the bed or with the clothes they were planning to wear:

"I had it by the side of the bed, so if I had a shower I just put it straight on." (P2 FG2).

"I…I always put my clothes for the next day out on the night before so the monitor last thing went on that." (P2 FG1).

However, there were some who forgot to put it on at the start of the day:

"OK Yes, I think there was only one day when I lost a few hours, having not putting back on having been swimming but apart from that it's tolerable. And as [1FG2] said, no, it was [3FG2], yeah, having it explained does help, but it's logical. Logical and tolerable! (laugh)." (P5 FG2).

"I think I had about three days were I didn't, and, err, kept putting it somewhere where, you know, it was mainly after a shower or something, and I'd forget. But most of the time I think I did." (P3 FG2).

4.6.2. Advice for next trial

4.6.2.1. Attracting participants

Participants were asked to consider the recruitment procedures used in this pilot study to help us increase recruitment of more PLwP in future exercise trials. They made various suggestions, such as using social media for advertising the research, and changing the wording of the advert/invitation:

"Have you tried the Facebook accounts? And there's various other groups. I think you could use social media a bit wider. There are other groups, I guess, it depends on the demographics, doesn't it? In terms of what people use. My children tell me that older people use Facebook these days [all laugh]*. So, yeah, I don't know whether work out what demographic you're aiming for, how they interact. I guess, do you know how other trials are done and how they get volunteers? Are they getting more or less? Are they using different sort of options?"* (P3 FG2).

Two participants agreed that the initial information advertising the trial has to appeal to the PLwP receiving the information, as they receive many requests to participate in research and they can pick and choose the ones that they like the sound of:

"4FG1: Yeah 'cause when you see these, erm, you get emails through suggesting you might be suitable for this, you might be suitable for that, you

do, sort of, pick the ones that you… [talking to P2 FG1]. That you like!" (P4 FG1).

Two participants from focus group 1 suggested that including the term 'exercise' in the trial information might be off-putting to some potential participants, and using words such as 'activity' instead of 'exercise' might make this type of study more accessible and less of a concern, and ultimately encourage those who are 'exercise-averse' to take part:

"Just something, a small point, I'd be careful about using exercise as a word. Maybe better to say activity or to not, erm, the word exercise is a red rag for quite a lot of people" (P1 FG1).

4.6.2.2. Multiple sites for data collection

Having only Keele University as the only site for data collection may have affected recruitment to the study:

"I was fine from where I come. I don't know where people were travelling from. It was fine and I had no issue with that. But I think you may get a wider network or audience, and more volunteers who are able to do it in other locations" (P3 FG2).

"it was quite a distance for me, I live near Matlock in Derbyshire" (P1 FG2).

Participants suggested that recruiting from multiple sites across the region might increase the number of participants as they would not have to travel so far, and a long journey might not be easy for some PLwP:

> *"Keele was a nice trip out. So I don't mind going to Keele, having said that, yes indeed I agree with the other comments made. Mainly if who you have is living locally, er, you might get wider audience or participation base for your studies to volunteer because other Parkinson's sufferers might find the trip to Keele too cumbersome for them."* (P4 FG2).

Indeed, some PLwP might not have the means or facilities to travel to Keele, and if recruiting from local Parkinson's UK groups across the region, taking the testing out in to the community to do local testing might be preferable to local group members:

> *"They might not have the opportunity to do that travelling at all. Whereas if you do something with a local group where they are used to meeting regularly, that might be, er, you would have to do the travelling then Aseel! [laugh]"* (P1 FG2).

4.7. Summary

Table 22 summarises the main key findings of the mixed methods results and relating them to study objectives.

Table 22: summary of the EXoCARP study findings.

Objective	**Quantitative results related to the objective**	**Qualitative results related to the objective**
1a: assess if recruitment methods were effective, by calculating the recruitment rate, number of people who contacted the research team, and number of people who were eligible to participate and ultimately gave informed consent.	• Recruitment rate (refers to the average number of participants recruited per month) was 1.92 participants per month. • Proportion of participants recruited from the number of people who contacted the research team was 65% (24 out of 37 participants). • Recruitment was 48% out of the targeted number (24 out of 50, from April 2019 to March 2020), and 80% out of the accepted sample size for pilot studies (24 out of 30). • Recruitment was boosted by two visits to Parkinson's UK groups in Stafford and Telford.	• Participants suggested that the researcher and equipment might need to go out to local Parkinson's UK groups and to collect data there to increase the recruitment. • Participants suggested to use social media to recruit participants in the next trial. • Participants suggested changing the wording of the advert/invitation from "exercise" to "activity" to attract more people.
1b: calculate the attrition rate from the number of participants recruited who subsequently dropped out.	• Attrition was 37% (9 out of the 24) mainly due to the COVID-19 pandemic. • Without accounting for COVID-19 related attrition, only two participants dropped out (8.3%). The attrition was less than the originally planned criteria for feasibility (<15% of the sample).	Not addressed
1c: evaluate the screening tool and inclusion/exclusion criteria.	• Screening tests used to assess the EXoCARP participants were easy to conduct, and effective in identifying participants who are not eligible to do the intervention or the outcome measures/tests. • Undiagnosed high blood pressure, albeit transitory / short-term, should be considered in the screening, leading to exclusion from performing the CPET.	Not addressed

1d: evaluate feasibility, acceptability and practicalities of using the outcome measures.	• Adherence rate (calculated as number of days participants wore the Actigraph, divided over the required number to wear) of wearing the activity monitors was 75.95% • All participants completed all the outcome measures at the sessions, except for five participants who had undiagnosed high blood pressure before running the tests (at the baseline session).	• Focus groups results indicate no problems with most of the participants, and some of them were already familiar with the spirometry from language therapy sessions. • Participants reported no problems in conducting the CPET when asked about that in the focus groups, except for the saddle of the cycle used. • Participants reported difficulties in filling the questionnaires by handwriting.
1e: explore feasibility of delivering the exercise intervention.	• Participants in the exercise group have done around 30 minutes per day on top of their usual physical activity, similar to what they were instructed to do.	• Participants reported that it was easy, or it starts difficult and with time became easier. • The frequency, intensity and duration of exercise were found to be acceptable to the participants but need more guidance in terms of the intensity.
1f: explore participants' experiences and the acceptability and suitability of the aerobic exercise intervention, the outcome measures and adherence to the intervention.	• The plot graphs indicate changes in PFT values. $FEV_{1,}$ FVC, and FEV_1/FVC values were increased with time in the exercise group, and decreased with time in the control group. • Plot graph for the CPET results show that almost no changes in term of peak HR, predicted $VO_{2\ peak}$, or test duration.	• Participants reported physical benefit and self-confidence after the intervention. • Physical ability, motivation, and mood, time, weather, and COVID lockdown regulations were reported to be barrier exercise. • Participants reported doing range of exercise types including stationary cycling, outdoor cycling, walking, jogging, running outdoors, taekwondo, dancing, swimming and treadmill walking
2. to assess pulmonary function in people with mild to moderate Parkinson's.	• 54% of participants were found to have abnormal pulmonary pattern: 11 obstructive; 1 restrictive; 1 mixed pattern; and 1 normal pattern.	• Two participants reported dyspnoea and difficulties to do the spirometry (FVC).

Chapter 5: Study 1 - Discussion

In chapter one, the motor and non-motor symptoms of Parkinson's, pulmonary function, obstructive and restrictive pulmonary diseases were introduced; and in chapter two, a review of the literature relating to pulmonary function in Parkinson's, cardiorespiratory response to exercise testing in Parkinson's, and the effects of aerobic exercise on cardiopulmonary function in Parkinson's were reviewed, summarised and discussed. The aims and objectives of this pilot and feasibility study were introduced at the beginning of chapter three. Chapter three presented the detailed methodology used in the study, and chapter four reported the results of the EXoCARP pilot and feasibility study.

This chapter involves a discussion concerning findings of the EXoCARP pilot and feasibility study in line with the findings of the systematic review in chapter two. Strengths and limitations of the study methodologies will be highlighted, along with pertinent findings. Finally, suggestions, recommendations and aspects to address for future research trials will be made.

5.1. The pilot and feasibility trial findings (Objective 1)

5.1.1. Recruitment and attrition (objective 1a and 1b)

Recruitment of the planned 50 participants was not achieved, with the trial recruiting 48% of the target number (24 out of 50), and 80% out of the accepted sample size for pilot studies (24 out of 30) (Lancaster et al., 2004). Recruitment was significantly affected by the COVID-19 pandemic in 2020, as recruitment to the trial was planned between April 2019 until December 2020. However, recruitment to the trial was stopped in March 2020 due to the COVID-19 pandemic and UK governmental regulations and University access and research restrictions during the first COVID-

19 lockdown. Thus, a period of nine months of recruitment was lost from the originally planned 20 months.

Although recruitment was not limited to a specific ethnic group, all participants were Caucasian. Parkinson's UK include members who live in the UK and have Parkinson's from different ethnicities. Thus, in the next study, the use of recruitment advertisements in different languages might help in recruiting more participants from ethnic minorities to be involved in the trial. However, the costing of translators may also need to be considered.

Attrition rate was 37% (9 out of the 24) mainly due to the COVID-19 pandemic, as seven participants were lost to follow-up because of University access and research restrictions during the COVID-19 lockdown. However, without accounting for COVID-19 related attrition, only two participants dropped out (8.3%). The attrition rate was less than the originally planned criteria for feasibility (<15% of the sample).

Recruitment was boosted by visits to two Parkinson's UK groups in Stafford and Telford, following which five participants were recruited after the Telford visit and three participants after the Stafford visit. This might give an indication about the importance of visiting Parkinson's UK groups to present the research idea, and not to fully depend on the online Parkinson's UK website and emails.

In the focus group, participants addressed that wording of the advertisement need to be changed from "exercise" to "physical activity" to attract more people. Additionally, they have reported that Keele University location as the only data collection site might be a reason for people who live far to not participate in the trial, and suggested mutli-site data collection.

5.1.1.1. Comparison of recruitment with other trials

The recruitment of the EXoCARP trial compares well with other exercise trials in PLwP. It has been pointed out that the main obstacle to the implementation of clinical trials in PLwP is recruitment (Valadas et al., 2011). For example, in a high-intensity exercise trial, recruitment was 68.8% of their targeted sample size (Harvey et al., 2019), while it was around 11% in another exercise trial over a period of eight months (Lima and Rodrigues-de-Paula, 2013), and 45% in another feasibility trial that assessed the effects of dancing on motor function (Shanahan et al., 2017).

Keele University's location was one factor that affected recruitment of participants, as suggested by participants in the focus groups: the researcher and equipment might need to go out into to local Parkinson's UK groups in the community to collect data there to increase the recruitment rate. The location for data collection and availability of transportation of participants need to be considered for the next trial. This is supported by the number of participants who contacted the researcher but could not travel to Keele University to attend the assessment sessions (n=6).

The COVID-19 pandemic was another factor that limited recruitment of participants for the EXoCARP trial. The UK governmental instructions to "Stay at home" and "Stay alert", in addition to PLwP being a high-risk group, affected the continuation of recruitment. Further details about how the COVID-19 pandemic affected PLwP's physical activity level are addressed in detail in the following chapter (Chapter 6).

Other reasons reported in the literature regarding factors that might affect recruitment while designing trials for PLwP include: fear of adverse reactions such as falls and balance impairments; fear of aggressiveness of the intervention or the outcome measures; and fear of the results (Valadas et al., 2011).

5.1.1.2. Implications for future trials

A total of 11 months was not enough to recruit the target sample size of 50. The original plan was 20 months (from April 2019 to December 2020) but the unexpected circumstances due to COVID-19 pandemic affected the trial data collection. Multi-site data collection is highly encouraged to improve data collection. However, this will have an impact in terms of cost of location (room/hall rent), movement of equipment, and the assessor's time. One assessor might not be enough in case of multi-site data collection. Additionally, in the case of multi-site data collection, piloting of the centres/locations that will be identified need to be assessed, and inter-rater reliability (the degree of agreement among assessors) in relation to the outcome measures and objective tests need to be conducted. Moreover, it is recommended to conduct more information-giving visits to Parkinson's UK groups to promote the research and boost recruitment in the next trial.

5.1.2. Evaluating screening tools of inclusion and exclusion criteria used in the EXoCARP trial (objective 1c)

5.1.2.1. Findings of the EXoCARP study

The screening tests used to assess the EXoCARP participants were quick, easy to conduct, and effective in identifying participants who were not eligible to complete the intervention or the outcome measures/tests. The AHA/ACSM Health/Fitness Facility Pre-Participation Questionnaire (Appendix 8) was found to be helpful in identifying those participants who could not be included in the trial, generally, and in the CPET specifically. However, the assessor (AA: a physiotherapist) took the clinical decision to not perform the CPET for five participants who had high blood pressure during the baseline session. These participants were not diagnosed with hypertension, but this decision was taken as a precautionary measure, to prevent or minimise risk of adverse events.

The findings indicate that the screening tools are appropriate for future trials. However, undiagnosed high blood pressure, albeit transitory / short-term, should be considered in the screening, leading to exclusion from performing the CPET.

5.1.3. Feasibility of the intervention and perceived benefits (objective 1e and 1f)

Adherence to the intervention

It was important to explore whether the intervention was feasible for PLwP. The success of the intervention was noticed by the number of extra minutes (median (IQR) = 37.2 (27.1, 45.4) minutes) that participants in the exercise group spent on doing the intervention on top of their usual MVPA (usual time spent on MVPA was 3.7(1.0, 8.9)), as recorded by the Actigraph.

Taking into consideration that participants in the exercise group reported doing a median (IQR) of 32.3 (28.9, 37.5) minutes of usual physical activity (i.e. not including the additional intervention exercise programme), with only 3.7 (1.0, 8.9) minutes within the MVPA intensity, the addition of 37.2 (27.1, 45.4) minutes per day for three days per week of MVPA during the intervention period is considered a success of the intervention.

It is important to mention that, originally, all participants in both groups were engaging in daily physical activities. This is confirmed by the physical activity survey, which showed that most participants, in both groups, were already doing between 21-30 minutes of aerobic exercise per day, three days per week, prior to enrolling in the study. Examples of regular physical activity included stationary cycling, outdoor cycling, walking, jogging, running outdoors, taekwondo, dancing, swimming and treadmill walking.

The intervention was selected based on aerobic exercise training studies that have resulted in improvements in cardiorespiratory fitness and maximal oxygen uptake (VO_{2max}) in PLwP (Burini et al., 2006; Fernández-del-Olmo et al., 2014; Mavrommati et al., 2017; Ridgel et al., 2016; Schenkman et al., 2012; Shulman et al., 2013). The intervention in most of these studies has involved exercise durations of 30 to 40 minutes per session, for two to five days per week. The eight -week period of the intervention in the EXOCARP trial had been chosen according to the recommendations in the British Thoracic Society (BTS) guidelines about the need of at least eight weeks of aerobic exercise to induce changes in pulmonary function or to improve quality of life in respiratory patients (British Thoracic Society, 2001).

The intervention was chosen to be an unsupervised community-based intervention, aiming towards a sustainable intervention. Unsupervised interventions have advantages and disadvantages. For example, participants might overestimate or underestimate their exercise level and ability to work at a specific intensity, or might conduct unsafe or incorrect exercise that is not suitable to their individual cases. However, to manage monitoring of the intensity, accelerometers were used, and participants were educated and instructed to conduct exercise in a safe manner to reduce/minimise side effects. The advantage of community-based unsupervised interventions is that they help people to change their exercise and physical activity culture, and to continue doing exercises after trials (sustainability) as the interventions do not require specific equipment or facilities.

Effectiveness of the intervention was not assessed as this was only a feasibility trial. However, changes in pulmonary function and CPET results were plotted in graphs. The figures could give an idea about how the outcome measures used might detect changes over time, and if any changes are needed to the outcome measures for

future trials. The graphs (figure 16) show that at the end of the intervention period there was an increase in pulmonary function outcomes (FEV_1, FVC and FEV_1/FVC) in the intervention group but not in the control group. However, minimal changes were seen when plotting the VO_{2peak} results over time in both groups (changes are <3.5 $ml.kg.min^{-1}$, which is less than one metabolic equivalent). Additionally, minimum changes were noticed in HR and test duration as well (refer to table 19). If the aim will be to assess the effectiveness of aerobic exercise on cardiac fitness, measured by CPET, then the intervention dose and prescription might need to be changed and tailored to each individual according to each participant's results in the baseline CPET. In this case, it is recommended that HR monitors are provided for participants to wear and aerobic exercise is prescribed within a specific HR window, in future trials.

The feasibility of the intervention was affected in participants who were engaged in the trial and then stopped doing the exercise due to the COVID-19 pandemic, as has been addressed in the second focus group. Thus, it is crucial to adapt the intervention for home-based or alternative exercise choices that could be used in unexpected circumstances, such as the COVID-19 pandemic, or any other future events. Subsequently, understanding the preferences of PLwP in terms of home-based or unsupervised exercise choices is important for future trials.

Acceptability of the intervention

Focus group participants confirmed that the intervention was acceptable from their point of view. For example, they reported that it was easy, or it started as difficult and with time became easier. The intervention dose (frequency, intensity and duration) was found to be acceptable. Regarding the mode/type of exercise, participants referred to different types of exercises used as "aerobic exercise" that have been chosen depending on either their preference, or availability of

equipment. This helped them not to be limited by one type of exercise, and to choose the preferred type according to their interests. However, participants suggested that they would prefer to be prescribed a more tailored/individualised intensity, which could be measured objectively (for example: measuring intensity by HR monitors to make sure that they are exercising to a consistent level/ within a specific window). Prescribing exercise using HR windows will have the advantage of working within the needed intensity for aerobic training even after adaptations (Manley, 1996, Chapter 3, Page 70). This is because the cardiovascular and respiratory system will attain tolerance with training (i.e. HR will decrease with training), and subsequently the person needs to increase the intensity of exercise (for example: speed of walking or cycling) to achieve the required HR window (Manley, 1996, Chapter 3, Page 70). In other words, using the HR as a method or prescribing the intensity of the intervention could help participants not to stay in their "comfort zone" or to exceed their "moderate intensity", and to progress the exercise intensity according to their improved capacity. Costing of heart rate monitors needs to be considered while planning for the next trial.

The development of the intervention in EXoCARP was not based on a behavioural change model. It has been reported previously that using behavioural change models could help to improve adherence to physical activity interventions (Samdal, 2017). For example: the use of goal setting and self-monitoring of behaviour when counselling overweight and exercise in adults and the use of a person-centred and autonomy supportive counselling approach were found to be important in order to maintain behaviour over time (Samdal, 2017). However, participants showed good adherence to the intervention in EXoCARP, so the use of a behavioural change model, such as goal setting, might not be needed in the next trial.

5.1.4. Acceptability and use of the selected outcome measures (objective 1d)

As part of the research objectives, acceptability of the outcome measures to participants was assessed. The outcome measures that were used in the EXoCARP study were chosen carefully in terms of validity, reliability, clinical usage in practice and responsiveness to change (Sim and Wright, 2000). In the following sub-sections, these issues will be discussed for each outcome measure and limitations of in each outcome measure will be summarised. At the end of this section, the impact on designing the next trial in terms of these outcome measures will be discussed.

5.1.4.1. Pulmonary function test (spirometry)

Spirometry is the gold-standard method to assess pulmonary function (Miller et al., 2005). The assessor used the standardised procedure, described in Chapter 3, according to the ATS/ERS guidelines for conducting spirometry.

All participants completed the pulmonary function test (spirometry) at baseline, with no exclusions. Focus group participants' results indicated acceptability of this test, and some of them were already familiar with the spirometry from speech and language therapy sessions. This perhaps helped to run the spirometry more easily. However, two participants found the test to be effortful while performing the forced expiratory volume test. The assessor did not find any difficulties in conducting the test with the included participants. One of these, who was in the exercise group, reported that he could not keep going with the test in the first session, and found the standardised motivational instructions to be stressful. But he reported an improvement in the experience during subsequent sessions and could notice an improvement in acceptability difference over time.

Although disposable paper mouthpieces were used, the assessor was sterilising the spirometry transducer in the time between each participant and the next one, while the next participant was completing the other tests. This took extra time and the more expensive disposable mouthpieces that have a filter inside might save the time used for sterilisation. However, the cost implications of this would need to be considered when planning the next trial.

Although assessing effectiveness was not an objective of this feasibility study, the plotted data indicated an increase in FEV_1, FVC, and FEV_1/FVC values over time in the exercise group and decrease over time in the control group. Additionally, the same participant, who reported difficulties in conducting the test at baseline, reported improvement in her breathing pattern and decrease in wheezing at the end of intervention and the follow up sessions.

Aerobic exercise refers to the use of oxygen to adequately meet energy demands during physical exercise (Kisner et al., 2017). In the general population, heart rate (HR) and respiratory rate increase during aerobic exercise to fulfil demands of the exercising skeletal muscles (Manley, 1996). Additionally, it has been found that regular aerobic exercise, such as walking, cycling, or swimming, of 30–60 minutes three times per week can improve lung function, improve oxygen consumption, and decrease shortness of breath in the general population (Myers, 2003). However, these effects have not been widely explored in PLwP.

Baseline findings of the pulmonary function test, and pulmonary impairments in the early stages of Parkinson's (Stages I, II and III in Hoehn and Yahr) will be discussed in detail in section 5.2 (objective 2 of the EXoCARP trial).

5.1.4.2. Cardiopulmonary Exercise Test (CPET)

CPET is the gold standard method to measure cardiac fitness and response to physical stress. The assessor did not find any difficulties while running the CPET, and the American Heart Association/American College of Sport Medicine guidelines were followed in the sessions.

The CPET was not, however, conducted with all the included participants. The assessor, an HCPC-registered physiotherapist, took the decision to exclude the CPET from the assessment tests for five participants due to them presenting with high blood pressure during the session, although they were not diagnosed with hypertension, in order to reduce/minimise potential adverse events. Missing this data was a loss for the study; however, safety of participants was prioritized. The researcher kept in mind the potential of undiagnosed, or even undeclared, hypertension.

Participants reported no problems in conducting the CPET when asked about that in the focus groups, except for the saddle used on the cycle, as some participants reported that the saddle was not comfortable. Accordingly, if the same cycle were to be used in the next trial, the saddle needs to be changed, and perhaps there should be more than one type with different sizes and designs to suit different people. This needs to be considered in the costing for the next trial.

Although this feasibility trial was not testing effectiveness of the intervention, or differences between PLwP and healthy people at the same ages, the plotted data for the CPET results showed almost no changes in terms of peak HR, predicted VO_{2peak}, or test duration. This raises the question of whether the protocol used, with 70% of the age predicted HR as the endpoint of the test, was challenging the cardiorespiratory system enough for the included sample. Taking into consideration

that most of the included participants were already physically active at the start of the study, subsequently, using the same CPET protocol in the following trials will need to be reviewed. The use of protocols with a higher sub-maximal level than 70%, or the use of a maximal CPET, need to be considered. However, if a maximal CPET is to be conducted for PLwP, a hospital-based environment with a cardiologist present will be needed as risk management for older adults with comorbidities, according to the ACSM recommendations (American College of Sports Medicine, 2013). This needs to be considered when planning the next trial. Alternatively, other maximal forms of tests could be considered, such as the incremental shuttle walk test. The incremental shuttle walk test has the advantages of being simple, cost-effective, and relevant to functional activities (American College of Sports Medicine, 2013). However, the incremental shuttle walk test might not be the best as well for people with gait and balance impairments such as PLwP, and might be challenging. Additionally, the CPET remains the golden standard test for measuring cardiac fitness, and the most accurate in estimating maximum oxygen consumption (American College of Sports Medicine, 2013).

5.1.4.3. Activity monitors acceptability

Adherence to wearing the activity monitors was 75.95% (mean (SD) 42.5 (8.8) days out of a maximum of 56 days). This was confirmed by the focus group participants when asked about their adherence. However, at the same time, they reported that wearing the monitors around the waist was uncomfortable, or the monitor did not fit with their clothes. Yet, after explaining that the data are more accurate when the monitor is worn around the waist compared to the wrist or ankle, participants agreed that it is feasible to wear them around the waist despite the potential discomfort. Perhaps more explanation about why the device needs to be worn on the waist needs to be given and discussed with participants at the first session in the next trial. This is important to address in the next study, because Actigraph data for

PLwP is not considered to be accurate when worn around the wrist, due to tremor and bradykinesia (Kim et al., 2019). Previous research recommended using accelerometers around the waist for PLwP (Kim et al., 2019; Nero et al., 2015; Wendel et al., 2018).

Median (IQR) number of steps per day for participants in the exercise group was 6021.6 (3522.7, 7001.0), and for the control group was 5568.3 (2089.5, 7178.3). This is in the middle of the average range of steps per day for healthy people who are above 65 years old (3,000-7,000 steps per day) (Bohannon, 2007). Results of the Actigraph was discussed previously in section 5.1.3.

5.1.4.4. Subjective outcome measures (questionnaires)

This trial did not set out to assess the effectiveness of the intervention using subjective outcome measures. However, an insight into the results are summarized below with comparison to previous exercise trials, where possible. Additionally, acceptability of the subjective outcome measures is discussed in this section.

The PDQ-39 results showed a similar level of quality of life for PLwP in all the dimensions, and in the median (IQR) total score at baseline of 0.27 (0.18, 0.37) in the exercise group, and 0.22 (0.07, 0.32) in the control group, compared to other exercise trials at baseline (Park et al., 2014; Rafferty et al., 2017). Participants in the exercise group showed an increase in the domains of ADL, Emotions, Stigma, Cognition, Communication, Bodily Discomfort, and the total score, as can be noted from the bar charts, with lower scores indicating better QOL (for more details see section 4.5.2.1.1 in Chapter four).

Participants who were in the exercise group showed a decrease (indicating improvement of the non-motor symptoms) in their NMSQ median score from 8.50 at

baseline to 7.00 at end of intervention. Baseline results of both groups indicate mild to moderate non-motor impairments. The potential improvement in NMSQ supports previous literature about the effects of exercise on non-motor symptoms (Amara and Memon, 2018; Dashtipour et al., 2015).

The Barthel Index was shown to be correlated with the ADL dimension of the PDQ-39 ($r=-0.467$, $p=0.02$). Subsequently, the Barthel Index could be removed from the battery of outcome measures used in the next trial, and assessing independence in ADL through the PDQ-39 might help to decrease the time needed to complete subjective outcomes. Although the Barthel Index has been used widely clinically, other scales and questionnaires have been found to have better sensitivity and specificity in PLwP. For example, the Hoehn and Yahr scale was found to have 98% specificity and 80% sensitivity in detecting dependency in ADL compared with 67% sensitivity and 78% specificity in the Barthel Index when assessed in PLwP (Bjornestad et al., 2016).

The PRMQ prospective memory results showed an improvement after the eight-week intervention period for participants who were in the exercise group, with no changes in the control group. Retrospective memory showed an increase in scores for both groups after the eight weeks. These results are very similar to results of a previous study that assessed the effects of aerobic exercise on prospective and retrospective memory in the healthy people ($p<0.05$) (Shamsipour Dehkordi et al., 2018). However, the effects of aerobic exercise on prospective and retrospective memory in PLwP was not assessed previously, and this could be an addition to the next trial to further investigate the benefits of aerobic exercise in Parkinson's.

Focus group participants reported that the questionnaires were acceptable, and some were familiar to participants either from previous trials or from routine clinical

assessments. However, reported difficulties in terms of handwriting due to Parkinson's symptoms suggest that, perhaps for the next trial, the use of an electronic device, such as an iPad or a smart tablet, to complete questionnaires, could be preferable and solve this handwriting problem associated with completing of paper and pen questionnaires.

5.1.5. Adverse reactions

No adverse reactions were reported in the EXoCARP trial. Although one participant reported the accelerometer to be uncomfortable, no adverse reactions were reported as a result of wearing it. Moreover, expected adverse reactions such as dizziness, imbalance, falls, pain, and depression from the outcome measures or from the intervention were not reported. Therefore, safety issues have not been identified as a concern and the same protocol could be repeated.

5.2. Pulmonary function in PLwP (Objective 2)

Assessing the prevalence of pulmonary impairment in PLwP in the early stages of the disease (H&Y stages I, II and III) was one of the objectives of this work. Interestingly, 54% of the included 24 participants showed an abnormal pulmonary pattern (11 participants with obstructive pulmonary pattern, one with restrictive pattern and one with mixed obstructive and restrictive pattern). However, these participants had not been diagnosed as having an abnormal pulmonary pattern through routine screening of lung function in PLwP, by the National Health Services (NHS), and were not aware about their lung impairment. As has been addressed in Chapter Two (section 2.3 Pulmonary Function in Parkinson's), the systematic search revealed that studies reported different findings on pulmonary patterns in PLwP.

Results of the current study also showed that participants who have abnormal pulmonary pattern (obstructive, restrictive or mixed pattern) have higher disease severity and are less active physically than participants who have normal pulmonary pattern. Motor symptoms worsen with progression of the disease; including rigidity, stiffness, bradykinesia and walking impairments; and respiratory impairments might be linked to these symptoms. Thus, respiratory impairments might be affected by both physical activity level and disease severity. These results, however, need to be confirmed in a larger study with an appropriate sample size.

There is no clear or definite cause for the abnormal lung patterns in PLwP, but factors such as kyphoscoliosis, chest wall rigidity and weakness of respiratory muscles lead to a decrease in the lung's recoil ability, loss of elasticity, decreased lung volumes, affect V/Q mismatch and lead to dynamic hyperinflation of the lungs (Baille et al., 2016; Black and Hyatt, 1971; Estenne et al., 1984; Sabaté et al., 1996; Santos et al., 2019). Rigidity of chest wall muscles might lead to a reduction in chest wall compliance due to stiffening of tendons and ligaments and ankylosis of costosternal and thoraco-vertebral joints (Shill and Stacy, 2002). Furthermore, postural instability in Parkinson's (Bloem, 1992) might also affect the mechanics of ventilation by affecting the diaphragm and, subsequently, reduction in the generated force by the diaphragm. Moreover, low level of physical activity due to the motor symptoms might lead to alveolar collapse and, subsequently, atelectasis, which might result in reduced lung volume and decreased lung compliance, and increase the elastic load (Dargaville et al. 2010). These factors can contribute to the abnormal pulmonary patterns in Parkinson's. Other factors that might lead to the abnormal pattern include: environmental factors (e.g. dust, weather and smoke) (Berry and Wise, 2010); immunological factors that could affect the defence of the respiratory system against foreign bodies and subsequently destroy the normal defence mechanism in the airways (e.g. destroying the mucocilliary escalator

system by viral and bacterial infections) (Wanner et al., 1996); or neurological reasons that might affect the respiratory drive in the medulla oblongata or impairment to the respiratory afferent or efferent neurons (Pyatigorskaya et al., 2016). It should be noted, however, that these factors are hypotheses for pulmonary impairment in Parkinson's, but have not yet been fully investigated.

These different factors that might contribute to pulmonary impairment in Parkinson's highlight the importance of targeting appropriate physiotherapy management according to the factors that could be assessed individually. For example, if chest wall rigidity is the main cause, then chest expansion exercise might need to be embedded in a pulmonary rehabilitation programme. Similarly, if kyphoscoliosis is the main cause, then postural training needs to be addressed. In all cases, aerobic exercise is the essential main element within pulmonary rehabilitation for long-term respiratory conditions (Cooper, 2001), on top of other individualised exercises such as postural training, chest expansion exercises, or respiratory training exercises. Furthermore, if PLwP started to report complications or symptoms such as dyspnoea or secretion retention, management of those symptoms in the earlier stages of Parkinson's is recommended to avoid further complications.

The findings of this study suggest two main changes to current practice in the management of PLwP: 1) routine screening of pulmonary function in the earlier stages of Parkinson's; 2) individualised physiotherapy programmes that include aerobic exercise in addition to other exercises, to address factors that could be causing abnormal pulmonary patterns. Management of pulmonary impairment in the earlier stages of Parkinson's might help to reduce or delay the impairment, and subsequently, reduce or delay the respiratory complications that occur in the end stages of the disease, which are considered to be the main cause of mortality in Parkinson's (Ebmeier et al., 1990).

It should be highlighted, however, that these findings about pulmonary function in PLwP are limited due to not assessing the full spirometry profile, and perhaps a plethysmography assessment is needed. Furthermore, assessment of respiratory muscles by means of a mouth pressure test might be needed to highlight respiratory muscle strength. This study lacked some external validity as smokers were excluded, and it would be interesting to explore the differences in characteristics (such as age, physical activity level, disease severity and dominant symptom) between those with and those without an abnormal pulmonary pattern in a wider sample size.

5.3. Summary and aspects to take forward to a future study

This pilot study investigated the feasibility of conducting a larger clinical trial to investigate the effects of aerobic exercise on cardiopulmonary function in the earlier stages of Parkinson's (H&Y Stages I, II and III).

Before finalizing plans for the next trial, consideration needs to be given to the challenges related to recruitment, assessment and screening, the intervention itself and the outcome measures. Results of the current feasibility trial reflect the need for further planning prior to the next trial, especially since this feasibility trial did not achieve the target sample size due to COVID-19 related issues. In particular, these include:

- The use of multiple recruitment sites to collect data is recommended to boost the recruitment rate, although with resolution of the COVID-19 pandemic and removal of restrictions to data collection experienced in this trial as a result of the pandemic, recruitment from a single-site in a future trial in the absence of a pandemic is likely to be more successful. However, it is

anticipated that data collection would be more challenging when multiple sites are used due to access to standardised equipment.

- Further piloting would provide better understanding of and insights into the use and potential effects of an individualised, intensive aerobic exercise programme, rather than a general exercise prescription.

In general, the outcome measures used in this trial were found to be acceptable to participants and, therefore, feasible to be used in the next trial.

- Objective assessments including the spirometry (PFT) and the CPET are recommended to be used in the next trial. However, one-way filter mouthpieces are recommended to be used for spirometry to save time spent in sterilising the transducer.
- If a maximal CPET will be conducted in the next trial, the presence of a cardiologist will be needed, if that is considered to be more appropriate. Alternatively, a maximal shuttle walk test could be used. Also, if the same cycle is going to be used for the next trial, more comfortable saddles with different types and designs are recommended to be there.
- Subjective assessment measures used in this trial were found to be acceptable and easy to administer. However, the Barthel Index could be removed, and ADL dimension of the PDQ-39 could be used instead to save time because the PDQ-39 is being used anyway to collect information for the other domains, and collecting the ADL data using it will help in saving more time for both the assessor and the participants.
- An electronic method of data collection for the questionnaires is recommended to avoid the need of fine movements needed for handwriting in Parkinson's.

In order to summarize the study recommendations to improve the quality for the future trial, a traffic light system has been used (Sheron et al., 2012; van Meijel et al., 2014). Table 23 shows the aspects of this feasibility study that are not recommended to be continued (in red), are recommended to be continued but some changes are required (in yellow), or are recommended to be continued without changes (in green).

Table 23: Aspects of the trial to consider for the next trial, presented using the traffic light system (where red denotes areas that should not continue in the next trial, yellow denotes area that need to continue but with some changes/modifications, and green denotes areas that should continue as it is).

Traffic light colour	**Aspect of feasibility**	**Considerations/changes if needed/aspects to continue or not continue**
	Devices	Cycle: Do not use the same saddle for CPET. Need to have different sizes/designs to suit different people.
	Outcome measure	Do not use the Barthel Index. Do not use the age-predicted maximal HR formula. Use a maximal CPET in a hospital-based setting with a cardiologist present, or use a maximal incremental shuttle walk test in the community.
	Recruitment method	Need to continue with using Parkinson's UK website, Parkinson's UK email address and Parkinson's UK local groups. However, using social media (Facebook, Twitter, etc) is recommended. Recruitment from NHS clinics for PLwP is also recommended. Aim to include a less-biased sample by marketing the trial to more sedentary PLwP and referring to 'activity' rather than 'exercise' in the marketing resources.
	Settings	Continue collecting data from Keele. But need to add other local areas to boost the recruitment rate. NHS/ hospital based environment is needed in case of running a maximal CPET.
	Screening methods, inclusion and exclusion criteria	Continue with the same inclusion/exclusion criteria and screening methods. However, another point is recommended to be added regarding high undiagnosed blood pressure and inclusion in the CPET.
	Intervention	Use the same intervention (community-based aerobic exercise programme), but with a tailored / individualised exercise prescription depending on results of the CPET at the first exercise session. Use

		heart rate monitors to help participants to monitor their exercise intensity within the prescribed window.
	Devices and tools used	Use the same spirometer devices but use disposable mouthpieces that have a filter inside to save time used in sterilisation. Use the same accelerometers but give more explanation about sensitivity of waist-worn devices data compared to wrist or ankle worn devices. Need a Tablet or an iPad for questionnaires data collection.
	Outcome measures	Use the same standardised pulmonary function test protocol. Continue using the Actigraph. Continue using the PDQ-39, PRMQ, NMSQ, physical activity survey and the GDS. Continue using daily exercise diaries. Continue conducting focus groups after the intervention and use thematic analysis to collect information about participant's experiences about the trial.
	Blinded assessor	Use the same method for blinding.

5.4. Strengths of the study

The EXoCARP trial was a single-blinded mixed-methods randomised controlled feasibility trial. The randomization process was set up in advance by a chartered statistician from Keele University (Professor Julius Sim), and the blinding was conducted and maintained by the research supervisor (Dr Sue Hunter) who delivered instructions to participants according to their allocated groups, to keep the assessor (Aseel Aburub) blinded. The research team had reviewed the trial protocol and the trial was registered in the ISRCTN registry (ISRCTN14167992; https://doi.org/10.1186/ISRCTN14167992).

The assessor was trained to conduct pulmonary function tests and spirometry analysis, and was certified as such by the British Thoracic Society. The training aimed to conduct the test according to the standards and regulations of the American Thoracis Society/ European Respiratory Society (ATS/ERS) in order to assure the quality of testing lung function.

The use of a mixed-methods design helped to explore in more depth participants' experiences of the trial. The combination of the quantitative and qualitative data provided richer insights into feasibility of planning and conducting a larger clinical trial in the future.

PPIE meetings helped to inform the study protocol prior to conducting the study. For example, people in the PPIE meetings considered whether they would be happy to wear a facemask during the CPET, and reflected that they would prefer not to, with many reporting that it might make them feel claustrophobic. Accordingly, the VO_{2peak} was estimated using the HR formula rather than direct measure by means of the oxygen consumption mask.

Finally, this is the first study of PLwP that has included aerobic exercise and pulmonary function tests. Cardiopulmonary function is often neglected in rehabilitation of PLwP and its routine assessment over time would be interesting to further expand knowledge about potential secondary complications of Parkinson's and their long-term management. This is to fill the gap that is in the European Physiotherapy Guidelines for Parkinson's Disease (2018), the National Institute for Health & Care Excellence (NICE) guidelines for Parkinson's disease (2019), and the Association of Chartered Physiotherapists in Respiratory Care guidelines (Bott, 2009) which included interventions for management of secretion retention, weak cough, and respiratory muscles training. However, these guidelines do not recommend interventions, such as aerobic exercise, to improve lung volumes in the early stages of Parkinson's. Thus, if aerobic exercise is found to be an effective intervention to improve lung function in the early stages of Parkinson's from a subsequent clinical trial, this evidence will contribute to filling the gap in these guidelines.

5.5. Limitations of the study

This feasibility trial is not without limitations. The COVID-19 pandemic severely limited recruitment to the trial and data collection; the national lockdown period began in March 2020, resulted in a smaller sample size (n=24) than was originally planned (n=50). Although we had some participants willing to travel from other regions, recruitment was limited to the local areas around Keele University, as the only assessment site was at the University. This affected recruitment to the study. Also, recruitment was conducted through Parkinson's UK email groups and was not conducted through larger recruitment possibilities, such as the NHS or Parkinson's social media groups. Furthermore, recruitment for the study attracted people who were relatively physically active and routinely engaged in regular exercise. The

advertisement should perhaps be re-worded to attract people with different exercise levels.

Furthermore, the intervention was not prescribed based on CPET results and, consequently, the intensity of exercise might not have been sufficiently high to result in improved cardiopulmonary function and changes in the CPET from baseline. Participants needed more guidance in terms of intensity and exercise prescription. Additionally, the CPET itself was conducted as a peak test using 70% of participants' maximal age-predicted HR, rather than a maximal exercise test. This is due to the need for a cardiologist to be on site if the maximal CPET is to be conducted.

Another limitation in this study is that there was no participants from other ethnic groups than Caucasians, although recruitment was not limited to a specific gender, ethnic group or age group (except for being an adult). Furthermore, the first focus group included four males with no females, although invitations to participate in the focus group were sent to all participants in the exercise group from any gender. The resultant demographic of the focus group participants was dependent on who responded and agreed to participate.

The development of the intervention in EXoCARP was not based on a behaviour change model. The objectives of the EXoCARP study were not seeking to change behaviour, but to see whether participants would adhere to the intervention (as part of the feasibility assessment). It so happened that this group of PLwP were all active prior to enrolling in EXoCARP; the sample was biased, and the study failed to recruit PLwP who were sedentary. Thus, in a future study or trial that aims to also recruit a more sedentary sample of PLwP, it might be beneficial to consider the

Social Cognitive Theory, using goal setting and self-efficacy models, in order to improve adherence to the exercise intervention.

Due to the limitation in recruitment, and inability of the participants to continue with their intervention during COVID-19 pandemic, there was a need to assess how the pandemic affected PLwP physical activity, and other questions arose about exercise during the pandemic in PLwP. This led the researcher to start Study 2 of this thesis (Chapter 6) which is about a survey questionnaire that assessed physical activity levels during the pandemic, exercise limitations, and people's preferences in term of indoor exercises.

Chapter 6: Study 2 - Physical activity during COVID-19 period: a survey questionnaire study

6.1. Exercise during COVID-19 questionnaire: Justification and brief introduction

The EXOCARP trial (ISRCTN14167992), at Keele University has been recruiting participants with Parkinson's from the community since April 2019. Participants were attending the exercise laboratory in the School of Allied Health Professions at Keele University to undertake pulmonary function tests (spirometry) and a cardiopulmonary exercise test on a cycle ergometer, with the researcher present and in close proximity during the tests. In March 2020, all research activities at Keele that involved face-to-face interaction were suspended temporarily, due to the COVID-19 pandemic and the social distancing measures implemented by the government. This has been the case for many similar research studies that have been suspended around the world.

COVID-19 caused a global pandemic as a results of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) (Lu et al., 2020). COVID-19 patients usually present with fever, pain, respiratory symptoms and sometimes digestive symptoms (Zhou et al., 2020). Being an older adult is one of the risk factors that are associated with aggressive COVID-19 symptoms leading to acute respiratory distress syndrome (ARDS) and, sometimes, death (Zhou et al., 2020). Because Parkinson's is a common neurodegenerative disease, the prevalence of which increases in older adults, PLwP are considered as a vulnerable group for COVID-19 (Tipton and Wszolek, 2020). Additionally, motor and non-motor symptoms have been noted to have significantly worsened in PLwP who have been infected by COVID-19, ending with ARDS and, unfortunately, death (Hainque,

2020). Although it may be too early to understand how COVID-19 has affected Parkinson's symptoms in the long-term, the danger is that COVID-19 acute symptoms, including loss of smell, dyspnoea, and sore throat, are hidden as they are already affected in Parkinson's, making it start silently and progress until the appearance of chronic symptoms and development of ARDS (Cilia et al., 2020). Thus, it is important to consider precautionary measures for this population.

One of the measures that have been put in place to protect people from COVID-19 infection was social distancing, and the government recommendation to, initially, "Stay at home", and then, subsequently, "Stay alert". However, the initial "Stay at home" message placed restrictions on the number of times people could go outside to exercise, with just one outing for exercise per day. Thus, limiting outdoor physical activities and mobility for people who are normally more active than this could result in them leading a more sedentary lifestyle for some people, potentially leading to worsening of their symptoms (Helmich and Bloem, 2020). The most recent physical activity recommendation for older adults is to perform 150 minutes of moderate exercise per week (UK Chief Medical Officers' Physical Activity Guidelines, 2019), and the research team were interested to explore whether PLwP were actually achieving this level of physical activity before the quarantine, and to understand how the COVID-19 lockdown had affected their physical activity and exercise. Additionally, it is important for future research to find out if PLwP are performing any indoor physical exercises, and if so, what type of physical activity that is, how often and for how long they are performing it, and whether they have engaged in any indoor group exercises, such as virtual exercise/fitness groups online, DVD exercises groups, or videogames that involve exercise and physical activity. This is important especially if the lockdown was to continue, or return, to help advise and support people to meet the target of 150 minutes of moderate exercise per week. This knowledge of current practice for PLwP at home will be helpful in the

development of future exercise trials that need to consider indoor exercises and self-management approaches. Furthermore, this could also help to implement the recommendations published recently regarding the importance of running self-management trials for Parkinson's at the moment (Helmich and Bloem, 2020). Thus, study 2 of this thesis aimed to understand how COVID-19 has affected PLwP in their ability to achieve the recommended dose and intensity of exercise per week to maintain health. Additionally, this study aimed to understand the preferences of PLwP in terms of self-management exercise programmes, so that these preferences can be considered and used to inform the design of future studies.

6.2. Objectives of the study

The primary objective of this study was to:

1. Understand how the COVID-19 quarantine affected physical activity and exercising in PLwP.

The secondary objectives of the study were to:

2. Find out whether PLwP are aware of the recommendation of the UK Chief Medical Officer's guidelines for older adults (Gibson-Moore, 2019), and if they were following these recommendations before and subsequently during the COVID-19 pandemic.
3. Investigate what methods or modes of exercise were used by PLwP to keep exercising during the COVID-19 restrictions.
4. Explore preferences of PLwP in terms of self-management and methods of home-based exercise, to inform planning for future studies.

6.3. Methodology

6.3.1. Ethical approval

Ethical approval was received from Keele University Ethical Review Panel (ERP) (Appendix 22), approved 09/09/2020, Faculty of Medicine and Health Sciences Research Ethics Committee (FREC) (School of Medicine, Keele University, Staffs, ST5 6JQ; 01782 734673; k.m.adams@keele.ac.uk) ref: MH- MH-200139.

6.3.2. Design

In order to answer the research questions and achieve study objectives, an online self-administered questionnaire was used. Self-administered questionnaires are the most common method of data collection in healthcare research (Bowling, 2009). Designing a questionnaire should include steps that could help achieve a high-quality, test-retest reliable and unbiased questionnaire. Thus, the process and steps recommended by Bowling (2009) were used while designing this questionnaire, which included:

1. Determine the target and study population and sample size
2. Decide the method of data collection and channel of questionnaire presentation
3. Designing the questions
    - Developing the items and the scales
    - Memory and timeframes
    - Wording and questions
    - Order of questions
4. Pilot and check reliability
5. Minimise bias

6.3.2.1. Determine the target and study population

The study population was PLwP, sampled from the 6000 members of Parkinson's UK Research Support Network.

6.3.2.1.1. Inclusion criteria

Adults who have been diagnosed with Parkinson's and receiving emails from Parkinson's UK Research Support Network or follows Parkinson's UK social media platforms were eligible to participate. Inclusion was not limited to a specific ethnic group, gender or age group.

6.3.2.1.2. Sample Size

Following a sample size calculation, based on the 6000 PLwP who are members in Parkinson's UK Research Support Network that receive research emails, with 95% confidence interval (CI) and 5% marginal error, the target sample size was 362 (Hill, 1998).

The sample size was calculated according to the following formula:

$$\text{Sample size} = \frac{\frac{z^2 \times p\,(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p\,(1-p)}{e^2 N}\right)}$$

Where: N = population size; e = Margin of error (percentage in decimal form); p =0.5; z = z-score. The z-score is the number of standard deviations a given proportion is away from the mean. With 95% CI, z-score was set as 1.96:

$$\text{Sample size} = \frac{\frac{1.96^2 \times 0.5(1-0.5)}{0.05^2}}{1 + \left(\frac{1.96^2 \times 0.5(1-0.5)}{0.05^2} \text{ X } 6000\right)}$$

Sample size= 362

6.3.2.2. Deciding the method of data collection and questionnaire presentation

The method of questionnaire presentation (e.g. aural, visual, text) affects the cognitive and physical burden placed on respondents (Bowling, 2009). Additionally, the mode of delivery (for example: paper-based, online, oral interviews) imposes different cognitive requirements and can affect the process of responding to questions, and subsequently the quality of the data (Bowling, 2009).

PLwP might suffer from tremor, and this could affect their ability to complete a paper copy of the questionnaire, and limit the numbers responding. Additionally, PLwP might have speech and language disorders, making it difficult to conduct a telephone interview questionnaire. Thus, an electronic questionnaire was distributed online, using Microsoft forms, via Parkinson's UK email (invitation letter in appendix 23). Using Parkinson's UK email invitations as the first point of recruitment would help to minimise completion of the questionnaire by people who might not have Parkinson's. However, if the sample size was not achieved by email invitations and subsequent reminders by the deadline, then the questionnaire would be circulated via Parkinson's UK social media to increase the sample size. However, we did not have any control over participants passing the questionnaire on to other people, with or without Parkinson's, even if they were instructed not to do so, though we explicitly asked them not to do so.

6.3.2.3. Designing the questions

6.3.2.3.1. Developing the items and the scales

In the process of planning and developing the items (questions) of the survey, it was crucial to list the research questions, create questions that could help in gathering information that could answer the research questions, think about the items and add more items, refine the questions and remove questions that were not essential, and finally relate the questions again to the research questions and study goals (Bowling, 2009).

While developing the items, the researcher consulted other researchers to discuss the points/items, looked at similar studies that assessed physical activity during the pandemic in other populations (Ammar et al., 2020; Schuch et al., 2020; Yamada et al., 2020), and piloted the questions with a group of PLwP that were participants in Study -1 (EXoCARP).

6.3.2.3.2. Memory and timeframes

Some points were taken into consideration while developing the survey items for this population, especially that PLwP might suffer from memory impairment. Bowling (2009) reported that there are four steps involved in answering questions in a survey:

- Comprehension of the question
- Recall of requested information from memory
- Evaluation of the link between the retrieved information and the question
- Communication of the response/ choosing the answers.

Thus, cognitive impairment was taken into consideration, specifically because the survey asks about the period during the quarantine. Accordingly, time-framed recall

bias (memory bias) was taken into consideration by following the recommendations to not ask about a period beyond the past six months, specifically for questionnaires targeting older adults (Crawley and Pring, 2000). Thus, the survey data collection period was between 7th of September 2020 and 22nd of October 2020, because the national lockdown in the UK started on 23rd of March 2020 and ended on the 22nd of April 2020.

6.3.2.3.3. Wording and questions

The form and wording of the items could affect answers and responses (Bowling, 2009). Thus, it was essential to consider using simple words, short phrases and simple sentences. Additionally, leading questions were avoided. Leading questions could direct participants to answers that are biased (Jackson and Furnham, 2000). For example: if the researcher asked a question like “When would you like to participate in our study?”, this might coerce people to give a date to participate rather than having the choice of not registering such as when asking “Would you like to participate in our study?”. Additionally, closed questions were avoided, where possible, and open questions were used such as the second example used above. This is because closed questions might limit participants’ choices / answers (Sim and Wright, 2000). However, in some items, it was crucial to use a closed question depending on the purpose of the question, but filtered questions were used subsequently in that case. Filtered questions were used in order to further investigate after asking closed questions. For example, when asked about familiarisation of participants with the physical activity guidelines and recommendations, the question was:

> *The physical activity guidelines and recommendations are for people with Parkinson’s to do 150 minutes of exercise per week. Are you familiar with these recommendations and were you doing exercise according to the*

recommendations before the quarantine? (please select one statement from below)

- *Yes, I am familiar with the physical activity recommendations and guidelines, and I was doing the recommended amount of exercise (150 minutes per week) before the lockdown.*
- *Yes, I am familiar with the physical activity recommendations and guidelines, but I was not doing the recommended amount of exercise (150 minutes per week) before the lockdown*
- *No I am not familiar with the physical activity recommendations and guidelines, but I was doing the recommended amount of exercise (150 minutes per week) before the lockdown.*
- *No, I am not familiar with the recommendations, but I was not doing the recommended amount of exercise (150 minutes per week) before the lockdown.*

However, this question was immediately followed by another question for people who were familiar with physical activity guidelines, in order to know how they were following it, and how many minutes of exercise they were performing:

How many minutes of exercise per week you were performing, on average, before the COVID-19 period?

- Please write the number of minutes here ……..

Where possible, a Likert scale or adverbial rating scale were used. A Likert scale consists of a statement with a number of agreement/disagreement options. An adverbial rating scale consists of a question with a number of options that are framed as adverbs (e.g. very often, often, sometimes, occasionally...). Bowling (2009) advises developing an odd number of options for such scales (preferably

five- or seven-point scales) to have a choice in the middle as an equilibrium item. Below is an example of an adverbial question:

How much did you feel that the advice for everybody to "Stay at Home" affected your physical activity?:

- *Completely restricted my physical activity*
- *Somewhat restricted my physical activity*
- *Minimally restricted my physical activity*
- *Did not change my physical activity at all*
- *Minimally increased my physical activity*
- *Somewhat enabled me to increase my physical activity*
- *Significantly increased my physical activity*

6.3.2.3.4. Order of questions

Bowling (2009) recommended that ordering of questions is very important in the process of answering and could help in avoiding distraction of the reader. It is recommended that researchers do not keep changing the topic of the questions and then return back to it (Bowling, 2009). Accordingly, the questionnaire was developed in a way that it included the following sections in the following order:

- A question to understand what PLwP do to protect themselves from COVID-19.
- Questions about familiarity of physical activity recommendations.
- Questions about physical activity level and mode (type of exercise) before the quarantine, during the "Stay at home" regulations, and during the "Stay alert" recommendations during COVID-19 pandemic.
- A question about their preference in terms of future self-management mode of exercise.

- Questions about Parkinson's UK exercise groups.
- Questions about any Parkinson's symptoms (if found) that deteriorated during the COVID-19 period.
- A final question if they have any comments about the study.

The final full questionnaire is in Appendix 24.

6.3.2.4. Piloting and reliability

Before distributing the questionnaire online through Parkinson's UK, the questionnaire was piloted by sending it to PLwP who were participants in a previous trial and who had provided written consent, with preferred contact details, to be contacted in relation to further research studies. This was to make sure that they were happy with the wording, could understand it easily, think that this is appropriate to share it through Parkinson's UK, and to suggest any changes (if needed). According to Bowling (2009), a sample size of at least 12 participants is recommended for piloting questionnaires. Thus, for piloting issues, the questionnaire was sent by email to participants of the study 1 in this thesis (the EXOCARP trial) who provided written consent to be contacted by email for future studies (n=24).

In order to assess test-retest reliability, participants who piloted the questionnaire were asked to complete it again after one week. The one-week gap was considered between sessions to minimize potential recall bias (Portney, 2020), but for the test-retest reliability check, each participant had a different Microsoft Forms link from the others. Figure 35 shows the different links that has been send to each participant. This is because we needed to check for agreement in the answers for the same participant after one week.

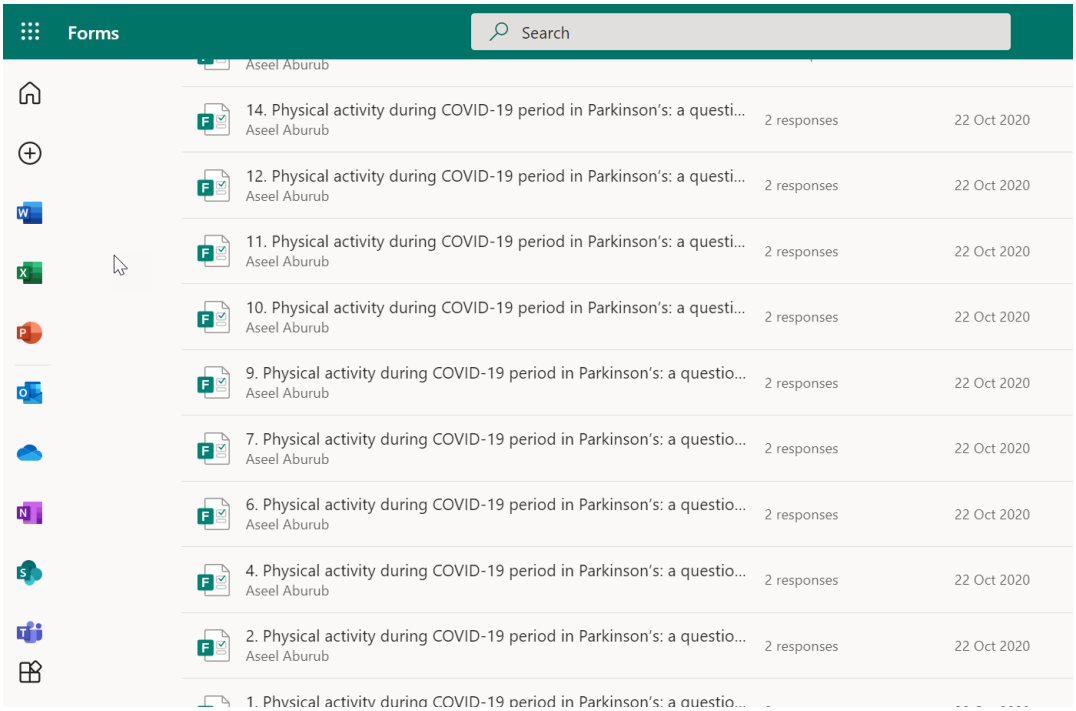


Figure 35: Screenshot showing a different link (form) for each responder in the pilot phase of the questionnaire to ensure that answers of each responder will be compared by his/her answers after one week, and not by answers of any other responders.

6.3.2.5. Minimising bias (non-response and recall bias)

The questionnaire was sent to Parkinson's UK members through Parkinson's UK email groups. This did not limit the non-response bias (Portney, 2020), which may be caused by the following: people might forget to complete and return the survey; people might be busy and not have time to complete it; the survey may be too long for them; people might not have internet internet/IT access; or people might be concerned about security and data integrity (Atif et al., 2012). Non-response bias is the bias that exists in the data because respondents to a survey are different from those who did not respond or responded late (Atif et al., 2012). Several techniques have been suggested to reduce non-response bias such as an attractive cover letter, clear instructions on how to answer the questions, gentle emails as

reminders, emphasizing the confidentiality of the material, reducing the number of questions, and flexible scheduling (Atif et al., 2012). Accordingly, while planning for data collection, minimising non-response bias was taken into consideration, and the survey questionnaire included clear instructions, with a total of 26 questions, and two gentle reminders were sent (appendix 25) by the Research Participation Lead in Parkinson's UK. However, all of these techniques will not fully prevent non-response bias, and the possibility of such bias should be acknowledged whenever there are missing returns.

6.3.3. Statistical analysis

Data were analysed using the SPSS, Version 21 (SPSS, Chicago)). Test-retest reliability assessment was conducted for questions that included numbers as an answer (for example: number of minutes), or questions that included choosing one answer only. These include questions number 2, 3, 4, 5, 7, 8, 11, 12, 15, 16, 18, and 19. Data reported for the test-retest reliability included medians and Kappa coefficient (indications of Kappa results: 0.0 – 0.20 slight agreement; 0.21 – 0.40 fair agreement; 0.41 – 0.60; moderate agreement; 0.61 – 0.80; substantial agreement; 0.81 – 1.00 almost perfect agreement) (Landis and Koch, 1977).

For the main study, no total scores were calculated, and only descriptive statistics including frequencies, proportions, counts and medians/modes of answers were recorded (for example: 105 participants answered that they use a stationary cycle, etc.). Figures for the answers were created using Microsoft Excel.

6.3.4. Thematic analysis of question 26

Answers to question number 26: "If you would like to, please add any additional comments about how the COVID-19 period and social distancing regulations have

affected your life", contained qualitative data. Thus, simple thematic analysis was used to analyse the responses to this question (for more details about thematic analysis, refer to section 3.5.12 in Study 1). Thematic analysis is a flexible method of analysis of qualitative data that is not restricted to a particular epistemological or theoretical perspective (Braun and Clarke, 2006).

6.4. Results

6.4.1. Pilot study

Twelve responders completed the questionnaire at day one, and re-filled it again after one week for the test-retest piloting without having access to their previous responses. Table 24 represents the test-retest reliability of the questions tested. As seen from table 24, the kappa coefficient=1 in most questions indicating almost perfect agreement. Medians of questions' scores at the test and the retest are reported in table 24.

Two participants spotted a repetition in a phrase (a typographical error) in the online questionnaire and contacted the research team to advise them of this while piloting the questionnaire. Accordingly, the repeated phrase was removed. No other comments were received from participants in the pilot phase.

Table 24: Results of the test retest reliability for the questionnaire.

Question	**Test Median (IQR)**	**Retest Median (IQR)**	**kappa coefficient**
2. What is your gender?	1.50 (1, 2)	1.50 (1, 2)	1.00
3. Please tell us about your level of mobility	1.00 (1, 2)	1.00 (1, 2)	1.00
4. How far can you walk?	3.00 (2.25, 3)	3.00 (2.25, 3)	1.00
5. How long have you been diagnosed with Parkinson's?	2.50 (1.63, 8)	2.50 (1.63, 8)	1.00
7. Are you familiar with these recommendations and were you doing exercise according to the recommendations before the quarantine?	1.00 (1, 1)	1.00 (1, 1)	1.00
8. How many minutes of aerobic exercise per week you were performing, on average, before the COVID-19 period?	185.00 (115, 200)	190.00 (115, 300)	0.63
11. How much did you feel that the advice for everybody to "Stay at Home" affected your physical activity:	2.00 (2, 2.75)	2.00 (2, 2.75)	1.00
12. How much did you feel that the advice for everybody to "Stay Alert" affected your physical activity :	2.00 (2, 3)	2.00 (2, 3)	1.00
15. Before the COVID-19 period, how regularly were you attending a Parkinson's UK exercise or fitness groups on a regular basis?	6.00 (2.5, 8)	6.00 (2.5, 8)	0.99
16. Because of COVID-19 social distancing regulation, have you missed attending your Parkinson's UK exercise group?	2.00 (1, 2)	2.00 (1, 2)	1.00
18. How do you feel about returning to your Parkinson's UK local group or exercise class?	2.00 (1, 2)	2.00 (1, 2)	0.82
19. Once lockdown have been lifted, will you go back to the Parkinson's UK exercise groups?	2.00 (1, 2)	2.00 (1, 2)	1.00

6.4.2. Results of the main study

In total, 441 participants submitted the online questionnaire, which was 121.8% of the targeted sample size, and 7.35% of the population sampled. Out of these, 25 responders only completed the consent section but did not complete any of the subsequent questions. Thus, 416 questionnaires were included in the analysis, which was 114.9% of the targeted sample size and 6.93% of the population sampled. Average time to complete the questionnaire was 14 minutes.

6.4.2.1. Demographics

Mean (SD) age was 70.43 (7.26) years, and time since diagnosis was 6.22 (5.05) years (table 25). A total of 191 participants described their gender as male, 221 as female, and 4 as "other". Information about ethnicity was not requested and therefore not reported.

6.4.2.2. Usual physical activity

Most participants (n=329, 79%) reported that they could walk independently without the need for walking aids, and for more than one mile (n=209, 50%) (figure 36). The mean (SD) time per week spent exercising was 203.83 (175.54) minutes (table 25).

Table 25: answers for questions 6, 10 and 13.

	Q6. Age (years)	**Q 10. Time since diagnosis (years)**	**Q13. Average time spent performing aerobic exercise per week before the COVID-19 period (minutes)**
Mean (SD)	70.43 (7.26)	6.22 (5.05)	203.83 (175.54)
Minimum	55.00	2 months	0.00
Maximum	85.00	33.00 years	1200.00

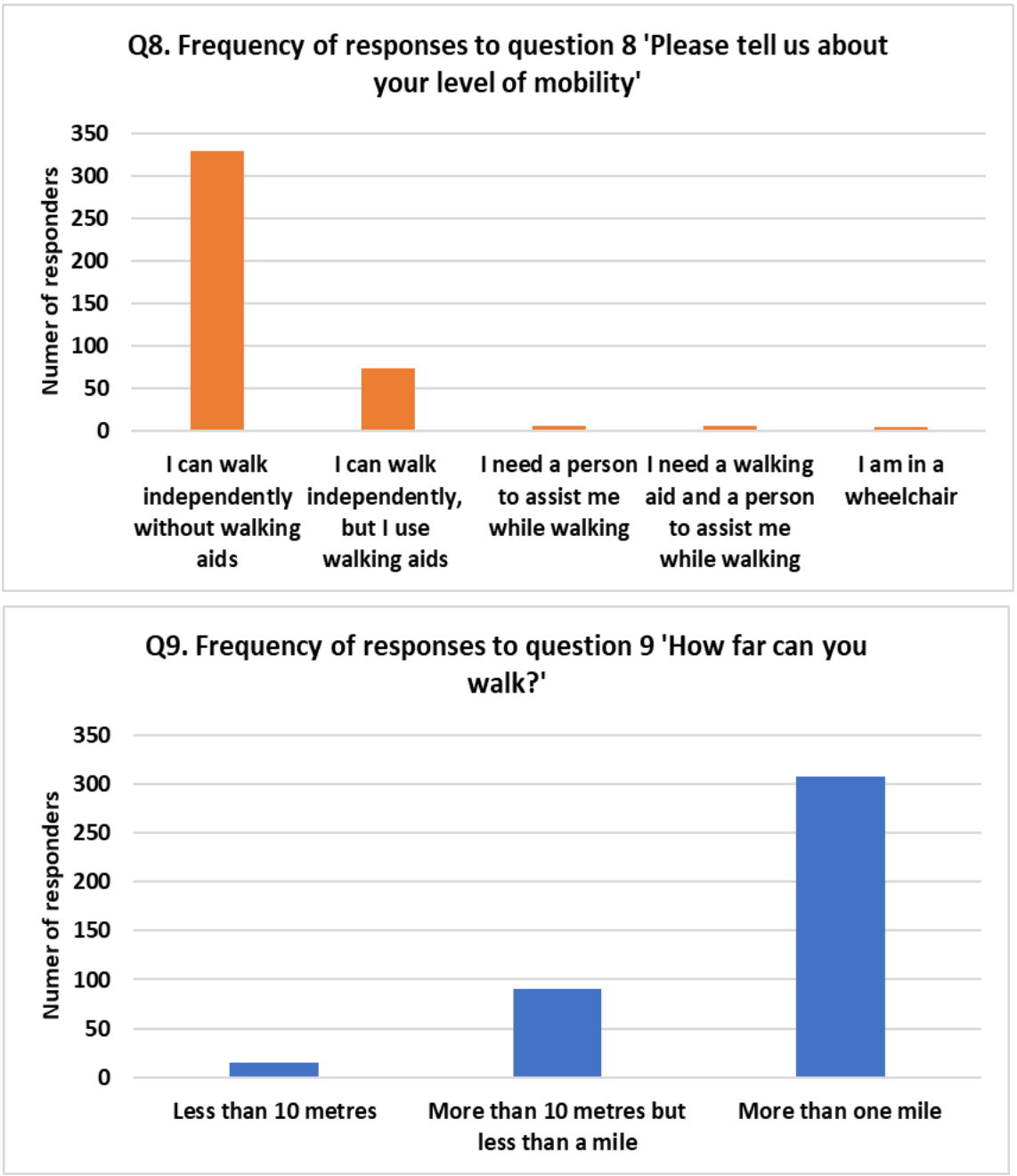


Figure 36: Answers to questions 8 and 9.

6.4.2.3. Precautionary acts to protect from COVID-19

Responders reported practising social distancing, hand washing, using hand sanitizer, staying at home, eating healthy food, getting some rest and sleep and shielding at home, respectively, as precautionary acts to protect themselves from getting the virus (figure 37). Other comments included practising exercise at home and taking vitamin D.

6.4.2.4. Usual physical activity before the pandemic

Prior to the pandemic, 343 (82%) responders reported that they were “walking outdoors” and 234 (56%) reported that “gardening” was their main exercise; 130 (31%) responders reported that they do not have any of the exercise equipment that were mentioned in the choices for that question (figure 38). Other types of usual exercise included yoga, table tennis, aqua-aerobic exercises, golf, Zumba, taekwondo, boxing, Pilates, and dancing.

6.4.2.5. COVID-19 pandemic effect on physical activity

A total of 170 (41%) responders reported that the instructions “Stay at Home” somewhat restricted their physical activity while 159 responders (38%) reported no change to their physical activity level with the instructions “Stay alert” (figure 39). A total of 40 responders reported strong negative experiences of the restrictive effects that the COVID-19 pandemic had not only on their physical activity but also on their life:

'Completely destroyed my life'

'Restricted everything in my life'

However, some activities such as gardening, which were done at home, were not affected:

'restricted everything except gardening'.

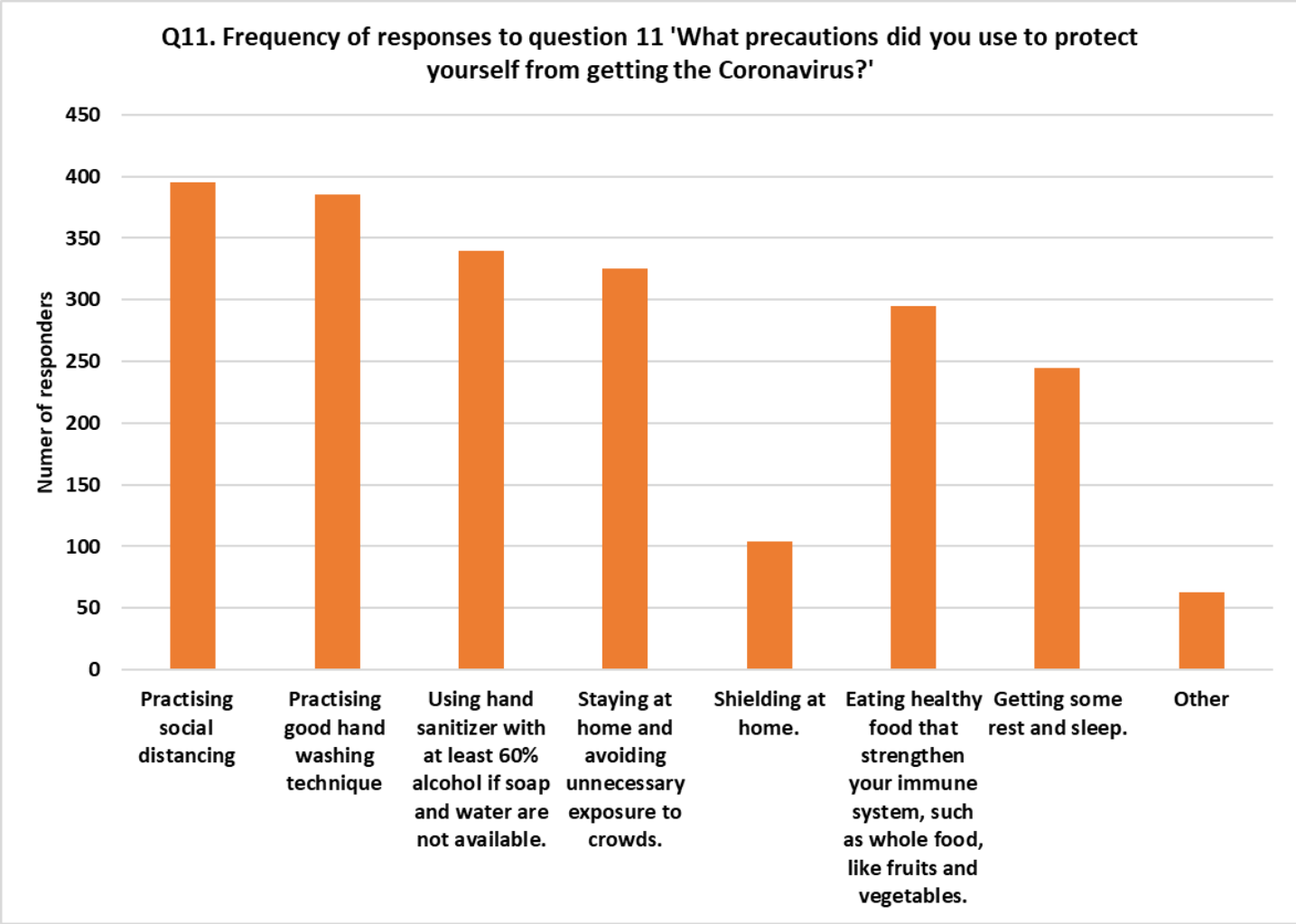
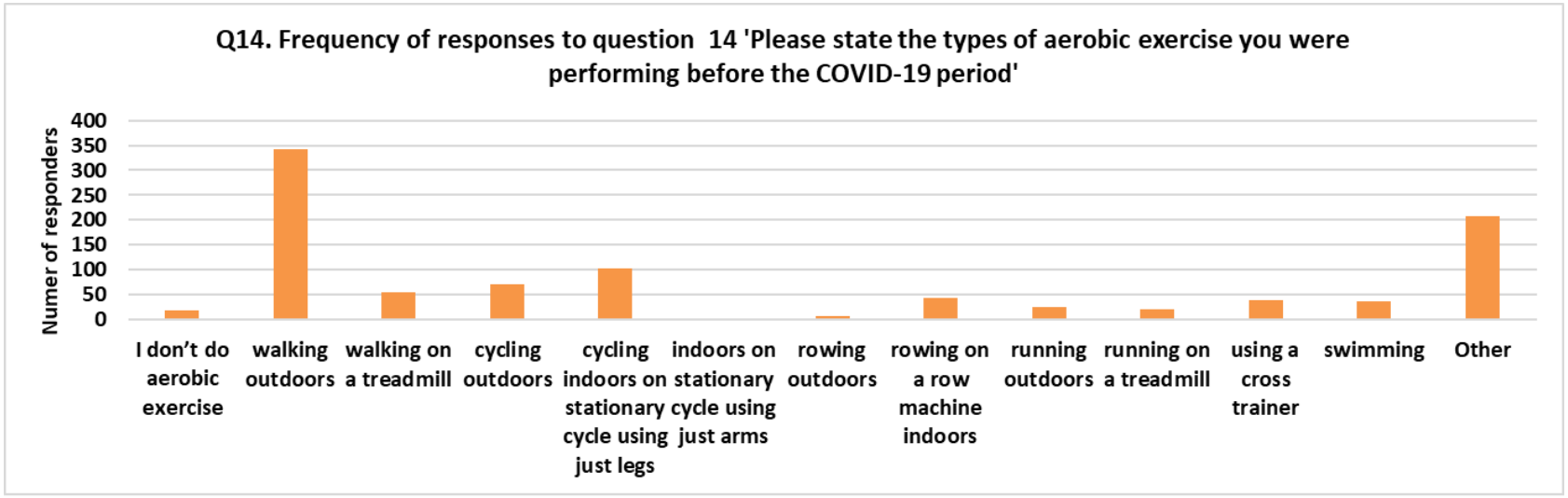


Figure 37: results of question 11.



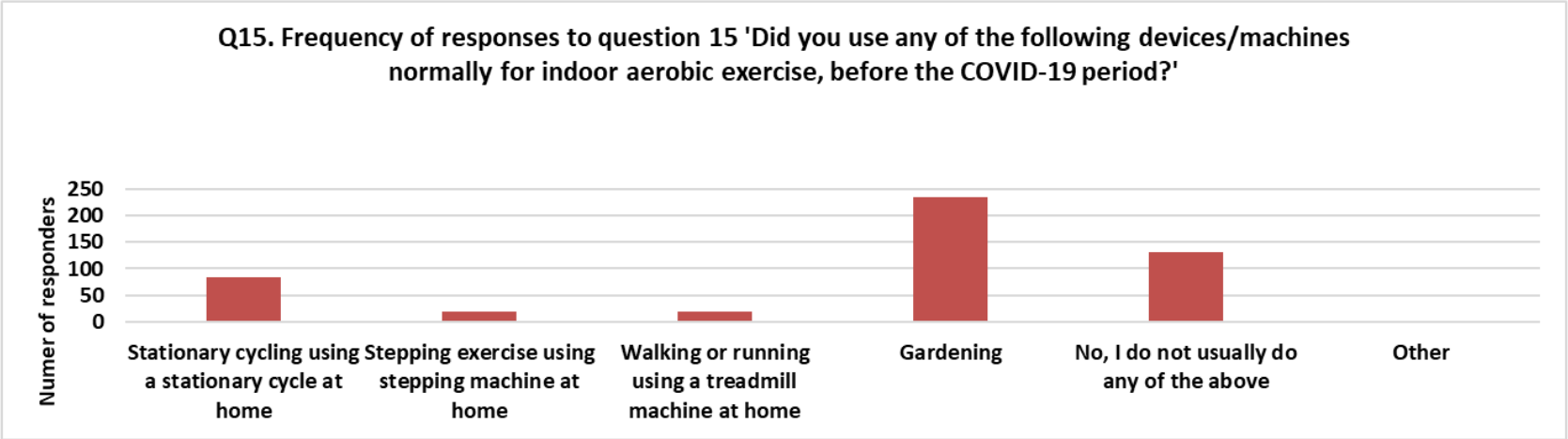


Figure 38: answers to questions 14 and 15.

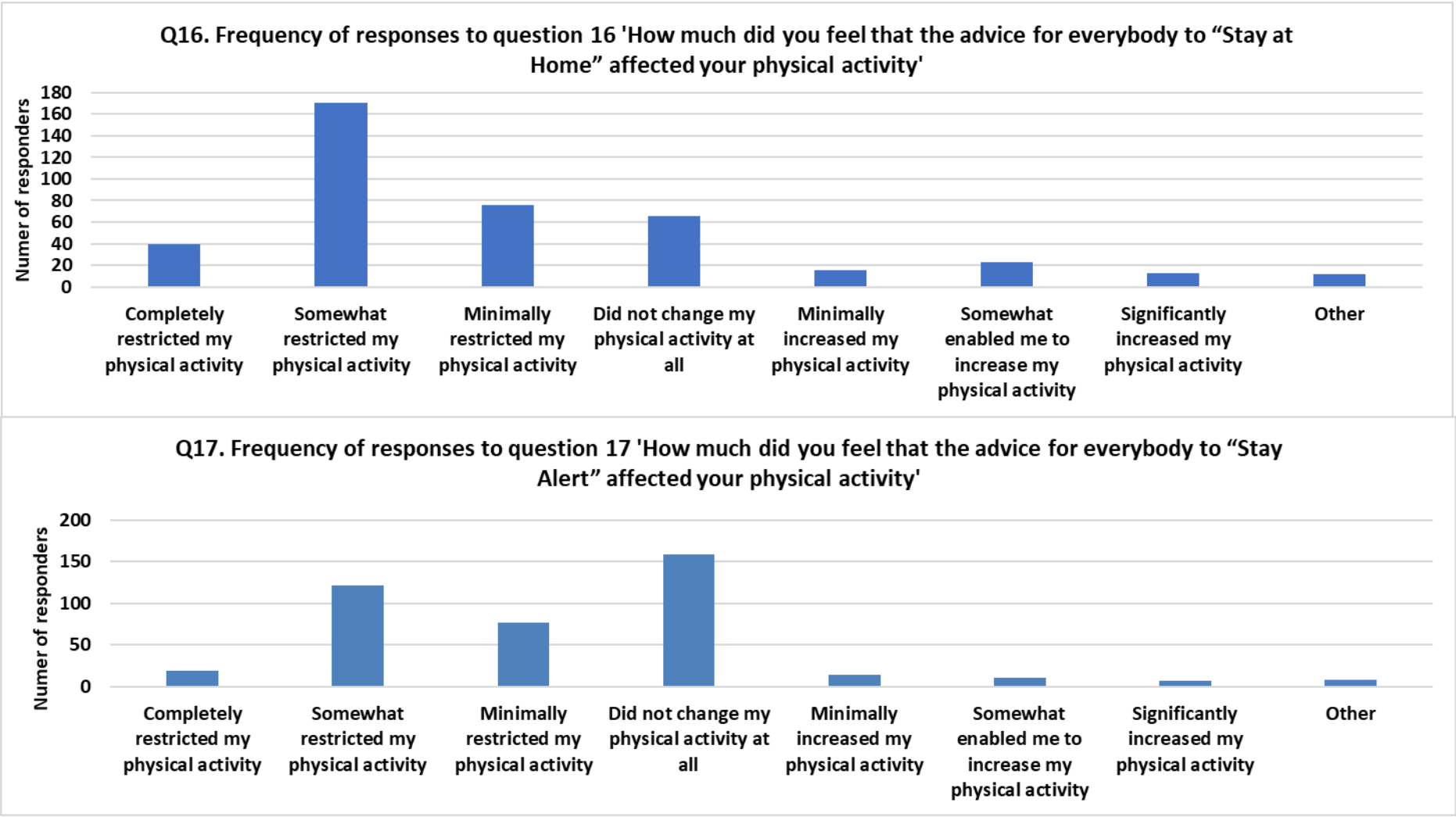


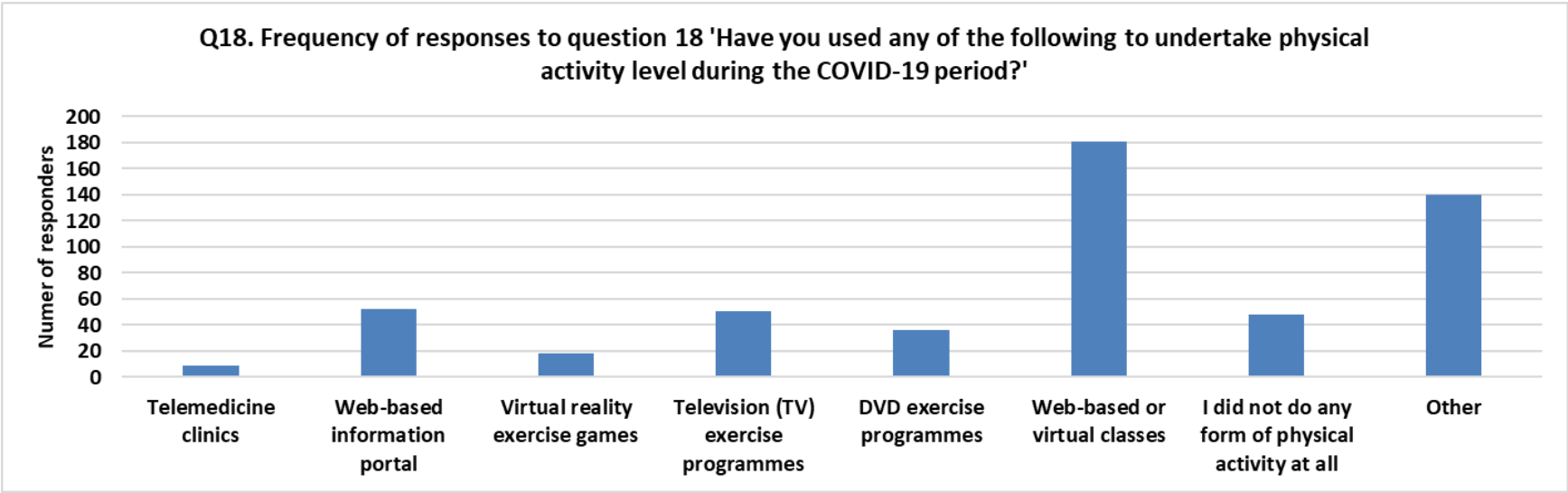
Figure 39: Answers to questions 16 and 17.

6.4.2.6. Adapting exercise during the pandemic

During the COVID-19 period, 181 (44%) responders reported using web-based virtual exercise classes, 52 (13%) were using a web-information portal for exercising, 51 (12%) engaged with TV exercises, and 36 (9%) reported using DVD exercises (figure 35). Gardening, followed by web-based virtual classes, were reported as activities that might help to exercise more at home (figure 40). Other comments included golf, Xbox, Wii fit, PlayStation, yoga and dog walking.

6.4.2.7. Parkinson's UK exercise groups

A total of 211 responders (51%) reported that they were not attending Parkinson's UK exercise fitness group at all before the COVID-19 period, 90 (22%) reported that they were attending regularly on a basis of once per week, and 76 (18%) reported attending more than once per week before the COVID-19 period (figure 36). For 219 (53%) responders, the question "Because of COVID-19 social distancing regulation, have you missed attending your Parkinson's UK exercise group?" was not applicable, whereas 174 (41%) responded with "Yes" and 23 (6%) responded with "No" (figure 41). Social contact and communication with other group members was the most frequent aspect that they missed from the Parkinson's UK groups, followed by the exercise itself and the physical activity, and the getting out of the house (figure 36). When asked about returning to Parkinson's UK groups, 158 responders (38%) reported that it was too risky at that time, and 130 (13%) reported that they felt that they would need to get back to the Parkinson's UK groups, while the others (n=130, 31%) chose "Not applicable" (figure 42).



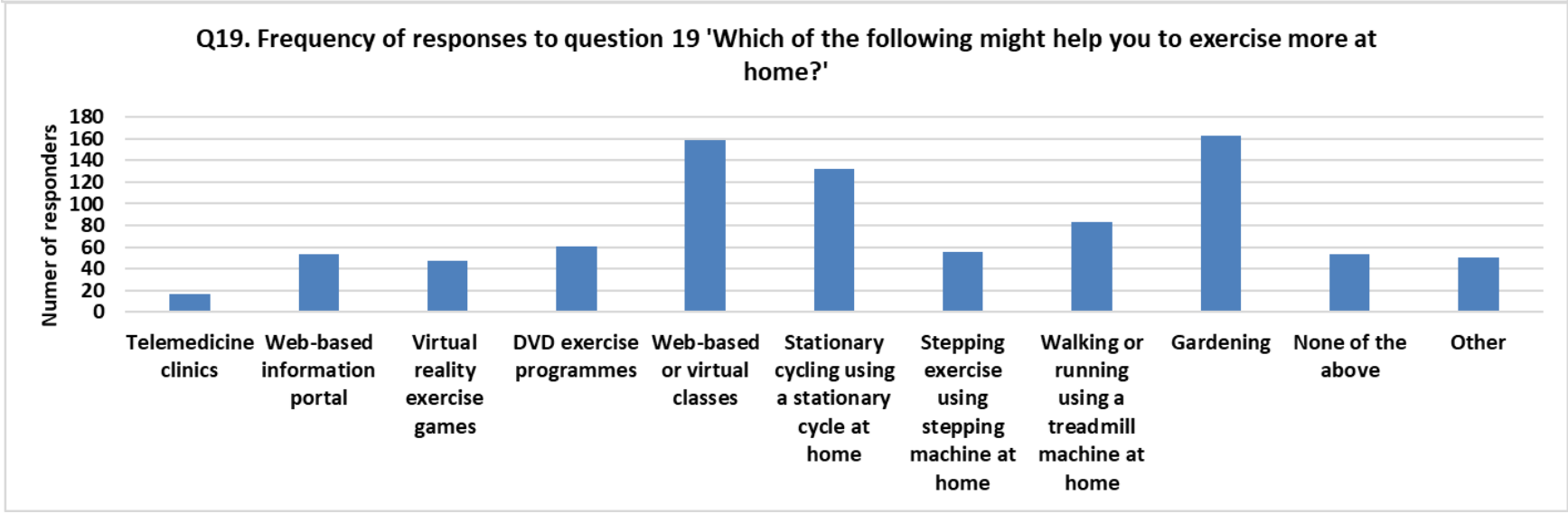


Figure 40: Answers for questions 18 and 19.

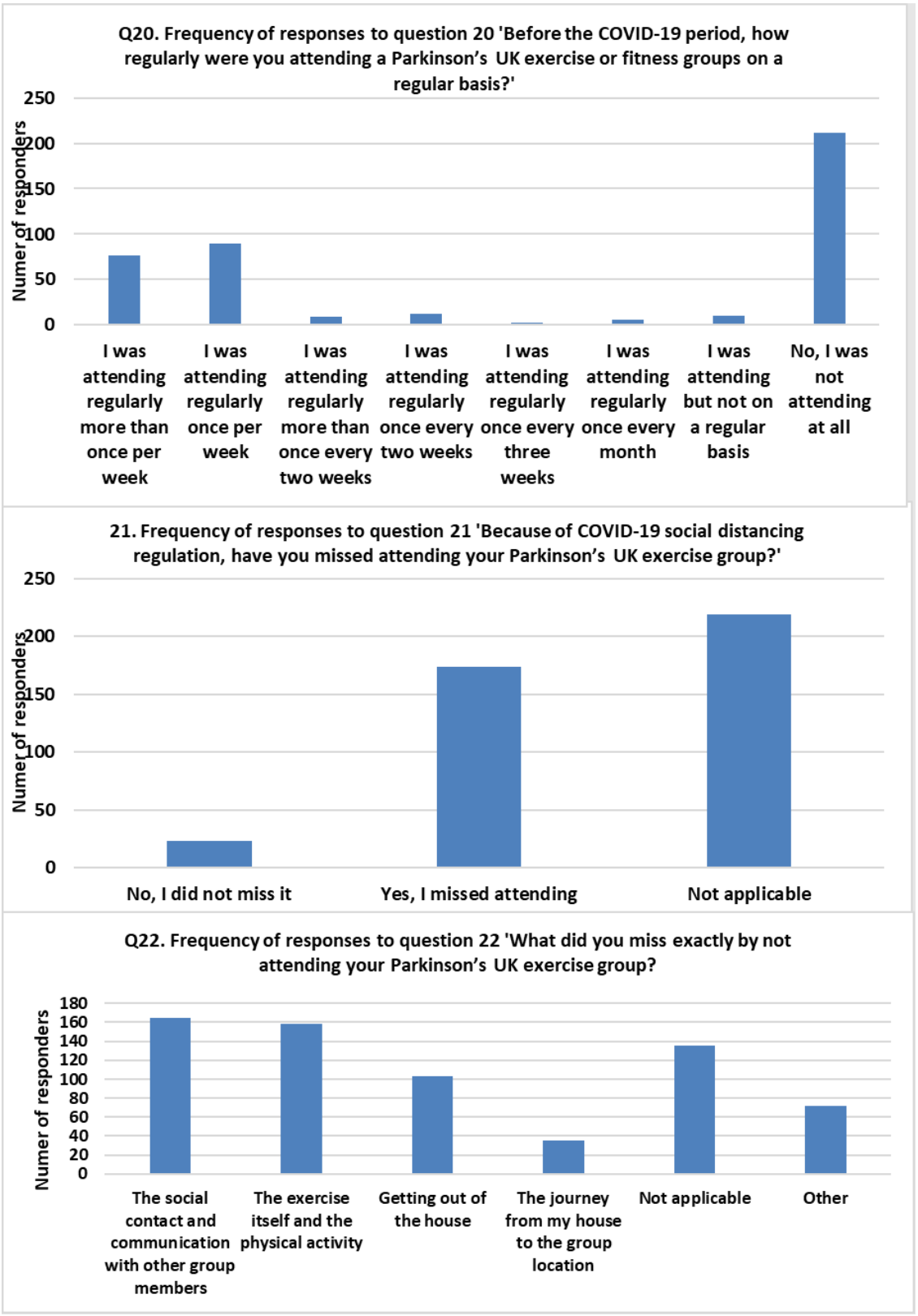


Figure 41: Answers to questions 20-22.

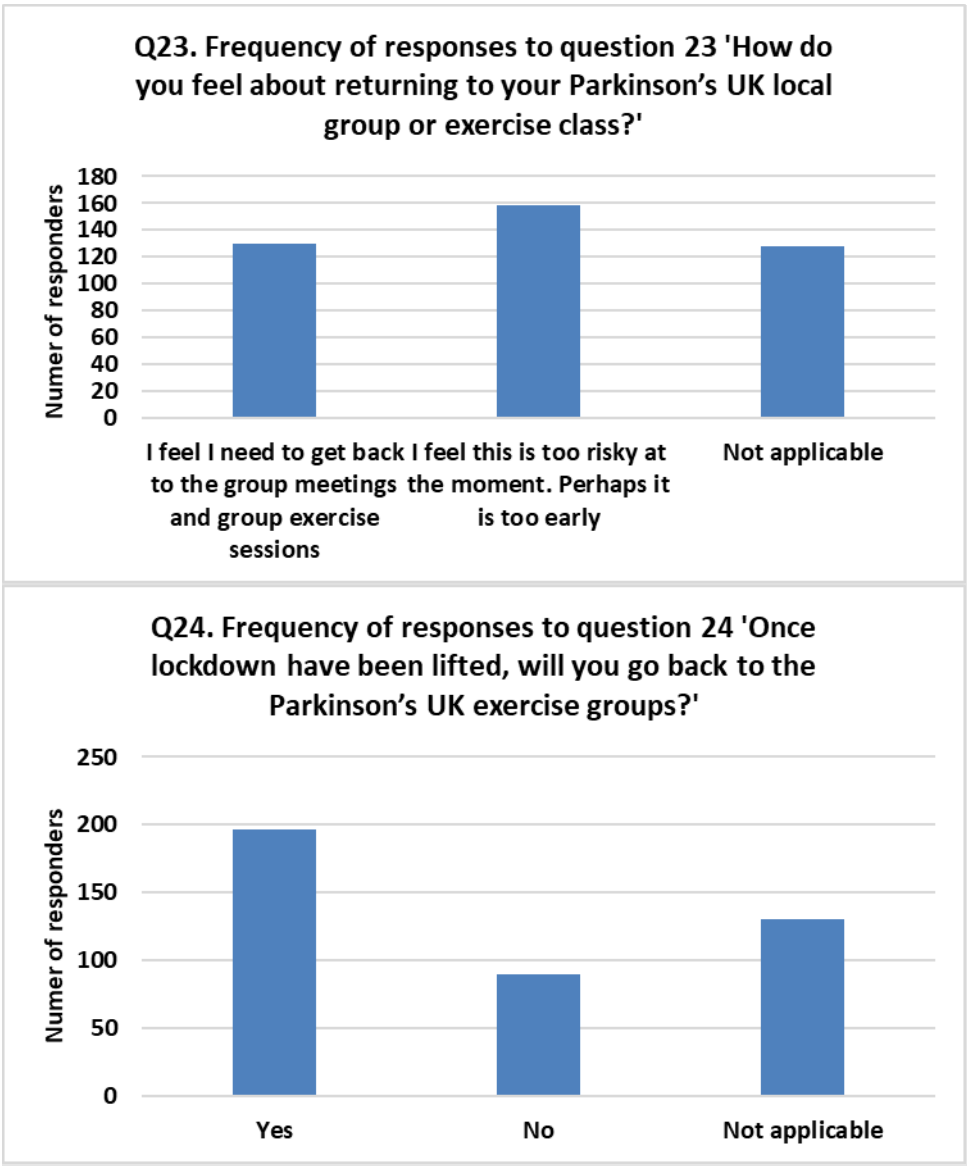


Figure 42: Answers to questions 23 and 24.

6.4.2.8. COVID-19 pandemic and Parkinson's symptoms

Bradykinesia, stiffness, tremor and fatigue were the symptoms that were most frequently reported to have worsened since the start of COVID-19 period (figure 43). One participant reported that worsening of symptoms is not always obvious, as it occurs slowly and perhaps without the person realising it is happening:

> *"I can't say that I've noticed any quantum worsening, but then it's an insidious enemy - it creeps up on you".*

6.4.2.9. Effects of the COVID-19 period and social distancing regulations on the lives of PLwP (question 26)

Three main themes (exercise, symptoms affected and social contact), and eleven subthemes arose from the thematic analysis. Table 26 represents the themes identified from the question 26 of the questionnaire.

Table 26: Topics and themes identified from Question 26 in the questionnaire.

Themes	**Sub-themes**
Exercise	Affected negatively (restricted exercise level). Exercise groups and sport centres. Factors that limited exercise participation. Affected positively (improved exercise level).
Symptoms affected	Worsening of mental, cognitive and physical symptoms
Social contact	Loss of social contact and isolation

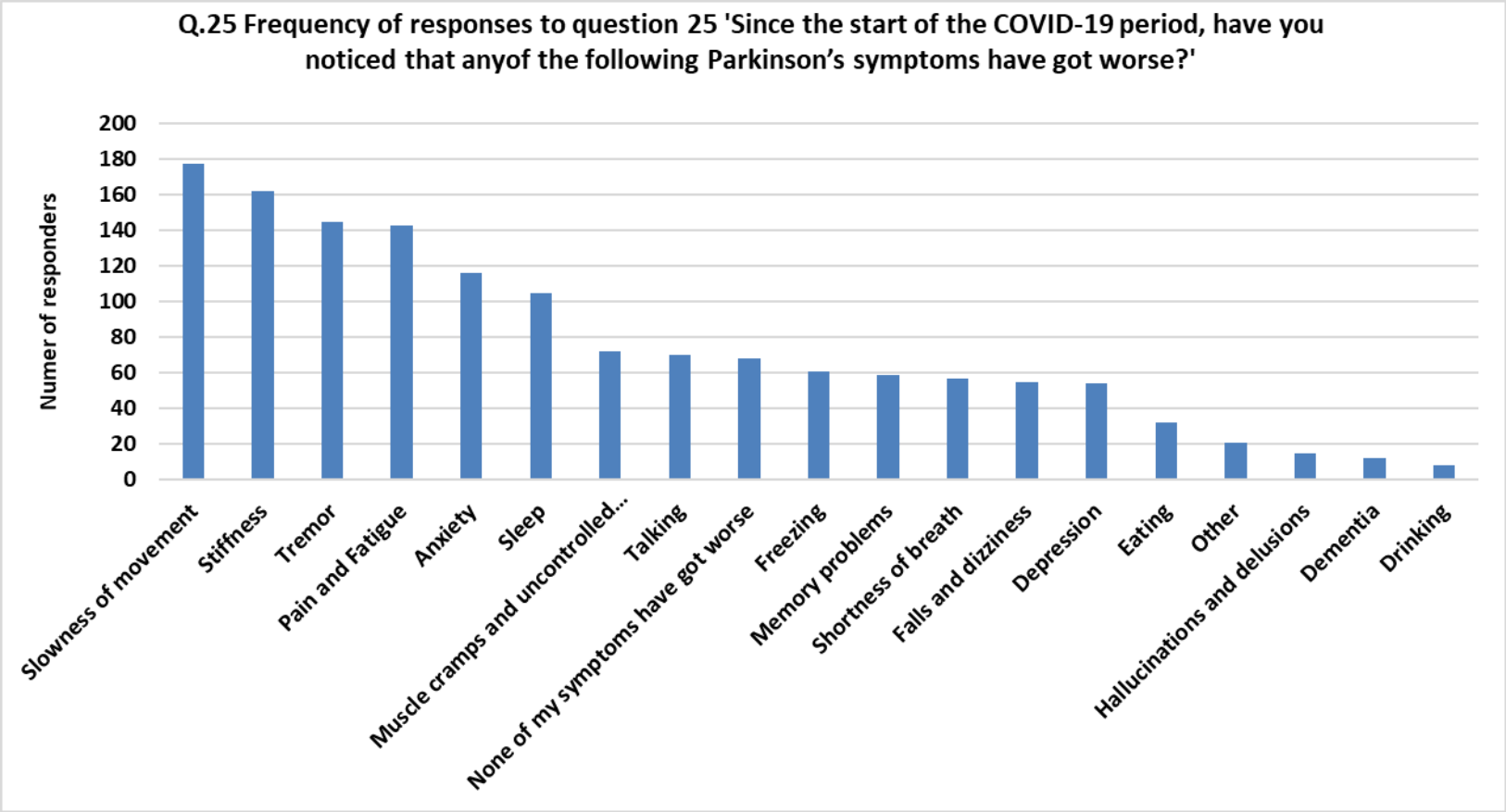


Figure 43: Answers to question 25.

6.4.2.9.1. Theme: Exercise

Sub-theme: Affected negatively (restricted exercise level)

In response to question 26, “If you would like to, please add any additional comments about how the COVID-19 period and social distancing regulations have affected your life”, comments highlighted that the types of exercise available and the restrictions on where people were allowed to exercise, due to the lockdown and social distancing regulations, was limiting their ability to undertake physical activity:

> “*The social distancing regs are restricting the range and location where exercise can be taken and being unable to exercise”.*

One comment suggested that this restriction on choice was affecting their mental health:

> *“The lack of freedom of choice to choose when you want to do any activity is very restrictive and can be depressing”.*

Sub-theme: Exercise groups and sport centres

Some reported that the closure of Parkinson’s UK exercise groups, fitness clubs and sport centres as the reason why they did not do exercise during the COVID-19 period:

> *“Closure of swimming pools for several months; closure of Parkrun on Saturday mornings; both of those reduced my exercise since March”*

“Reduced my attending my local sports centre for several months as it was closed my aerobics class cancelled. My yoga class closed and will not be restarting!”

“unable to attend the fortnightly Parkinson’s group meetings (they still have not restarted)”

Furthermore, some classes were just no longer available due to funding issues to charity centres for Parkinson’s during the pandemic, thus further limiting opportunities to continue to exercise during this period of time:

“*I cannot return to dance classes as funding has been withdrawn*”.

The benefits of group exercise and peer support were also highlighted in some comments as effects of the pandemic restrictions on the lives of PLwP:

“Exercising in a group is not only good physically but also gives great support for each other”,

“Prevented participation in regular club events i.e. group cycle rides, table tennis club events”

Sub-theme: Factors that limited exercise participation

The decreased physical activity and exercise level also was attributed to the lack of social contact with their peers, which they used to get while exercising in a group setting:

> *"I realise how important the ballet and exercise classes have become to me since losing them. Also now aware of importance of social contact of work, generally going out and even group therapy - Exercise *much* easier when done in a group"*.

Some comments included environmental factors that affected their exercise level. These included lack of space to exercise at home,

> "*I have a very small studio flat, so I cannot exercise at home, by Youtube, or Zoom*"

anxiety about becoming infected with COVID-19 when exercising outdoors where there are many other people,

> "*I have missed being able to go out walking as freely as I was used to. We usually walk along a canal towpath not far away (because it is flat) but it has not felt safe to do so - too many people*"

and lack of motivation:

> *"Also difficult to motivate to do exercise even though I know the importance of exercise"*

> *"am completely demotivated regarding exercise"*

“Very restrictive . Exercise almost stopped and difficult to motivate myself to do on my own”.

Exercising at the gym was another factor that responders highlighted as offering a structured routine and time that can be dedicated to exercise, providing equipment, instructors and motivation:

“*I find attending my normal gym gives me the discipline of having a set time to myself to exercise & my instructors enthusiasm and personal knowledge of my health and family circumstances keeps me motivated and addresses any issues that I have the social contact“*

The trend for on-line exercise classes during the pandemic lockdown, using Zoom for example, was beneficial for some, but there was still difficulty accessing the equipment that had been previously used use during these exercise classes:

“*Parkinson’s exercise class went on-line (Zoom) which has been very helpful but the equipment we used to use (rowing machine, punch ball etc) in the village hall was obviously unavailable*”

Sub-theme: Affected positively (improved exercise level)

On the other hand, some people were benefiting from time at home and increased their physical activity during lockdown period:

“*I got far more exercise during lockdown -- approx 25 miles on bike (nearly 3 hrs) per week*”

"*I have discovered "reach your peak online", with that 5 times a week plus lots of stretch routines they provide, plus cycling, badminton, online live Zumba, walking hillwalking basketball training, I have a lot to do".*

Mainly, online or virtual exercise classes were reported to be 'better than nothing', and featured in comments of those who reported to have increased their exercise level:

"*During lockdown, I got into the routine of starting the day with exercise: PD Warrior warm up and Joe Wicks for seniors on Youtube"*

"*I have added Pilates and Tai Chi to my exercise regime as they are taught by my PD Dance teacher through Zoom. I walk with a friend once*",

Online classes were also beneficial for some people who could not be included in exercise group before COVID-19 period due to location/travel issues:

"*Stopped live dance classes but enabled Zoom live PD warrior with Hallamshire Physiotherapy. I live near Hertford and searched in vain for three years for a local pd warrior class. Lockdown enabled me to join the Sheffield based Zoom classes which greatly benefited and improved my symptoms*"

"*I feel that the COVID crisis has actually meant that there are more opportunities to exercise from home and there is wonderful new market in*

terms of exercise opportunities. Apart from regular, brilliant PD Warrior classes run by some trainers in Bristol (I'm in London), I've participated in Yoga classes from Bridlington and weight bearing training from the States".

6.4.2.9.2. Theme: Symptoms affected

Sub-theme: Worsening of mental, cognitive and physical symptoms

Beside physical activity level and exercise, responders reported other effects of the COVID-19 period on their life, symptoms, and disease progression, such as:

- Anxiety, depression, fear and mental wellbeing:

  "*The threat of catching COVID-19 did, however, cause some anxiety*"

  "*I found it very distressing at times. Anxiety levels rose significantly*"

  "*The main impact has been my mental wellbeing*"

  "*Increased sense of isolation and loneliness from not being able to meet friends and family and other group participants in person*"

  "*My panic attacks have been worse*"

  "*Very anxious prescribed propananol. Low mood under more stress not sleeping*"

  "*Fear of contracting deadly virus meant less time spent outdoors*"

  "I am alive, but not living!".

- Fatigue and lack of energy:

  "I feel weaker with a lack of energy and fatigued. I sometimes feel a bit lethargic".

- Progression of the disease:

  “I found that my progression of Parkinson’s caused me to ask for an urgent appointment to start medication”,

  “my Parkinson's became much worse, very quickly. I was surprised at this as it is supposed to be a slowly progressing disease”.

- Back pain:

  “As I exercised less my walking became harder and my backaches became worse. A vicious circle!!”

- Stiffness and flexibility

  “Stiffness and flexibility affected”.

6.4.2.9.3. Theme: Social contact

Sub-theme: Loss of social contact and isolation

In addition to exercise limitation, social contact was affected, resulting in social isolation and loneliness in some cases, and this loss of social contact reported very frequently in the comments:

“I also have family abroad and can not see them due to risk and restrictions”

“*Increased sense of isolation and loneliness from not being able to meet friends and family and other group participants in person*”

“I miss not being able to hug my children and grandsons and other members of my family”

“*Serious illness of my sister which led to her death. Contact with her was affected both during her illness and at her subsequent funeral”*.

6.5. Discussion

This is the first study reporting how the COVID-19 pandemic affected exercise and physical activity in PLwP. During the COVID-19 outbreak, the proportion of responders who decreased their duration of intensity of exercise or did not exercise at all increased, and the proportion of responders continuing exercise at sports facilities decreased. This survey on PLwP showed that the COVID-19 outbreak, and its subsequent restrictions, had a significant impact on the lives of PLwP in general, including social, physical and mental effects. Furthermore, this survey helps to complement findings of the feasibility study (EXoCARP), in terms of the intervention design; including interventions in a larger clinical trial in the future that could not be affected by further outbreaks of COVID-19 and the resultant restrictions on activity, or by other crises or pandemics, is important.

Exercise was affected mainly during the COVID-19 period with the government’s instructions “Stay at home”. This could be explained by answers of 343 people (82% of the sample) who reported outdoor walking as the main aerobic exercise that they were performing before the pandemic. Subsequently, because the instruction was to 'Stay at home', people who were previously walking outdoors, cycling outdoor or doing any form of outdoor exercise stopped doing so.

Additionally, comments about the closure of sport/fitness clubs, and exercise groups might be another reason for the decrease or restriction of their physical activity levels. This was also confirmed by comments about lack of freedom to choose the exercise mode, location, space and time. As has been noted previously in the literature, freedom to choose the preferred type of exercise is a major factor that affects adherence and compliance to physical activity and physiotherapy programmes (Iso-Ahola, 2009). Subsequently, this factor was hugely affected by the restrictions during the pandemic.

The sample that participated in the study revealed that most of them were familiar with the physical activity recommendations for PLwP to perform 150 minutes of exercise, with a median of 203 minutes per week reported. This indicates a good level of awareness and health education about the importance of exercise for this population. However, 135 responders (32%) did not know about the recommendations and were not familiar with the physical activity guidelines. Subsequently, further education from clinicians and Parkinson's organisations needs to be disseminated as much as possible, to promote physical activity and exercise to PLwP.

People who performed exercise during the pandemic reported that they have engaged most frequently with web-based and virtual exercise classes as their indoor activity during the pandemic. In the comments of the last question of the questionnaire (question 26), people reported many websites and online groups (anonymised here) with which they have engaged, as well as television programmes.

When asked about their preference for exercise that could be conducted at home, respondents reported gardening and web-based exercise as number one, followed

by stationary cycling and treadmill walking and DVD exercises. These preferences are important and should be considered for future exercise trials, self-management programmes, and physiotherapy management for PLwP, to enhance opportunity for exercise and adherence to any trial intervention protocols. It is highly recommended that future research considers self-managed and minimally-supervised exercise programmes for PLwP, to encourage sustainability and continuation of the exercise programme beyond the trial (Estabrooks et al., 2011). This is particularly important for the implementation of findings where the trial exercise programme is found to be effective. However, the benefits of developing exercise habits are well-documented, and any such behaviour change that can be sustained and reflects the recommended guidance for exercise frequency and intensity is likely to be of benefit to PLwP (Estabrooks et al., 2011). Furthermore, with many hospitals and outpatient centres limiting their face-to-face sessions, sustainable solutions and platforms for interventions to shift the current model of care for physiotherapy programmes for this population are needed, to overcome any pandemics or future circumstances. However, few points for these solutions need to be taken into consideration while planning for these types of interventions in future trials, including access to internet/telehealth, training for both patients and physiotherapists, and safety measures for minimally supervised or unsupervised exercise sessions.

Recent studies are implementing new minimally supervised interventions to increase physical activity and exercise levels in older adults such as using virtual reality avatars to enhance exercise (Horne et al., 2020), video games including Wii and Xbox (Carrasco et al., 2020), and peer-support online physical activity groups (Crozier et al., 2020). These interventions are needed in such circumstances, and results of the survey support the urge of developing such interventions for PLwP.

This survey revealed many comments about the issue of social contact and how the COVID-19 pandemic affected responders' social life with their families, friends, and other PLwP. This also was reported by several comments about depression and loss of confidence due to the decrease in social contact with other people. Some comments indicated great sadness and feelings of depression, and some indicated how PLwP feel lonely and isolated while in home. Additionally, anxiety and mental health disorders might be hugely affected, according to the questionnaire results. These results are consistent with studies that assessed mental and sleep health during the pandemic (Helmich and Bloem, 2020). Perhaps physical inactivity during the pandemic contributed to worsening in these symptoms, because it was reported previously that exercise helps to reduce anxiety, depression, cognitive impairment and improve sleep quality in PLwP (Amara and Memon, 2018; Memarian et al., 2017; Wassom et al., 2015).

It was reported previously, long before the pandemic, that PLwP suffer from isolation and decrease in their social activity and quality of life (Forsaa et al., 2008; Karlsen et al., 2000). The social isolation was attributed to the feeling of shame about their speech impairments, slowness of movement, freezing of gait, tremor or the lack of facial expressions that is covered by the Parkinson's Mask Face life (Forsaa et al., 2008; Karlsen et al., 2000). While in the coronavirus months, the self-isolation, shielding at home or social distancing regulations imposed further loneliness and social effects on top of their pre-COVID-19 isolation. With the uncertainty brought about by the current pandemic, it is advantageous to start thinking about altering the current model of care for psychological health and mental health for PLwP.

Furthermore, most PLwP who were attending Parkinson's UK exercise groups (77%) reported that they missed attending the groups; specifically, they indicated

that they were missing the social contact and the exercise classes. This finding indicates the importance of Parkinson's UK peer support group for PLwP. These groups usually offer social support and physical exercise that is usually conducted by an exercise specialist or a physiotherapist. However, around half of those thought it too risky to return to the groups now, whilst the other half thought that they did need to return to the groups. The threat of potential closure of Parkinson's UK groups, making them no longer available to PLwP, due to lack of funding (through non-attendance), would limit the opportunity for peer support, social contact, and regular exercise developed specifically for PLwP.

While the main focus of this survey was about exercise and physical activity during the pandemic, rather than mental health, understanding mental and social effects of the pandemic could help to improve exercise duration or intensity for this population. For example, trials that used group-exercise interventions reported higher exercise engagement and adherence than self-exercise trials (Hackney et al., 2007; Mitchell et al., 1987). These results are important in terms of building future studies. For example, a virtual online group exercise trial, with a space for social contact, might be a suggestion for consideration.

Bradykinesia, stiffness, tremor and fatigue were at the top of the list of symptoms that were reported as having worsened since the start of the COVID-19 period. The progression of these symptoms was previously reported to be less in people who perform aerobic exercise and physical activity interventions (Dashtipour et al., 2015; dos Santos Delabary et al., 2018; Fox et al., 2018; Schmitz-Hübsch et al., 2006). Subsequently, these results support the importance of our recommendations to start remote exercise trials to reduce symptoms, improve quality of life and continue care-management while in confined environments or restricted circumstances.

Strengths and limitations

This is the first study to report how the COVID-19 pandemic affected exercise and physical activity in PLwP. Additionally, this study has provided knowledge about exercise preferences in PLwP in terms of indoor exercises. Findings of this study are important while planning for future research that include exercise in PLwP.

This study is not without any limitations. The study could not address the non-response bias in full. The survey was sent to participants by email. The disadvantage of using emails includes: the potential for participants not to open the email; the potential for the email to be received into another folder other than the main inbox (for example, junk folders, advertisements and spams); people might not have internet connection or internet connection might be disrupted during the time period set aside for completion of the online survey; some participants might have changed their email address and not informed Parkinson's UK, who sent the questionnaire to those on their email list; or some participants might have difficulties completing the whole survey online, maybe due to cognitive or visual reasons, or maybe due to lack of technological skills. These factors might have limited recruitment, response rate, and data collection. Not requesting ethnicity from the participants was a limitation as there might be important differences between ethnic groups in terms of their usual physical activity levels and their preference for exercise (e.g. DVD, groups, at home or at Parkinson's UK groups) and this should be considered in future surveys.

Summary

This survey questionnaire revealed a decrease in physical activity in PLwP while in the COVID-19 pandemic. This might be due to the restricted freedom to choose exercise mode and type, or due to the closure of Parkinson's UK exercise groups or

sport clubs and facilities. Additionally, the survey showed that the social aspect of exercise was hugely affected, and people were missing the social contact mostly in exercise groups.

Furthermore, the survey summarizes that people prefer online virtual exercise classes, stationary cycling and treadmill running, and DVD exercises as remote/indoor exercise methods, and think they might help them during the pandemic.

Accordingly, the results of this survey indicate the importance of designing remote or minimally supervised exercise trial interventions, taking into consideration people's preferences regarding mode of exercise, and social contact. This finding complements the findings of the mixed-methods feasibility study (EXoCARP), highlighting that an exercise intervention for a future clinical trial needs to be designed so that it is feasible to conduct should such restricted circumstances arise again.

Chapter 7: Reflexivity

Reflexivity is often regarded as a crucial element within qualitative research (Clissett, 2008). This is mainly because qualitative researchers do not regard themselves as objective observers, but as participants in a dynamic relationship with their research (Colaizzi, 1978; Ryan and Golden, 2006). Thus, reflexivity could be one of the methods to increase the credibility of qualitative research to enhance quality and to increase the transparency of the researcher's position (Patton, 2002; Walker et al., 2013). Additionally, the researcher's personal and professional factors might affect the results, and it is recommended that these factors are reported in qualitative research (Mannix et al., 2015). For example, the researchers' gender, age, and experience (including clinical experience) might affect the interpretation and analysis of the qualitative data. Thus, this section will include my own reflections on aspects of the research, including PPIE meetings and group visits, focus groups, COVID-19 pandemic restrictions, and recruitment through Parkinson's UK.

7.1. PPIE meetings and group visits' reflections and observations

In this PhD, I spent time facilitating the PPIE meetings (three groups) and visiting Parkinson's UK local groups (four groups) for recruitment. These visits improved my confidence towards the research idea and methodology. PPIE meetings were very helpful in confirming the choice of method of assessment regarding using the cycle rather than the treadmill for the CPET, and shaped our methodology by group members reporting claustrophobia and being uncomfortable to exercise while wearing a mask. The PPIE meetings gave me confidence about the project idea and methods before submitting the ethical committee application, and before starting data collection.

During Parkinson's UK local groups visits, we were sometimes invited to attend their own exercise sessions before presenting our research project for recruitment. Thus, I had the opportunity to observe two exercise sessions and to reflect on them. I noticed that the physiotherapists who ran both sessions played an important role in motivating group members to exercise, understand what is helpful and what is needed for the members, and understanding the meaning of aerobic exercise. I observed that one physiotherapist acted as an assertive person for her group members, choosing motivational music from previous decades while running aerobic exercise, and showing an understanding of different disease severity levels by choosing an alternative for each movement for those who were unable to do it. In contrast, the other physiotherapist was asking PLwP to perform flexibility exercises, but calling the session an "aerobic exercise session", and without considering different disease severity levels. There is no guidance about not performing flexibility exercise for PLwP. However, flexibility exercises are prescribed to reduce rigidity, stiffness and kyphoscoliosis, and to improve gait in PLwP (Gobbi et al., 2009; Reuter et al., 2011; Schenkman et al., 1998). There is no literature to support the use of flexibility exercises as an alternative to aerobic exercise for PLwP. Although there is no specific guidance in the literature about a specific exercise limit for PLwP as a "threshold" to hit aerobic exercise and not to stay in the "comfort zone", but through the observations of that visit (the second visit) and through my previous experience, I felt that PLwP with different disease severity might have different "aerobic thresholds". This observation led me to think about future research about aerobic thresholds in different disease severities in PLwP. Also, while thinking about the two sessions, I would support the use of an assessment tool (for example: Borg RPE scale or heart rate monitors) to make sure that PLwP are exercising at the required level of intensity and hitting their aerobic threshold individually.

7.2. Focus groups reflection

As a PhD student and a researcher, this was the first time I have conducted exploratory research collecting and analysing qualitative data, since all my previous research studies involved the collection and analysis of only quantitative data. When I first sent the proposal of EXoCARP trial and discussed it with my supervisor, the supervisor suggested adding the focus group. I did not feel confident that time, and I was trying to avoid adding the qualitative part to my PhD. I did not realise the importance of qualitative research on that day, until I read more about mixed methods trials. When I conducted the first focus group, I realised how qualitative data could add value to the trial, and how participants' opinions could be important when planning for the future trial. Subsequently, I became "in love" with qualitative studies, and I think using it in my future work will lead me to learn more and to get more knowledge needed in the studies.

Thus, I have considered the first focus group to be a trial for myself, to reflect and to be well-equipped for the following focus groups and any following qualitative research. Additionally, the PhD supervisor guided me to register in a workshop entitled "Running a Focus Group" at Keele University, beside the regular supervisory meetings and advice on running focus groups. The workshop was good for beginners to understand how to run focus groups, how to manage discussions while running the interviews, how to get the most out of participants in interviews, and how to perform a simple thematic analysis. I have learnt from it how to transcribe a record, identify codes and themes for qualitative data.

An important dimension in reflexivity for this study was my professional background as a physiotherapist and as a researcher of neurodegenerative diseases (Parkinson's and Multiple Sclerosis), which could influence data collection and analysis (Finlay and Ballinger, 2006). My interest in this area of research stemmed

from my research background working with PLwP, in addition to lecturing on both cardiopulmonary and neurological rehabilitation. This might have influenced the focus group questions and my unconscious perception of the anticipated answers. For example, I was anticipating that participants would mention balance impairment, vision impairment, fatigue, shortness of breath, freezing of gait, and rigidity as answers to the question about barriers that limited participants to exercise.

However, I did not anticipate an answer such as “time” as a barrier for them to do exercise, taking into consideration that most of them were retired. Anticipating the answers might have affected data collection in the first focus group. This is because I was waiting to hear these specific answers and might not have dug deep enough in relation to other factors. While asking the questions, I may have subconsciously asked them if there were any other factors and moved on to the next question without investigating or asking participants to expand their responses in more detail. Moreover, I was trying to avoid the use of any professional jargon, or words that participants may not understand, and focused on using lay language instead. This put an extra effort on myself as an international student whose first language is not English. Additionally, if participants had speech problems, it required an extra effort for me during the focus groups and again while transcribing the audio records. Speech disorders that some participants had was one of the issues that I need to reflect on. For some sentences, I was asking the same participant to repeat the sentence (two times), after which I avoided asking for it to be to repeated again. I felt that asking the participant to repeat too many times might embarrass the participant and might lead the participant to avoid discussing with the group.

7.3. COVID-19 pandemic restrictions: concerns from a PhD student point of view

The pandemic governmental regulations affected higher education in different degrees (diplomas, bachelor's, master's or PhD). However, undergraduates were lucky to have alternatives and solutions to minimise any changes in their studies. Master's degree students as well had opportunities to adapt their studies according to the governmental regulations during the pandemic. However, PhD students, specifically those with face-to-face data collection projects, were very limited in terms of alternatives and had to wait for months hoping that this crisis would end! From a PhD student view, I was very concerned and stressed about Study – 1 (EXoCARP) data collection in the first two months of the pandemic. I was afraid that the data that was collected would not be enough, or the results might not be publishable! However, after thinking about physical activity of PLwP during the pandemic, I started discussing my supervisor about Study 2 to understand if there is a pandemic inside the pandemic, that is physical inactivity! Subsequently, my concerns were relieved after developing the online survey and I was happy with the fast data-collection of it.

7.4. Ethnic diversity

One of the issues that I could not achieve through EXoCARP was to collect data for people from diverse ethnicities. When the recruitment invitation was sent to members of Parkinson's UK, it was not limited to only Caucasians, but those who responded were only Caucasian. This led me to think about the importance of translating the advertisements of my future studies to more than one language. Perhaps the translation of the advertisement might attract other ethnicities. I have worked as a physiotherapy lecturer and clinical tutor in Jordan and in United Arab Emirates (both countries are in the Middle East), and from my experience, majority of the people from the Middle East do not consider exercise as an important need

that need to be conducted regularly. Perhaps cultural perception of exercise is different from a region to another. Furthermore, I have noticed that females in the Middle East might be much more sedentary than females in the UK. Even myself, as a Jordanian woman, I consider myself as a “sedentary” person, as I do not do exercise regularly. I believe this matter is related to how exercise is introduced and included in people’s lives since childhood.

7.5. Recruitment through Parkinson’s UK

Recruitment of participants in both Study 1 and Study 2 was conducted by using Parkinson’s UK email groups. I would reflect how happy I was about the prompt response a researcher could get from Parkinson’s UK research team, and how cooperative they were in circulating, and recirculating the invitation letters in both studies. I would say: recruitment through Parkinson’s UK made my life easier through both studies! I Tweeted this reflection on my Twitter profile to help other researchers by using Parkinson’s UK research help in data collection.

7.5. Summary

In summary, I would recommend running PPIE meetings while planning for future studies, to ensure the interests of people, and to gain knowledge about people’s views to confirm the choice of methods to be used in future studies. Additionally, observing exercise/ interventions sessions of people before running trials might give the researcher ideas about the importance of managing the intervention to get the best outcomes. Moreover, qualitative data adds value to quantitative data to give a more comprehensive picture, and subsequently, pragmatism is recommended for my future work.

Chapter 8: General discussion

This thesis studied the feasibility of conducting a trial about aerobic exercise intervention and cardiopulmonary function in PLwP. The thesis included: an introduction about Parkinson's, its symptoms, and a brief introduction about pulmonary impairment (Chapter 1); reviews about pulmonary function and cardiopulmonary fitness in Parkinson's and a systematic review of the effects of aerobic exercise on cardiopulmonary function in Parkinson's (Chapter 2). Chapters 3—5 reported the methodology, method, findings and discussion of Study 1, the EXoCARP trial; and Chapter 6 reported, in full, study 2, an online questionnaire study. A personal reflection about the PPIE meetings, focus groups and qualitative research (Chapter 7). This final Chapter 8, offers a discussion about the work presented in the whole thesis, and recommendations for future research and clinical practice.

The two reviews (Chapter 2) showed variations in evidence about cardiopulmonary impairment in the early stages of Parkinson's. Both reviews have shown that only a small number of studies have investigated impaired pulmonary function and cardiac fitness in the early stages of Parkinson's. The first review revealed that pulmonary function might worsen with the progression of Parkinson's. Findings of the first review could be explained by an increase in rigidity of chest wall muscles with progression of Parkinson's, which may result in kyphoscoliosis (Baille et al., 2016; Santos et al., 2019); this may, in turn, lead to decrease in lung volume (Black and Hyatt, 1971; Sabaté et al., 1996), decrease in lung elasticity, stretching and recoiling ability (Estenne et al., 1984). EXoCARP (Study 1) included assessment of pulmonary function and revealed that PLwP have obstructive, restrictive, mixed or normal pulmonary patterns at the early stages of Parkinson's. Thus, it is recommended that NHS needs to conduct spirometry as a routine test for PLwP at

different stages of Parkinson's to avoid any complication out of respiratory impairments.

The second review in this thesis showed that studies that assessed cardiovascular response to exercise in Parkinson's have reported contradictory results, with some reporting lower and insufficient cardiovascular response to exercise and some reporting normal profiles. These variations in findings might be attributed to the sample size, gender differences or CPET protocols used in the studies. Therefore, there was a need to assess cardiovascular response to exercise in EXoCARP to establish the feasibility of conducting the test before moving to the next trial. In addition, there is a need to investigate rehabilitation programs that could improve cardiovascular response to exercise in Parkinson's.

The third review revealed positive effects of aerobic exercise on cardiopulmonary function in Parkinson's. The review showed that the studies used similar intensities and frequencies recommended by the World Health Organization (WHO) (30–45 minutes of moderate intensity, three times per week) (World Health Organization, 2020). However, the review revealed that no studies were conducted to assess the effects of aerobic exercise on pulmonary function in Parkinson's. Taking into consideration that respiratory impairments are the main cause of mortality and morbidity in the advanced stages (stages IV and V in Hoehn and Yahr) of Parkinson's, it is important to find an intervention that improves pulmonary function in the early stages, rather than waiting for the progression of the disease and progression of the impairment. Thus, it was crucial to assess the effects of aerobic exercise on pulmonary function in the early stages of Parkinson's. However, before conducting a large trial, a feasibility trial was needed to assess the practicalities of conducting the assessment tests, the intervention and study design. Subsequently, Study 1 (the EXoCARP) was conducted.

The primary purpose of the EXoCARP trial was to pilot and establish feasibility of recruitment to, and delivery of, a clinical trial of an eight-week community-based and patient-led aerobic exercise programme compared with usual care to improve pulmonary function and cardiovascular response to exercise in PLwP. The EXoCARP trial was a mixed methods pilot and feasibility study of an aerobic exercise programme compared with usual care, involving focus group interviews to explore acceptability and feasibility of the exercise intervention and the outcome measures. However, while conducting the trial, COVID-19 pandemic governmental regulations in 2020 led to suspension of the trial and any face-to-face data collection, to minimise the infection rate of the virus. Subsequently, recruitment to the trial was affected by the pandemic. Although EXoCARP data collection was affected by the pandemic, recruitment rate was 80% out of the accepted sample size for pilot studies (24 out of 30) (Lancaster et al., 2004). Compared with 45% (Shanahan et al., 2017), and 11% (Lima and Rodrigues-de-Paula, 2013) in other feasibility trials that included exercise in PLwP. The trial results revealed the need for multiple recruitment sites to collect data and boost the recruitment, and to re-wording the invitation letter to attract more people.

Assessment tools used in EXoCARP were found to be easy and effective, but there is a need to exclude undiagnosed high blood pressure to avoid any adverse events while conducting the CPET in the future study. The aerobic exercise intervention used in EXoCARP was found to be feasible and acceptable to the participants, and this was confirmed with the activity monitors results (participants in the exercise group conducted the required duration and intensity of exercise as asked to do (median (IQR) = 37.2 (27.1, 45.4) minutes of MVPA per day). However, participants asked for an individualised prescription of intensity of exercise. Prescribing intensity based on HR baseline CPET results, and using HR monitors to assure that

participants are doing the correct intensity might be helpful in the following trial. Although participants in both groups reported doing 21-30 minutes of exercise, these minutes were light physical activity not MVPA. This might suggest the need of monitoring intensity in clinical practice for PLwP, not only in research. This study suggests using the same intensity and duration in the next trial (30-40 minutes for 2-5 times per week) similar to previous studies (Burini et al., 2006; Fernández-del-Olmo et al., 2014; Mavrommati et al., 2017; Ridgel et al., 2016; Schenkman et al., 2012; Shulman et al., 2013). Using a community-based exercise intervention could help in terms of sustainability of the intervention rather than clinical-based exercise settings (Estabrooks et al., 2011).

The outcome measures used in the trial were found to be acceptable to participants and feasible to be used in the next trial. However, a maximal CPET with the presence of a cardiologist might be needed to challenge the cardiopulmonary fitness in PLwP in the next trial. Also, PLwP might prefer to use tablets / IPADs to fill the questionnaires in the next trial, rather than hand writing due to tremor and bradykinesia.

The suspension of the EXoCARP trial during the pandemic led to limitations in recruitment, and inability of the participants to continue with their intervention during the COVID-19 pandemic. Therefore, there was a need to assess how the pandemic affected engaging in physical activity for PLwP, and other questions arose about exercise undertaken by PLwP during the pandemic. This led to Study 2 of this thesis (Chapter 6), an online survey questionnaire that explored physical activity during the pandemic, exercise limitations and people's preference in term of indoor exercises. Study 2 revealed that PLwP had a decrease in physical activity while in the COVID-19 pandemic. This might be due to the restricted freedom to choose exercise type, and/ or due to the closure of Parkinson's UK exercise groups or sport

clubs. Moreover, the survey results showed that people prefer online virtual exercise classes, stationary cycling and treadmill running, and DVD exercises as remote/indoor exercise methods and think they might help them during the pandemic.

Recommendations for future research

Overall, the work reported in this thesis recommends that future clinical trials need to include an aerobic exercise intervention that meets the preferences of PLwP, that is flexible to accommodate any sudden changes in circumstances, such as pandemics and restrictions on social contact and outdoor activity, by including indoor exercises (for example: internet-based exercises and DVDs). The thesis recommends using community-based aerobic exercise 30 minutes per day for 3-5 days per week on a moderate to vigorous intensity. Monitoring intensity is recommended by giving participants HR monitors to assure exercising at the required intensity. Additionally, the thesis results recommend using the same assessment tools, but to exclude undiagnosed high blood pressure. Moreover, using the same outcome measures in the next trial is recommended but with a maximal intensity in CPET, and tablets / iPad for questionnaires filling (Section 5.3 includes a summary for the recommendations using the traffic light system).

Clinical recommendation

Results of the thesis suggests the need for a routine assessment of pulmonary function in the early stages of Parkinson's. Additionally, we recommend including people's preference in term of exercise in their usual physiotherapy/exercise interventions, as an alternative plan to any unexpected circumstances such as pandemics.

Planned publications out of the thesis

The following manuscripts are planned to be published:

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. Cardiopulmonary response to exercise in early staged of Parkinson's. To be published in the Movement Disorders Clinical Practice.

Aburub, A., Sim, J., & Hunter, S. M. A pandemic within the pandemic! Physical activity challenges in Parkinson's during COVID-19 ages: an online survey study. To be published in the Movement Disorders Clinical Practice.

Aburub, A., Ledger, S. J., Sim, J., & Hunter, S. M. Aerobic exercise and cardiopulmonary function in early stages of Parkinson's: a feasibility trial. To be published in the Movement Disorders Clinical Practice.

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Appendices:

Appendix 1 (PEDro scale)

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999

Notes on administration of the PEDro scale:

All criteria	**Points are only awarded when a criterion is clearly satisfied**. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.
Criterion 1	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.
Criterion 2	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	*Concealed allocation* means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".
Criterion 4	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.
Criteria 4, 7-11	*Key outcomes* are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 5-7	*Blinding* means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 8	This criterion is only satisfied if the report explicitly states *both* the number of subjects initially allocated to groups *and* the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 9	An *intention to treat* analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 10	A *between-group* statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.
Criterion 11	A *point measure* is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. *Measures of variability* include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.

Appendix 2 (Ethical approval letter)

7 March 2019

Dear Aseel,

Project Title:	Aerobic exercise to improve cardiopulmonary function in people with Parkinson's: a mixed method pilot study
REC Project Reference:	MH-180006
Type of Application	Main application
Amendment Reference:	MHFI-0003
Amendment Date:	13 February 2019

Keele University's Faculty of Medicine and Health Sciences Research Ethics Committee (FMHS FREC) reviewed the above application and amendment.

Favourable Ethical opinion
The members of the Committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation. There are no conditions attached to this favourable opinion.

Reporting requirements
The University's standard operating procedures give detailed guidance on reporting requirements for studies with a favourable opinion including:

- Notifying substantial amendments
- Notifying issues which may have an impact upon ethical opinion of the study
- Progress reports
- Notifying the end of the study

Approved documents: The documents reviewed and approved are:

Document	Version	Date
All documents submitted with MH-180006 & MHFI-0003		

Yours sincerely,

Appendix 3 (Approval letter for the ethical ammendment)

24 April 2019

Dear Aseel,

Project Title:	Aerobic exercise to improve cardiopulmonary function in people with Parkinson's: a mixed method pilot study.
REC Project Reference:	MH-180006
Type of Application	Amendment - MH-190023
Amendment Date:	18 April 2019

Keele University's Faculty of Medicine and Health Sciences Research Ethics Committee (FMHS FREC) reviewed the above amendment.

Favourable Ethical opinion
The members of the Committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation. There are no conditions to this opinion.

Reporting requirements
The University's standard operating procedures give detailed guidance on reporting requirements for studies with a favourable opinion including:

- Notifying substantial amendments
- Notifying issues which may have an impact upon ethical opinion of the study
- Progress reports
- Notifying the end of the study.

Approved documents
The documents reviewed and approved are:

Document	Version	Date
Amended Protocol	0.3	18.04.2019

Yours sincerely,

Dr Ed Chadwick
Committee Chair

Keele University

Appendix 4 (consent form)

CONSENT FORM

Title of Project: The effects of aerobic exercise on cardiopulmonary function in people with Parkinson's disease.

Name and contact details of Principal Investigator:

Aseel Aburub

School of Health and Rehabilitation Sciences, Keele University, Staffordshire, United Kingdom 01782733809

a.a.m.aburub@keele.ac.uk

Please initial box if you

agree with the statement

1. I confirm that I have read and understood the information sheet dated …… (version no …….) for the above study and have had the opportunity to ask questions ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time ☐

3. I agree to take part in this study. ☐

4. I agree to allow the dataset collected to be used for future research projects ☐

5. I agree to be contacted about possible participation in future research project ☐

Name of participant	Date	Signature
Researcher	Date	Signature

CONSENT FORM

(for use of quotations)

Title of Project: The effects of aerobic exercise on cardiopulmonary function in people with Parkinson's disease.

Name and contact details of Principal Investigator:

Aseel Aburub

School of Health and Rehabilitation Sciences, Keele University, Staffordshire, United Kingdom 01782733809

a.a.m.aburub@keele.ac.uk

Please initial box if you

agree with the statement

1. I agree for my quotations to be used ☐

2. I do not agree for my quotations to be used ☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 5 (UK Brain Bank Criteria)

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

****From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.***

Appendix 6 (Hoehn and Yahr Scale)

The FIVE Stages of Parkinson's Disease

Dr. Margaret M. Hoehn, the author of the most frequently cited paper in professional articles dealing with Parkinson's disease discusses the Hoehn and Yahr Scale used throughout the world to classify patients participating in research studies. She has deliberately used the word "Parkinson's" since the term applies to all forms of the disorder including Parkinson's disease.

The method of designating the severity of Parkinsonism by what is now known as the Hoehn and Yahr Scale was published in 1967. The original definition (underlined) of the FIVE stages of severity is as follows:

Stage I:
Unilateral involvement only, usually with minimal or no functional impairment.

The patient has tremor, rigidity, slowness and paucity of movement, or poor condition in the arm and/or legs on one side of the body. Occasionally one side of the face is involved, producing an asymmetry of expression that may look very like the effects of a mild stroke or Bell's palsy. This stage of Parkinson's is often missed entirely. For example when the diagnosis is made at a more advanced Stage, the patient may remember having noticed an intermittent tremor of one hand many years before. Old home movies may show that the patient didn't swing one arm as much as the other did while walking. One hand or foot may have been clumsier than the other may have. Often these symptoms are so mild that no formal medical attention is sought. If sought it is not uncommon that the physician is unable to make a diagnosis, either by the most assiduous and astute physical examination or by the most advanced technology. Sometimes the disease must evolve over many years before a diagnosis can be made with certainty.

"Usually" was inserted into the original definition to modify "minimal" or no functional impairment: because, very rarely, a patient presents with very severe and disabling unilateral symptoms: extreme and violent tremor or rigidity and akinesia in one limb so severe that the limb is virtually paralyzed. Most doctors worry about a stroke or tumor – which they should. When all necessary tests show nothing, one must wait and observe. Eventually Stage II may emerge.

Stage II:
Bilateral or midline involvement, without impairment of balance.

Months or years later similar symptoms and signs are noticed on the opposite side of the body, or other signs appear in "midline" what physicians call "Axial" signs. These may include: bilateral loss of facial expression (masking); decreased blinking; speech abnormalities; soft voice, monotony, fading volume after starting to speak loudly, slurring, stiffness (rigidity) of truncal muscles making the patient appear awkward and stiff or resulting in neck and back pain; postural abnormalities causing stooping, generalized slowness in, but still capable of, carrying out all activities of daily living, sometimes an aggravation to those waiting for the patient to complete tasks.

Usually the diagnosis is easy at this Stage if it has been preceded by a clear cut tremor or other symptom on one side. But not all Parkinsonism patients have tremor or other definite signs of Stage I unilateral Parkinsonism. If Stage I was missed and the predominant symptoms at Stage II are only slowness and a lack of spontaneous movement, the diagnosis may still be in doubt. For example, even in Stage II, Parkinsonism may be interpreted as only advancing age.

Stage III:
First signs of impaired righting reflexes. This is evident as the patient turns or is demonstrated when he or she is pushed from standing equilibrium with the feet together and eyes closed.

Loss of balance, with the inability to make the rapid, automatic and involuntary movements necessary to protect against falling, is one of the most troubling and dangerous aspects of Parkinsonism and one of the least easily treated. Even when manifested by only slight unsteadiness, it is the criterion separating Stage II and Stage III. All other aspects of Parkinsonism are evident and usually diagnosis is not in doubt.

However, the most important factor identifying Stage III (as opposed to stage IV) is that the patient is still fully independent in all activities of daily living (dressing, hygiene, eating, etc.) Although somewhat restricted, has work potential depending upon the type of employment. A normal life can be.

Stage IV:
Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

The patient is unable to lead an independent life because of the need for help with some activities of daily living. It is this inability to live alone which marks the transition from Stage III to Stage IV. No matter how difficult it is for him/her, if the patient still is able to live alone, his/her disease is at Stage III not Stage IV. The patient at Stage IV however, does remain able to stand and walk unassisted.

Stage V:
Confinement to bed or wheelchair unless aided.

The patient may exhibit: inability to arise from a chair or get out of bed without help; a tendency to fall when standing or turning; freezing, stumbling or pulsion when walking. Without someone immediately present to provide assistance, the patient is in danger of falling.

A typical example of diagnosis using this method of staging would be: "a 64 year old with Stage III PD, more marked on the left than the right, of seven years duration." Another would be: "A 55 year old with severe fluctuations in response to Sinemet, with PD of Stages II/IV, of ten years duration." The second example indicates that the patient is at Stage II when at his best or "on" and at stage

IV when at his worst or "off." This gives the reader a succinct description of the progression of the disease and the current status of the patient.

This method of grading severity is rather a potpourri, combining the symptoms of the patient, the physical signs as observed by the physician and the patient's functional ability. In some instances, it is not applicable. For example, while general experience has been that is the onset of disturbances of balance that heralds future disability, some patients may have such severe tremor that they are incapacitated even though balance in intact. Others may have mild disturbance of balance for many years without losing independence. There are occasional patients who are more incapacitated by severe unilateral disease than are others by milder bilateral disease.

Sometimes Stage I is skipped and the onset is bilateral or generalized. Similarly, many patients never reach Stage V. Patients should not fearfully conclude that when their balance becomes unstable they should immediately start watching for signs indicating that they soon will be dependent upon others. The scale is not linear; that is the patient does not remain at each stage for the same number of years; nor does any stage necessarily represent a given amount of pathology in the brain.

In spite of these drawbacks, this method of grading severity has proved practical over many years. It is a simple method, allowing for easily reproducible assessments of the general status and functional level of the patient by independent examiners. Because the definitions of the Stages are very precise, the scale obviates the confusion arising from such poorly defined terms as mild, moderate or severe disease.

This has been particularly useful in assessing the reported results of new treatments and in designing research projects, because patients respond differently depending on the disease, age of the patient and other factors. A patient at Stage II can become almost normal with adequate therapy; a patient at Stage IV will have residual symptoms, and improvement is never as marked or dramatic. Obviously, it is important to know the status of patients being described as "successfully" or "unsuccessfully" treated before determining whether a new therapy should be tried in an individual patient.

There are other scales for grading the severity of Parkinsonism: The Unified Parkinson's Disease Rating Scale (UPDRS), the modified Columbia Scale, The Webster Scale, The Schwab and England Disability Scale, the Northwestern University Disability Scale and numerous others, each having its own proponents and usefulness.

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PARKINSON'S RESOURCE ORGANIZATION
74-090 El Paseo Suite 104
Palm Desert, CA. 92260
760 773-5628

For more information on Parkinson's please visit
www.parkinsonsresource.org

"Working so no one is isolated because of Parkinson's"

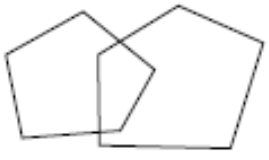
Appendix 7 (Mini Mental State Examination-MMSE)

SMART

MINI MENTAL STATE EXAMINATION (MMSE)

Patient's name:

Hospital number:

ONE POINT FOR EACH ANSWER	DATE			
ORIENTATION				
Year Month Day Date Time	____/5	____/5	____/5	____/5
Country Town District Hospital Ward	____/5	____/5	____/5	____/5
REGISTRATION				
Examiner names 3 objects (eg apple, table, penny) Patient asked to repeat (1 point for each correct). THEN patient to learn the 3 names repeating until correct.	____/3	____/3	____/3	____/3
ATTENTION AND CALCULATION				
Subtract 7 from 100, then repeat from result. Continue 5 times: 100 93 86 79 65 Alternative: spell "WORLD" backwards - dlrow.	____/5	____/5	____/5	____/5
RECALL				
Ask for names of 3 objects learned earlier.	____/3	____/3	____/3	____/3
LANGUAGE				
Name a pencil and watch.	____/2	____/2	____/2	____/2
Repeat "No ifs, ands, or buts".	____/1	____/1	____/1	____/1
Give a 3 stage command. Score 1 for each stage. Eg. "Place index finger of right hand on your nose and then on your left ear".	____/3	____/3	____/3	____/3
Ask patient to read and obey a written command on a piece of paper stating "Close your eyes".	____/1	____/1	____/1	____/1
Ask the patient to write a sentence. Score if it is sensible and has a subject and a verb.	____/1	____/1	____/1	____/1
COPYING				
Ask the patient to copy a pair of intersecting pentagons: 	____/1	____/1	____/1	____/1
TOTAL	____/30	____/30	____/30	____/30

Appendix 8 (AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire)

AHA/ACSM Health/Fitness Facility Pre-participation Screening Questionnaire

Assess your health status by marking all true statements

History

You have had:

_____ a heart attack
_____ heart surgery
_____ cardiac catheterization coronary
_____ angioplasty (PTCA)
_____ Pacemaker/implantable cardiac defibrillator
_____ rhythm disturbance
_____ heart valve disease
_____ heart failure
_____ heart transplantation
_____ congenital heart disease

Symptoms:

_____ You experience chest discomfort with exertion.
_____ You experience unreasonable breathlessness
_____ You experience dizziness, fainting, or blackouts
_____ You take heart medications

Other health issues

_____ You have diabetes
_____ You have asthma or other lung disease
_____ You have burning or cramping sensation in your lower legs when walking short distances
_____ You have musculoskeletal problems that limit your physical activity.
_____ You have concerns about the safety of exercise
_____ You take prescription medication(s).
_____ You are pregnant.

If you marked any of these statements in this section, consult your physician or other appropriate health tare provider before engaging in exercise. You may reed to use a facility with a medically qualified staff.

Cardiovascular risk factors

_____ You are a man older than 45 years.
_____ You are a woman older than 55 years, have had a hysterectomy, or are postmenopausal
_____ You smoke, or quit smoking within the previous 6 months.
_____ Your blood pressure is >140190 mm Hg.
_____ You do not know your blood pressure.
_____ You take blood pressure medication.
_____ Your blood cholesterol level is >200 mg/dl.
_____ You do not know your cholesterol level.

_____ You have a close blood relative who had a heart attack or heart surgery before age 55 (father or brother) or age 65 (mother or sister).

_____ You are physically inactive (i.e., you get <30 minutes of physical activity on at least 3 days per week).

_____ You are >20 pounds overweight

If you marked two or more of the statements in this section you should consult you physician or other appropriate health rare provider before engaging in exercise. You might benefit from using a facility with a professionally qualified exercise staff to guide your exercise Program.

_____ None of the above

You should be able to exercise safely without consulting your physician or other appropriate health care provider in a self-guided program or almost any facility that meets your exercise program needs.

Modified from American College of Sports Medicine and American Heart Association. ACSM/AHA Joint Position Statement: Recommendations for cardiovascular screening, staffing, and emergency policies at health/fitness facilities. Medicine and Science in Sports and Exercise 1998:1018.

Appendix 9 (Invitation letter)

Date:

Dear (……),

Re: The effects of aerobic exercise on cardiopulmonary function in people with Parkinson's disease.

I am a PhD student in the School of Health and Rehabilitation at Keele University, supervised by Dr Sue Hunter, a physiotherapist and researcher. I am undertaking a research project to evaluate cardiopulmonary (heart and lung) function in people who are diagnosed with Parkinson's and investigate the effects of aerobic exercise on their cardiopulmonary function. This will ultimately help to provide an improved standard of care for people with Parkinson's. You are invited to consider taking part in this study. Before you decide, it is important for you to understand why the research is being done and what you would have to do.

Please take the time to read the information on the following pages carefully and, if you wish, discuss it with relatives and friends. If you would like more information, or would like to volunteer to take part, please contact me using the contact details below and let me know how you would like me to get in touch with you. Please take your time to decide whether or not you wish to take part and feel free to ask any questions you may have.

Remember that you do not have to participate in this study. Furthermore, if you do volunteer and then change your mind, you would be free to leave the study at any time and there would be no need for you to give a reason. Your routine medical care would not be affected in any way.

I suggest that you keep this letter so that you can show it to anyone concerned with your medical care. If you have any questions or queries, please do not hesitate to contact Aseel Aburub by email at a.a.m.aburub@keele.ac.uk or Dr Sue Hunter by email at s.m.hunter@keele.ac.uk.

Yours Sincerely,

Aseel Aburub

a.a.m.aburub@keele.ac.uk

01782 733809

School of Health and Rehabilitation

Keele University

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Staffordshire

ST5 5BG

Appendix 10 (Information sheet)

Keele University

Study Title: The effects of aerobic exercise on cardiopulmonary function in people with Parkinson's disease.

Invitation

You are being invited to consider taking part in the research study "The effects of aerobic exercise on cardiopulmonary function in people with Parkinson's disease". This project is being undertaken by Aseel Aburub, a PhD student at Keele University, supervised by Dr. Sue Hunter, Dr. Sean Ledger, Professor Nicola Edelstyn and Professor Julius Sim.

Before you decide whether or not you wish to take part, it is important for you to understand why this research is being done and what it will involve. Please take time to read this information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is unclear or if you would like more information.

Aims of the Research

Respiratory (breathing) impairment is considered to be the main cause of death in the later stages of Parkinson's. Although there is evidence of respiratory impairment in the early stages of the disease, these symptoms do not appear until the end-stage. Aerobic exercise has been shown to improve respiratory function in asthmatic patients and in healthy people, but effects of aerobic training on respiratory function in people with Parkinson's have not been investigated. If aerobic exercise could decrease or delay respiratory impairment in Parkinson's, this might reduce respiratory complications, improve quality of life, and reduce treatment costs. Thus, this study will investigate the effects of an eight-week program of aerobic walking on respiratory function in people with Parkinson's.

Why have I been invited?

You have been invited to take part because you are a member of a Parkinson's support group. Permission has been granted from your group lead for me to approach all members to invite them to take part in this study, which will recruit 34 people with Parkinson's.

Do I have to take part?

You are free to decide whether you wish to take part or not. If you do decide to take part, you will be asked to sign a consent form. You will be given a copy of this participant information sheet and your signed consent form to keep. You are free to withdraw from this study at any time and without giving reasons. If you decide to withdraw from the study, we will destroy securely any documentation that contains personal identifiable information, but we will need to use other data collected up to the point of your withdrawal. You are free to withdraw from the study at any time and this will not affect your continuing medical care.

What will happen if I take part?

If you would like to take part, we will agree with you and arrange a suitable time for you to attend an appointment at Keele University for your assessment. There, you will be asked to sign a written consent form indicating that you are happy to take part in the study. We will collect some information about you, including name, gender, age, height, weight, and medical history; and you will then be asked to complete the following tests:

1. An exercise test (which will be repeated on three subsequent occasions during the trial, at weeks 4, 8 and 12):
   You will perform an exercise test on a static bike (cycle ergometer). The exercise intensity will begin at a low level and will be advanced in stages, depending on your fitness level, but will not exceed an intensity that raises your heart rate to more than 70% of your maximum heart rate (calculated by 220 minus your age), estimated to be between 84 (for a 100-year-old person) and 119 (for a 50-year-old person), depending on your age (the average resting heart rate is 72 beats per minute). The test can be stopped at any time if we observe or you report any signs of fatigue or any type of discomfort. However, these symptoms are not anticipated and are considered to be unlikely. Heart rate, breathing rate and the amount of oxygen that you consume will be measured during the test. The test may take approximately 8-15 minutes to be completed. Before the test you will be asked to have a rest for 30 minutes. Thus, we allocate one hour for this test to be done.

2. A breathing (lung function) test:
   You will be asked to do a lung function test by using a nosepiece and mouthpiece that is connected to a device; this is called spirometry. You will be asked to simply breath in and out quickly, and the device will record the amount of air you breath in and out, and the force of your breathing. This test will take approximately 30 minutes.

3. Completion of questionnaires.
   As part of the assessment you will be asked to complete a questionnaire about your general physical functionality, memory, sleep and general health perception.

After these tests, you will be randomly allocated to one of two groups: one group will be given an 8-week exercise program to do at home, on top of your usual care; the other group will receive usual care. Participants in both groups will be asked to wear

a physical activity monitor. You will be given devices that record your physical activity level. You will be asked to wear it around your waist during the day except for swimming of showering. At the end of a 12 week period, you will be asked to participate in a discussion (focus group) to discuss any feedback you have about the study. The discussion will be audio recorded. In preparing the data from the process evaluation for analysis, all the audio tapes will be transcribed in full into text.

What are the benefits (if any) of taking part?

The results obtained from the tests may help in quantifying your exercise capacity and may be helpful in evaluating what type of physical activities are appropriate and safe for you. Participating in this pilot study will help us to find out whether the exercise programme improves fitness and function, is an acceptable programme that people with Parkinson's can do at home, and will help us to plan a larger trial.

What are the risks (if any) of taking part?

During the exercise test, participants may in certain exceptional circumstances, e.g. under intensive aerobic exercise, experience abnormal changes to blood pressure, fainting, angina, and in rare instances heart attack or stroke. However, in this study, the anticipated and planned intensity of the exercise will be restricted and limited to the fact that people have Parkinson's disease, are older adults, and therefore will not be exercising at an intensive aerobic level. The level of exercise intensity will be closely monitored throughout and will be limited by the calculated 70% of maximum age-related heart rate. For example, for a 50-year-old person, the estimated maximum age-related heart rate would be calculated as 220 – 50 years = 170 beats per minute (bpm). The 70% levels would be 170 x 0.70 = 119 beats per minute. Similarly, for an 80-year-old person, the estimated 70% maximum heart rate would be 220 – 80 = 140 x 0.70 = 98 beats per minute. The exercise intensity would be monitored so that these heart rates (according to age) were not exceeded throughout the test. It is worthy of note that the average adult resting heart rate is around 70 beats per minute, e.g. when sitting in a chair.

How will information about me be used?

All personal information collected about you will be treated as confidential and privileged. It will not to be accessible to anyone except the research team members. The information and data, however, may be used for statistical analysis or scientific purposes with your right of privacy maintained. For example, we will want to calculate the average age and the male:female ratio of people in the study. Your height and weight will be used to help us to interpret the data from the exercise, breathing and walking tests.

Who will have access to information about me?

We would like to reassure you that your personal details would be kept strictly confidential. No one, except the named investigators involved in the collection of data (Aseel Aburub, Dr. Sue Hunter, and Dr. Sean Ledger), will have access to these details and no identifying details will appear in our published results according to Keele University confidentiality guidelines.

Who is funding and organising the research?

This research is not being funded externally and is part of Aseel Aburub's PhD studies, organised and overseen by Keele University.

What if there is a problem?

If you have a concern about any aspect of this study, you may wish to speak to the researchers who will do their best to answer your questions. You should contact *Aseel Aburub* on *a.a.m.aburub@keele.ac.uk*. Alternatively, if you do not wish to contact the researchers you may contact *Dr. Sue hunter* on *s.m.hunter@keele.ac.uk*

If you remain unhappy about the research and/or wish to raise a complaint about any aspect of the way that you have been approached or treated during the course of the study please write to [name to be inserted when confirmed] who is the University's contact for complaints regarding research at the following address:-

Research Governance Officer

Directorate of Engagement and Partnerships

IC2 Building

Keele University

ST5 5NH

E-mail: [*to be confirmed*]

Tel: 01782 733306

Contact for further information

Aseel Aburub or Dr. Sue Hunter

a.a.m.aburub@keele.ac.uk *or* s.m.hunter@keele.ac.uk

01782733809

School of Health and Rehabilitation

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Appendix 11 (The Modified Borg scale Rating of Perceived Exertion Scale)

6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Borg-RPE-Scale®
© Gunnar Borg 1970, 1985, 1998

BORG PRODUCTS USA

Instructions to the Borg-RPE-Scale®

During the work we want you to rate your perception of exertion, i.e. how heavy and strenuous the exercise feels to you and how tired you are. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or aches in the chest.

Use this scale from 6 to 20, where **6** means "No exertion at all" and **20** means "Maximal exertion."

9 Very light. As for a healthy person taking a short walk at his or her own pace.

13 Somewhat hard. It still feels OK to continue.

15 It is hard and tiring, but continuing is not terribly difficult.

17 Very hard. It is very strenuous. You can still go on, but you really have to push yourself and you are very tired.

19 An extremely strenuous level. For most people this is the most strenuous exercise they have ever experienced.

Try to appraise your feeling of exertion and fatigue as spontaneously and as honestly as possible, without thinking about what the actual physical load is. Try not to underestimate, nor to overestimate. It is your own feeling of effort and exertion that is important, not how it compares to other people's. Look at the scale and the expressions and then give a number. You can equally well use even as odd numbers.

Any questions?

BORG PRODUCTS USA

Appendix 12 (Parkinson's Disease Quality of Life Questionnaire PDQ-39)

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
1.	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2.	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3.	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4.	Had problems walking half a mile?	☐	☐	☐	☐	☐
5.	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6.	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7.	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8.	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question*** before going onto the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
9.	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10.	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11.	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12.	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13.	Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐
14.	Had problems writing clearly?	☐	☐	☐	☐	☐
15.	Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16.	Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17.	Felt depressed?	☐	☐	☐	☐	☐
18.	Felt isolated and lonely?	☐	☐	☐	☐	☐

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

	Never	Occasionally	Sometimes	Often	Always
19. Felt weepy or tearful?	☐	☐	☐	☐	☐
20. Felt angry or bitter?	☐	☐	☐	☐	☐
21. Felt anxious?	☐	☐	☐	☐	☐
22. Felt worried about your future?	☐	☐	☐	☐	☐
23. Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24. Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25. Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26. Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27. Had problems with your close personal relationships?	☐	☐	☐	☐	☐

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
28.	Lacked support in the ways you need from your spouse or partner? *If you do not have a spouse or partner, please tick here* ☐	☐	☐	☐	☐	☐
29.	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐
30.	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31.	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32.	Felt your memory was bad?	☐	☐	☐	☐	☐
33.	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34.	Had difficulty with your speech?	☐	☐	☐	☐	☐
35.	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

	Never	Occasionally	Sometimes	Often	Always
36. Felt ignored by people?	☐	☐	☐	☐	☐
37. Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38. Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39. Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***.

Thank you for completing the questionnaire.

Appendix 13 (Parkinson's Non-Motor symptoms Questionnaire)

PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

Non-motor symptoms questionnaire

This questionnaire should be completed and **given to your GP, specialist or Parkinson's nurse at your next appointment.** Please **do not** return it to Parkinson's UK. Thank you.

Name:..... **Date:**..... **Age:**.....

Centre ID: Male ☐ Female ☐

Have you experienced any of the following in the last month?

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998. Developed and validated by the International PD Non Motor Group.

Non-movement problems in Parkinson's

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

		Yes	No
1	Dribbling of saliva during the daytime.	☐	☐
2	Loss or change in your ability to taste or smell.	☐	☐
3	Difficulty swallowing food or drink or problems with choking.	☐	☐
4	Vomiting or feelings of sickness (nausea).	☐	☐
5	Constipation (less than three bowel movements a week) or having to strain to pass a stool.	☐	☐
6	Bowel (faecal) incontinence.	☐	☐
7	Feeling that your bowel emptying is incomplete after having been to the toilet.	☐	☐
8	A sense of urgency to pass urine makes you rush to the toilet.	☐	☐
9	Getting up regularly at night to pass urine.	☐	☐
10	Unexplained pains (not due to known conditions such as arthritis).	☐	☐

		Yes	No
11	Unexplained change in weight (not due to change in diet).	☐	☐
12	Problems remembering things that have happened recently or forgetting to do things.	☐	☐
13	Loss of interest in what is happening around you or in doing things.	☐	☐
14	Seeing or hearing things that you know or are told are not there.	☐	☐
15	Difficulty concentrating or staying focused.	☐	☐
16	Feeling sad, 'low' or 'blue'.	☐	☐
17	Feeling anxious, frightened or panicky.	☐	☐
18	Feeling less interested in sex or more interested in sex.	☐	☐
19	Finding it difficult to have sex when you try.	☐	☐
20	Feeling light-headed, dizzy or weak standing from sitting or lying.	☐	☐
21	Falling.	☐	☐
22	Finding it difficult to stay awake during activities such as working, driving or eating.	☐	☐
23	Difficulty getting to sleep at night or staying asleep at night.	☐	☐
24	Intense, vivid or frightening dreams.	☐	☐
25	Talking or moving about in your sleep, as if you are 'acting out' a dream.	☐	☐
26	Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move.	☐	☐
27	Swelling of the legs.	☐	☐
28	Excessive sweating.	☐	☐
29	Double vision.	☐	☐
30	Believing things are happening to you that other people say are not.	☐	☐

Chaudhuri KR, Martinez-Martin P, Schapira AHV, Stocchi F, Sethi K, Odin P et al (2006) 'An international multicentre pilot study of the the first comprehensive self-completed non motor symptoms questionnaire for Parkinson's disease: The NMSQuest study' *Mov Disord*; 21(7):916-923.

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998. Developed and validated by the International PD Non Motor Group.

Appendix 14 (Barthel Index)

Barthel Index of Activities of Daily Living

Instructions: Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on scoring and interpretation.

The Barthel Index

Bowels
0 = incontinent (or needs to be given enemata)
1 = occasional accident (once/week)
2 = continent
Patient's Score: _____

Bladder
0 = incontinent, or catheterized and unable to manage
1 = occasional accident (max. once per 24 hours)
2 = continent (for over 7 days)
Patient's Score: _____

Grooming
0 = needs help with personal care
1 = independent face/hair/teeth/shaving (implements provided)
Patient's Score: _____

Toilet use
0 = dependent
1 = needs some help, but can do something alone
2 = independent (on and off, dressing, wiping)
Patient's Score: _____

Feeding
0 = unable
1 = needs help cutting, spreading butter, etc.
2 = independent (food provided within reach)
Patient's Score: _____

Transfer
0 = unable – no sitting balance
1 = major help (one or two people, physical), can sit
2 = minor help (verbal or physical)
3 = independent
Patient's Score: _____

Mobility
0 = immobile
1 = wheelchair independent, including corners, etc.
2 = walks with help of one person (verbal or physical)
3 = independent (but may use any aid, e.g., stick)
Patient's Score: _____

Dressing
0 = dependent
1 = needs help, but can do about half unaided
2 = independent (including buttons, zips, laces, etc.)
Patient's Score: _____

Stairs
0 = unable
1 = needs help (verbal, physical, carrying aid)
2 = independent up and down
Patient's Score: _____

Bathing
0 = dependent
1 = independent (or in shower)
Patient's Score: _____

Total Score: _____

(Collin et al., 1988)

Scoring:

Sum the patient's scores for each item. Total possible scores range from 0 – 20, with lower scores indicating increased disability. If used to measure improvement after rehabilitation, changes of more than two points in the total score reflect a probable genuine change, and change on one item from fully dependent to independent is also likely to be reliable.

Sources:

- Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud.* 1988;10(2):61-63.
- Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J.* 1965;14:61-65.
- Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud.* 1988;10(2):64-67.

Guidelines for the Barthel Index of Activities of Daily Living

General

- The Index should be used as a record of what a patient *does*, NOT as a record of what a patient *could do*.
- The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
- The need for supervision renders the patient not independent.
- A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives, and nurses will be the usual source, but direct observation and common sense are also important. However, direct testing is not needed.
- Usually the performance over the preceding 24 – 48 hours is important, but occasionally longer periods will be relevant.
- Unconscious patients should score '0' throughout, even if not yet incontinent.
- Middle categories imply that the patient supplies over 50% of the effort.
- Use of aids to be independent is allowed.

Bowels (preceding week)

- If needs enema from nurse, then 'incontinent.'
- 'Occasional' = once a week.

Bladder (preceding week)

- 'Occasional' = less than once a day.
- A catheterized patient who can completely manage the catheter alone is registered as 'continent.'

Grooming (preceding 24 – 48 hours)

- Refers to personal hygiene: doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements can be provided by helper.

Toilet use

- Should be able to reach toilet/commode, undress sufficiently, clean self, dress, and leave.
- 'With help' = can wipe self and do some other of above.

Feeding

- Able to eat any normal food (not only soft food). Food cooked and served by others, but not cut up.
- 'Help' = food cut up, patient feeds self.

Transfer

- From bed to chair and back.
- 'Dependent' = NO sitting balance (unable to sit); two people to lift.
- 'Major help' = one strong/skilled, or two normal people. Can sit up.
- 'Minor help' = one person easily, OR needs any supervision for safety.

Mobility

- Refers to mobility about house or ward, indoors. May use aid. If in wheelchair, must negotiate corners/doors unaided.
- 'Help' = by one untrained person, including supervision/moral support.

Dressing

- Should be able to select and put on all clothes, which may be adapted.
- 'Half' = help with buttons, zips, etc. (*check!*), but can put on some garments alone.

Stairs

- Must carry any walking aid used to be independent.

Bathing

- Usually the most difficult activity.
- Must get in and out unsupervised, and wash self.
- Independent in shower = 'independent' if unsupervised/unaided.

(Collin et al., 1988)

Appendix 15 (Prospective-Retrospective Memory Questionnaire)

REMEMBERING TO DO THINGS

Prospective-Retrospective Memory Questionnaire as described in:

Smith, G., Della Sala, S., Logie, R.H. & Maylor, E.A. (2000). Prospective and Retrospective Memory in Normal Aging and Dementia: A Questionnaire Study. *Memory*, 8, 311-321.

In order to understand why people make memory mistakes, we need to find out about the kinds of mistakes people make, and how often they are made in normal everyday life. We would like you to tell us how often these kind of things happen to you. Please indicate by ticking the appropriate box.

Please make sure you answer all of the questions on both sides of the sheet even if they don't seem entirely applicable to your situation.

Please provide the following details about yourself. Age _____ Male/Female _____

How many year of formal education have you had? _____

Have you suffered from brain or head injury resulting in hospitalisation (Y/N) _____

Please give brief details

Please answer all of the questions as accurately as possible.

	Very Often	Quite Often	Sometimes	Rarely	Never
Do you decide to do something in a few minutes' time and then forget to do it?	☐	☐	☐	☐	☐
Do you fail to recognise a place you have visited before?	☐	☐	☐	☐	☐
Do you fail to do something you were supposed to do a few minutes later even though it's there in front of you, like take a pill or turn off the kettle?	☐	☐	☐	☐	☐

	Very Often	Quite Often	Sometimes	Rarely	Never
Do you forget something that you were told a few minutes before?	☐	☐	☐	☐	☐
Do you forget appointments if you are not prompted by someone else or by a reminder such as a calendar or diary?	☐	☐	☐	☐	☐
Do you fail to recognise a character in a radio or television show from scene to scene?	☐	☐	☐	☐	☐
Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?	☐	☐	☐	☐	☐
Do you fail to recall things that have happened to you in the last few days?	☐	☐	☐	☐	☐
Do you repeat the same story to the same person on different occasions?	☐	☐	☐	☐	☐
Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it's there in front of you?	☐	☐	☐	☐	☐
Do you mislay something that you have just put down, like a magazine or glasses?	☐	☐	☐	☐	☐
Do you fail to mention or give something to a visitor that you were asked to pass on?	☐	☐	☐	☐	☐
Do you look at something without realising you have seen it moments before?	☐	☐	☐	☐	☐
If you tried to contact a friend or relative who was out, would you forget to try again later?	☐	☐	☐	☐	☐
Do you forget what you watched on television the previous day?	☐	☐	☐	☐	☐
Do you forget to tell someone something you had meant to mention a few minutes ago?	☐	☐	☐	☐	☐

Appendix 16 (Geriatric Depression Scale)

Geriatric Depression Scale: Short Form

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? YES / **NO**
2. Have you dropped many of your activities and interests? **YES** / NO
3. Do you feel that your life is empty? **YES** / NO
4. Do you often get bored? **YES** / NO
5. Are you in good spirits most of the time? YES / **NO**
6. Are you afraid that something bad is going to happen to you? **YES** / NO
7. Do you feel happy most of the time? YES / **NO**
8. Do you often feel helpless? **YES** / NO
9. Do you prefer to stay at home, rather than going out and doing new things? **YES** / NO
10. Do you feel you have more problems with memory than most? **YES** / NO
11. Do you think it is wonderful to be alive now? YES / **NO**
12. Do you feel pretty worthless the way you are now? **YES** / NO
13. Do you feel full of energy? YES / **NO**
14. Do you feel that your situation is hopeless? **YES** / NO
15. Do you think that most people are better off than you are? **YES** / NO

Answers in bold indicate depression. Score 1 point for each bolded answer.

A score > 5 points is suggestive of depression.
A score ≥ 10 points is almost always indicative of depression.
A score > 5 points should warrant a follow-up comprehensive assessment.

Source: http://www.stanford.edu/~yesavage/GDS.html
This scale is in the public domain.

The Hartford Institute for Geriatric Nursing would like to acknowledge the original author of this Try This, Lenore Kurlowicz, PhD, RN, CS, FAAN, who made significant contributions to the field of geropsychiatric nursing and passed away in 2007.

A series provided by The Hartford Institute for Geriatric Nursing,
New York University College of Nursing

Appendix 17 (Physical activity survey questionnaire)

Survey questionnaire

The following is a survey questionnaire that aims to seek information about your physical activity level. The answers you give will be used in the development of a study that will assess the effects of aerobic training on cardiopulmonary function in Parkinson's. All the information will be used with confidentiality and privacy. Please note that you will not be asked to add your name or contact number in the survey, and you will not be identifiable from the survey. If you agreed to participate in the survey, please answer the next 10 questions.

1. Please state your current medication for Parkinson's.

2. At what time do you usually take your medication? Please select one answer:
   a. From 7:00 a.m. to 9:00 a.m.
   b. From 9:01 a.m. to 11:00 a.m.
   c. From 11:01 a.m. to 12:00 p.m.
   d. From 12:01 p.m. to 2:00 p.m
   e. Other (please specify in the space below)

3. 'Aerobic' exercise includes physical activity that makes you breathe harder or makes your heart beat faster, such as walking, running, swimming, cycling, rowing, cross trainer). Do you do any aerobic exercise? Please select as many as apply from the list below:
   a. No – I don't do aerobic exercise
   b. Yes - walking outdoors
   c. Yes – walking on a treadmill
   d. Yes - cycling outdoors
   e. Yes - cycling indoors on stationary cycle using just legs
   f. Yes - indoors on stationary cycle using just arms
   g. Yes - rowing outdoors
   h. Yes – rowing on a row machine indoors
   i. Yes – running outdoors
   j. Yes – running on a treadmill
   k. Yes - using a cross trainer
   l. Yes – swimming

4. Please state how many minutes per day you do the aerobic exercise. Please select one answer from the list below:
    a. I don't do aerobic exercise
    b. 10-20 minutes
    c. 21-30 minutes
    d. 31-40 minutes
    e. 41-50 minutes
    f. More than 50 minutes

5. Please state how many days per week you do the aerobic exercise. Please select one answer from the list below:
    a. I don't do aerobic exercise
    b. One day per week
    c. Two days per week
    d. Three days per week
    e. Four days per week
    f. Five days per week
    g. Six days per week
    h. Seven days per week

6. Do you experience shortness of breath, and if so, when do you feel it? Please select as many answers from the list below that apply to you:
    a. No, I don't feel shortness of breath
    b. Yes, I feel short of breath when climbing stairs
    c. Yes, I feel short of breath when walking short distances e.g. around the house
    d. Yes, I feel short of breath walking longer distances e.g. outdoors walking to the shop
    e. Yes, I feel short of breath during aerobic exercise (as in question 3)
    f. Yes, I feel short of breath during gym exercises
    g. Yes, I feel short of breath when lying down
    h. Yes, I feel short of breath all the time
    i. Other (please describe in the space below)

7. Are you a smoker?
    a. Yes – I smoke cigarettes
    b. Yes – I smoke a pipe
    c. No, I don't smoke

8. If you currently smoke, please state below how many cigarettes / how much tobacco you smoke per day:

9. Do you have the ability to get on and off a stationary cycle / exercise bike? Please select one answer from the list below:
    a. Yes, I could do this easily by myself
    b. Yes, I could do this by myself but with a struggle
    c. Yes, I could do this with assistance
    d. No, I would be scared to try
    e. No, I have tried and I can't
    f. I don't know
    g. Other

10. Do you have the ability to walk independently (without assistance)? Please select one answer from the list below:

    a. Yes, I can walk independently without any walking aid or other form of external support
    b. Yes, I can walk independently but with a walking aid
    c. No, I need physical assistance or support from one other person to walk
    d. No, I need physical assistance or support from more than one other person to walk
    e. I am unable to walk

Appendix 18 (Physical activity diary)

Aerobic exercise diary

Participant number:

Week	Date	Duration of exercise	Aerobic exercise type (for example: walking, cycling, rowing … etc)
1			
2			
3			
4			
5			
6			
7			

8			
Any other notes:			

Appendix 19 (The first draft of the focus group questions)

	a *priori* topic
How did you find the aerobic exercise? Was the aerobic exercise programme suitable for you? What do you think about the overall aerobic exercise programme? How often you were exercising?	Suitability of the exercise programme
Prompt questions: Was the aerobic exercise easy? Did you enjoy doing the aerobic exercise?	
Did you have difficulty in performing the aerobic exercise program? Can you explain?	Barriers
Prompt question: Can you please specify any difficulties (if found)?	
Was the exercise programme useful? What benefits you achieved after doing the aerobic exercises?	Perceived benefits

Did you find any difficulties while wearing the activity monitors? Explain

Did you remember to wear the activity monitor daily?

Activity monitors

Were the tests done during the four assessments sessions difficult? Could you explain, please?

Outcome measures

Have any other comments about the project?

Appendix 20 (The final version of the Focus group questions)

Focus group questions

Date:
Name of Facilitator: Aseel Aburub
Name of Note taker:
Introduction to the process
I would like to welcome and thank you for agreeing to attend a focus group discussion regarding participation in the study "Aerobic exercise to improve cardiopulmonary function in people with Parkinson's: a mixed method pilot study".. Before starting, I'm providing you a copy of the consent form which has previously been completed and a copy from the questions that we are going to discuss now. Please, answer any questions that may arise as comprehensively as possible. Please note that:

- The Focus Group interview will take no longer than one and a half hours.
- The interview will be audiotaped by two devices.
- The information that is collected about you during the course of the study and the audio-records will be kept strictly confidential. Everyone needs to respect this please.
- You are going to be anonymous in any dissemination work undertaken external or internal to the University, and quotations that will be used in any work will be completely anonymous.
- The information provided by you during this interview will be used to inform a future study looking at aerobic exercise and cardiorespiratory function in Parkinson's.
- If you do not want to participate or if you want to leave, you are entitled to do so, but please let me know.

Please let me know if you have any questions or if you need any clarifications. I would gently ask if it is OK to turn on the tape recorder now to conduct the interview. I would like to remind you that there is no right or wrong answer and you can just give your honest opinion. I would be grateful if you can speak clearly and only one person at a time.
Now I am going to start the audio-recording.

Interview schedule

Questions:	**a priori topics**
I would like to hear from you about your experiences of doing the aerobic exercise programme.	
1. <u>How did you find the aerobic exercise?</u> ***Prompt questions:*** • *Was the aerobic exercise programme suitable for you?* • *What do you think about the overall aerobic exercise programme?* • *Was the aerobic exercise easy?* • *Did you enjoy doing the aerobic exercise?* • Prompt question: How often you were exercising?	Suitability of the exercise programme

1. **Did you have difficulty in performing the aerobic exercise program?**

***Prompt question**:*
- *Can you explain?*
- *Can you please specify any difficulties (if found)?*
- *Was there anything that stopped you being able to exercise?*

Barriers

2. **Was the exercise programme useful?**

Prompt question:
- Do you feel there were any benefits for you in doing the aerobic exercise programme?

Perceived benefits

3. **Did you find any difficulties while wearing the activity monitors?**

***Prompt questions**:*
- *Please can you explain that a little more*

4. **Did you remember to wear the activity monitor every day?**

Prompt questions:
- *Why do you think you forgot to wear it?*
- *Is there anything we could have done / you could have done to have reminded you to wear the monitor?*

Activity monitors

5. **I am interested in your experience of the tests that were done during the four assessments sessions. Did you find any of them particularly difficult or unpleasant, or were there any problems for you?**

Prompt questions:
- *Could you explain this a little more, please?*
- *What made the test difficult / unpleasant / uncomfortable?*

Outcome measures

6. **Do you have any other comments you would like to make about the study?**

I would like to thank you for your time today. Now I am going to stop the audio-recording.

Appendix 21 (answers to the COREQ checklist for the focus groups).

No. Item	Guide questions/description	Answers
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	Aseel Aburub (AAb: interviewer) Dr Sue Hunter (SH: observer)
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	AAb: PhD student, MSc, BSc (PT). SH: PhD, BSc (PT)
3. Occupation	What was their occupation at the time of the study?	AAb: PhD student and physiotherapy lecturer. SH: Senior lecturer
4. Gender	Was the researcher male or female?	AAb: Female SH: Female
5. Experience and training	What experience or training did the researcher have?	AAb: research teaching and clinical experience SH: Research teaching and clinical experience
Relationship with		

participants		
6. Relationship established	Was a relationship established prior to study commencement?	N/A
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	N/A
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	AAb: had the assumption that PLwP have time to fit in exercise in their diaries, not as active as needed.
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Phenomenology
Participant selection		
10. Sampling	How were participants selected? e.g. purposive,	All participants who were in the exercise

	convenience, consecutive, snowball	group were invited to the focus groups without any exemption
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Invited by email
12. Sample size	How many participants were in the study?	Focus group 1=4 Focus group 2=5
13. Non-participation	How many people refused to participate or dropped out? Reasons?	3 did not respond
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Focus group 1: at Keele University (School of Allied Health Sciences meeting room). Focus group 2: online using Google Meet app.
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	In focus group 1: one partner of a participant
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data	Focus group1: four males (>63 years old).

		Focus group 2: 2males and 3 females (>55 years old).
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors?	Yes
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Audio
20. Field notes	Were field notes made during and/or after the inter view or focus group?	During the interview by the observer (SH)
21. Duration	What was the duration of the interviews or focus group?	Focus group 1: one and a half hour Focus group 2: One hour
22. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings		
Data analysis		

23. Number of data coders	How many data coders coded the data?	Two
24. Description of the coding tree	Did authors provide a description of the coding tree?	N/A
25. Derivation of themes	Were themes identified in advance or derived from the data?	Themes were identified in advance, and two more themes were added after observing the focus groups
26. Software	What software, if applicable, was used to manage the data?	NVivo
Reporting		
27. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Yes
28. Data and findings consistent	Was there consistency between the data presented and the findings?	N/A
39. Clarity of major themes	Were major themes clearly presented in the findings?	Yes

30. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes

Appendix 22 (Ethical approval letter for the physical activity during COVID-19 period in Parkinson's questionnaire)

Keele University FMHS Faculty Research Ethics Committee
health.ethics@keele.ac.uk

9th September 2020

Dear Aseel

Project Title:	Exercise during COVID-19 in Parkinson's: an online questionnaire
REC Project Reference:	MH-200139
Type of Application	Main application

Keele University's Faculty of Medicine and Health Sciences Research Ethics Committee (FMHS FREC) reviewed the above project application.

Favourable Ethical opinion
The members of the Committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the project

1.	None

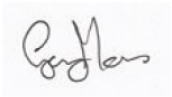
Reporting requirements
The University's standard operating procedures give detailed guidance on reporting requirements for studies with a favourable opinion including:

- Notifying substantial amendments
- Notifying issues which may have an impact upon ethical opinion of the study
- Progress reports
- Notifying the end of the study

Approved documents
The documents reviewed and approved are:

Document	Version	Date
All documents submitted with MH-200139		

Yours sincerely,



Dr Gary Moss
Chair

Appendix 23 (invitation email to the physical activity during COVID-19 period in Parkinson's questionnaire)

Date:

Dear (……),

Re: Physical activity during COVID-19 period in Parkinson's: a survey questionnaire pilot study

I am a PhD student in the School of Health and Rehabilitation at Keele University, supervised by Dr Sue Hunter, a physiotherapist and researcher. I am undertaking a research study to explore the effects of COVID-19 period on physical activity in people with Parkinson's. This will ultimately help to provide an understanding of the physical activity levels of people with Parkinson's, and whether they are achieving the recommended physical activity level; and to explore their views and opinions about types of exercise that could be done as part of a self-management exercise programme. The study will collect answers through an online questionnaire.

However, before we send the questionnaire through Parkinson's UK, we need to check that it is of a good quality, well structured, easily administered and well-worded. Thus, you are invited to consider taking part in this study (piloting the questionnaire as part of the study design, before we share it). Also, we need to check the reliability of the questionnaire. Thus, we are going to re-send it again after one week from your reply. This could help us to understand if the answers to the survey are consistent over time.

If you would like more information please do email the researcher at the email address below. If you would like to volunteer to take part, please fill the attached questionnaire and send it back to me using the contact details below. Please take your time to decide whether or not you wish to take part and feel free to ask any questions you may have.

Remember that you do not have to participate in this study. Furthermore, if you do volunteer and then change your mind, you would be free to leave the study at any time and there would be no need for you to give a reason. Your routine medical care would not be affected in any way.

I suggest that you keep this letter so that you can show it to anyone concerned with your medical care. If you have any questions or queries, please do not hesitate to contact Aseel Aburub by email at a.a.m.aburub@keele.ac.uk or Dr Sue Hunter by email at s.m.hunter@keele.ac.uk .

Yours Sincerely,

Aseel Aburub (Physiotherapist)

a.a.m.aburub@keele.ac.uk

01782 733809

School of Health and Rehabilitation

Keele University

Keele

Staffordshire

ST5 5BG

Appendix 24 (The physical activity during COVID-19 period in Parkinson's questionnaire)

Physical activity during COVID-19 period in Parkinson's

This questionnaire asks about physical activity in people with Parkinson's before and during the COVID-19 period of lockdown, social distancing and shielding. Data collected from this questionnaire will be used anonymously in a research study which aims to explore changes in physical activity level during that COVID-19 period from March 20th 2020 to September 20th 2020. There is no need to provide any personal information such as your name or contact information.

If you have any comments or queries, please contact a.a.m.aburub@keele.ac.uk
If you need to know more about the study, please read the detailed information sheet from the below link:

https://drive.google.com/file/d/1y7U3pT7PNndq2XOmFFF6Tg6DV3piwpTS/view?usp=sharing

By answering the online questionnaire, you are agreeing to be part of the study. No need to write any personal information such as your name or contact details.

Section 1: Consent

Before you consent to participating in the research, please read the participant information sheet and then choose yes if you agree on the first 5 questions, or choose no if you do not agree to go to the end of the form. If you have any questions or queries before signing the consent form please speak to the researcher.

1. I have read and understood the research information sheet dated 02/07/2020 (version 1.0) or the project has been fully explained to me. (If you will answer No to this question please do not proceed with this consent

form until you are fully aware of what your participation in the project will mean).

- • Yes
  No

2. I have been given the opportunity to ask questions about the project, ask questions and have had these answered satisfactorily.

- Yes
- No

3. I understand that my taking part is voluntary. I also understand that I can discontinue participation at any point and I can also withdraw myself and my data from the research at anytime before submitting the questionnaire. I do not have to give any reasons for why I no longer want to take part and there will be no adverse consequences if I choose to withdraw.

- Yes
- No

4. I understand that data collected during this research will be processed in accordance with data protection law as explained in the Participant Information Sheet

- Yes
- No

5. I agree to take part in the above research

- Yes
- No

Section 2:

6. What is your age in years?
   - Please type your answer here:
7. What is your gender?
   - Male

- Female
- Other

8. Please tell us about your level of mobility:
    - I can walk independently without walking aids
    - I can walk independently, but I use walking aids (for example: stick or walker/stroller)
    - I need a person to assist me while walking
    - I need a walking aid and a person to assist me while walking
    - I am on a wheelchair

If the answer of Question 3 was 1, 2, 3 or 4 then go to Question 4. If the answer was 5, then go to Question 5.

9. How far can you walk?
    - Less than 10 metres
    - More than 10 metres but less than a mile
    - More than a mile

10. How long have you been diagnosed with Parkinson's?
    - Please type your answer here:
      …… years
      …… Months

11. What precautions did you use to protect yourself from getting the Coronavirus? (you can tick more than one choice):
    - Practicing social distancing (to stay at least 6 feet away from other people).
    - Practicing good hand washing technique (to wash your hands with soap and warm water for at least 20 seconds by rubbing your palms together, tips of your fingers, including your thumb, and the back of your hand).
    - Using hand sanitizer with at least 60% alcohol if soap and water are not available.
    - Staying at home and avoiding unnecessary exposure to crowds.
    - Shielding at home.
    - Eating healthy food that strengthen your immune system, such as whole food, like fruits and vegetables.
    - Getting some rest and sleep.
    - Other …..

12. The physical activity guidelines and recommendations are for people with Parkinson's to do 150 minutes of aerobic exercise per week. 'Aerobic' exercise includes physical activity that makes you breathe harder or makes your heart beat faster. Are you familiar with these recommendations and were you doing exercise according to the recommendations **before the quarantine**? (Please select one statement from below)

- Yes, I am familiar with the physical activity recommendations and guidelines, and I was doing the recommended amount of exercise (150 minutes per week) before the lockdown.
- Yes, I am familiar with the physical activity recommendations and guidelines, but I was not doing the recommended amount of exercise (150 minutes per week) before the lockdown.
- No I am not familiar with the physical activity recommendations and guidelines, but I was doing the recommended amount of exercise (150 minutes per week) before the lockdown.
- No, I am not familiar with the recommendations, but I was not doing the recommended amount of exercise (150 minutes per week) before the lockdown.

13. How many minutes of aerobic exercise per week you were performing, on average, **before the COVID-19 period**?
    - Please write the number of minutes here ……..

14. Please state the types of aerobic exercise you were performing **before the COVID-19 period** (for example: walking in the community, cycling, jogging, running …etc.):
    - I don't do aerobic exercise
    - walking outdoors
    - walking on a treadmill
    - cycling outdoors
    - cycling indoors on stationary cycle using just legs
    - indoors on stationary cycle using just arms
    - rowing outdoors
    - rowing on a row machine indoors
    - running outdoors
    - running on a treadmill
    - using a cross trainer
    - swimming
    - other (please specify)……..

15. Did you use any of the following devices/machines normally for indoor aerobic exercise, **before the COVID-19 period**?
    - Stationary cycling using a stationary cycle at home
    - Stepping exercise using stepping machine at home
    - Walking or running using a treadmill machine at home
    - Gardening
    - Other: ……..
    - No, I did not usually use any of the above before the COVID-19 period

16. How much did you feel that the advice for everybody to **"Stay at Home"** affected your physical activity :
    - Completely restricted my physical activity
    - Somewhat restricted my physical activity
    - Minimally restricted my physical activity
    - Did not change my physical activity at all
    - Minimally increased my physical activity
    - Somewhat enabled me to increase my physical activity
    - Significantly increased my physical activity
    - Explain: ……

17. How much did you feel that the advice for everybody to **"Stay Alert"** affected your physical activity :
    - Completely restricted my physical activity
    - Somewhat restricted my physical activity
    - Minimally restricted my physical activity
    - Did not change my physical activity at all
    - Minimally increased my physical activity
    - Somewhat enabled me to increase my physical activity
    - Significantly increased my physical activity
    - Explain: ……

18. Have you used any of the following to undertake physical activity level **during the COVID-19 period**? (You can choose more than one choice if applicable):
    - Telemedicine clinics
    - Web-based information portal
    - Virtual reality exercise games (video games, for example: Xbox, Wii or PlayStation)
    - Television (TV) exercise programmes
    - DVD exercise programmes
    - Web-based or virtual classes
    - Other (Please type here)…….
    - I did not do any form of physical activity at all

19. Which of the following might help you to exercise at home?
    - Telemedicine clinics
    - Web-based information portal
    - Virtual reality exercise games (video games, for example: Xbox, Wii or PlayStation)
    - DVD exercise programmes
    - Web-based or virtual classes
    - Stationary cycling using a stationary cycle at home
    - Stepping exercise using stepping machine at home

- Walking or running using a treadmill machine at home
- Gardening
- Other (Please type here)…….
- None of the above

20. **Before the COVID-19 period,** how regularly were you attending a Parkinson's UK exercise or fitness groups on a regular basis?
    - I was attending regularly more than once per week
    - I was attending regularly once per week
    - I was attending regularly more than once every two weeks
    - I was attending regularly once every two weeks
    - I was attending regularly once every three weeks
    - I was attending regularly once every month
    - I was attending but not on a regular basis
    - No, I was not attending at all.

21. Because of COVID-19 social distancing regulation, have you missed attending your Parkinson's UK exercise group?
    - No, I did not miss it.
    - Yes I missed attending.

If answered yes, move to Q17, if answered no move to Q18

22. What did you miss exactly by not attending your Parkinson's UK exercise group? You can choose more than one answer if you wish:
    - The social contact and communication with other group members.
    - The exercise itself and the physical activity.
    - Getting out of the house.
    - The journey from my house to the group location
    - Other points, please specify: ……

23. How do you feel about returning to your Parkinson's UK local group or exercise class?
    - I feel I need to get back to the group meetings and group exercise sessions
    - I feel this is too risky at the moment. Perhaps it is too early

24. Once lockdown have been lifted, will you go back to the Parkinson's UK exercise groups?

- Yes
- No

25. Since the start of the COVID-19 period, have you noticed that any of the following Parkinson's symptoms have got worse?
    - None of my symptoms have got worse
    - Tremor
    - Stiffness
    - Slowness of movement
    - Falls and dizziness
    - Freezing
    - Muscle cramps and uncontrolled movements
    - Pain
    - Fatigue
    - Sleep
    - Eating
    - Drinking
    - Talking
    - Memory problems
    - Anxiety
    - Dementia
    - Depression
    - Hallucinations and delusions
    - Shortness of breath
    - Other (please specify): ……

26. If you would like to, please add any additional comments about how the COVID-19 period and social distancing regulations have affected your life: *free text*

Thank you for taking the time to complete this questionnaire.

If you would like to submit your answers, please click on the 'submit' button.

Appendix 25 (The invitation email that has been sent to Parkinson's UK members to participate in study-2)

Hello,

We have an opportunity for people with Parkinson's to take part in some research looking at physical activities during lockdown.

Physical activity levels during COVID-19 in Parkinson's.

Aseel Aburub, a PhD student and Physiotherapy lecturer at Keele University, is investigating how physical activity may have changed for people with Parkinson's during COVID-19 lockdown.

The aim of the research is to better understand what changes may have happened and also to collect what people with Parkinson's prefer as physical activities and exercises.

What is involved?

You'll be asked to complete a short online questionnaire that should take on longer than 15minutes.

For more information, please read the information sheet

Who do the researchers need?

362 people diagnosed with Parkinson's and are happy to fill in an online questionnaire.

Interested in taking part?

Please go to the online questionnaire.

If you have problems accessing the questionnaire or questions about it please contact Aseel via email (a.a.m.aburub@keele.ac.uk) or phone (01782 733809) before 28 Oct 2020

Go to the questionnaire

This opportunity is not managed by Parkinson's UK.

Maybe this research isn't for you?

We realise that not every piece of research is right for everyone.

To find more opportunities near you, use our postcode searchable Take Part Hub which is regularly updated with new research looking for people like you.

Best wishes,
Research Participation Lead