Fatigue in people with Parkinson's disease; the effects of exercise.

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Abstract

This thesis comprises a systematic review and an intervention study. The systematic review included a meta-analysis and investigated treatment methods for fatigue. Fourteen studies (n=1890) were included in the systematic review and results from the meta-analyses (mean difference -0.25; CI -0.67:0.16; z-score 1.20 and mean difference -0.36; CI -0.78:0.06; z-score 1.67) concluded that currently there are no effective methods for the treatment of fatigue in people with Parkinson's disease.

The intervention study (n=105; intervention group: n=54; control group: n=51) comprised three parts. In the first part different measures of fatigue were explored in relation to activity levels and exercise tolerance. The second part investigated the adherence to the community based six-month exercise programme. The final part of the main study explored the effects of the exercise programme in a single blinded randomised controlled trial.

In the first part of the main study significant negative correlations were found between self-reported fatigue and respiratory exchange rate (r=-0.309; p=0.002); Rate of Perceived Exertion breath (r=-0.282; p=0.024); Rate of Perceived Exertion of the legs (r=-0.261; p=0.033) and GENEActiv light activity (r=-0.209; p=0.049). The correlation between self-reported fatigue and the respiratory exchange rate implies that self-reported fatigue may decrease if exercise tolerance is improved by for example an exercise programme.

The second part of the main study demonstrated an adherence of 24 out of 54 in participants that were randomly assigned to the exercise programme, with no intervention-related adverse events, showing that the proposed programme was feasible for people with Parkinson's disease.

The final part of the study, exploring the effects of the exercise programme in all patients, showed a small reduction in disease severity (Unified Parkinson's disease Rating Scale part III, Cohen's d: 0.25; 95% confidence interval: 0.02-0.49) in the treatment group compared to the control group. Scores on the self-reported fatigue decreased slightly in both groups subsequent to the exercise programme, but did not reach significance.

This is the first study to explore the effects of a combined (aerobic and anaerobic) exercise community based longer term (six months) exercise programme on fatigue in people with Parkinson's disease. Results show that both arms of the interventions were adhered to reasonably well and small effects were found showing exercise improved disease severity in people with Parkinson's disease; no effects were found in relation to fatigue.

Presentations and Publications relevant to the thesis

The work contained in this thesis is that of the author. The following publications contain, in part, findings from the thesis or relevant findings discussed in the thesis that are the work of the author and collaborators.

Franssen, M., Collett, J., Dawes, H. “Engagement of and adherence to a community based exercise programme in people with Parkinson’s disease”. Conference: Society for Research and Rehabilitation. 2015: February 3.

Franssen, M., Collett, J., Wade, D., Dawes, H. “The relationship of fatigue with perceived and measured physical functioning and activity levels in people with Parkinson’s disease”. *Non-Motor Dysfunctions in Parkinson’s disease and Related Disorders.* 2014: December 5-7 (conference proceedings).

Franssen, M., C. Winward, et al. (2014). "Interventions for fatigue in Parkinson's disease: A systematic review and meta-analysis." Mov Disord 29(13): 1675-1678.

Franssen, M., Collett, J., Meaney, A., Bogdanovic, M., Wade, D., Farmer, A., Tims, M., Izardi, H., Dawes, H. “Motor symptoms and Quality of Life in people with Parkinson's disease”. Conference: Society for Research and Rehabilitation (Clinical Rehabilitation), Volume: 27

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Abbreviations

bpm	Beats per minute
CM	Centromedian nucleus of thalamus
CMa	Cingulate Motor area
COMT	catechol-*O*-methyltransferase
CR10	Category Ratio Scale 10
DOPA	dihydroxyphenylalanine
fMRI	Functional magnetic resonance imaging
FSS	Fatigue Severity Scale
GABA	Gamma aminobutyric acid
GP	General Practitioner
GPe	Globus Pallidus External
GPi	Globus Pallidus Internal
HR_{max}	Maximal Heart Rate
ICF	International Classification of Functioning, Disability and Health
L-Dopa	L-3,4- dihydroxyphenylalanine
M1	Primary Motor Cortex
MDS-UPDRS	Movement Disorder Society Sponsored Revised Unified Parkinson's Disease Rating Scale
MFI	Multidimensional Fatigue Inventory
MH	Mental Health
MOA-B	Monoamine oxidase inhibitor B
MWT	Minute Walk Test
NADH	Nicotinamide adenine dinucleotide
PASE	Physical Activity Scale for the Elderly
PEDro	Physiotherapy Evidence Database
PFS	Parkinson's Fatigue Scale
PH	Physical Health
PMC	Premotor cortex
POMS	Profile of Mood states
PPN	Penduculopetine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RER	Respiratory Exchange Rate
RPEbreath	Rating of Perceived Exertion for breathing
RPElegs	Rating of Perceived Exertion for legs
SD	Standard Deviation
SF-36	Short Form 36
SMA	Supplementary Motor Area
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
Th	Thalamus
TMS	Transcranial Magnetic Stimulation
$\dot{V}CO_2$	Rate of elimination of carbon-dioxide
$\dot{V}O_2$	Rate of oxygen consumption

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Chapter 1 Parkinson's disease

Summary

This chapter provides a general introduction to Parkinson's disease. The pathology of Parkinson's disease is explained, focusing on pathways in the brain, and the differences in these pathways between healthy people and people with Parkinson's disease. Aetiology, prevalence and incidence are discussed, followed by clinical features of Parkinson's disease, including motor and non-motor symptoms with particular emphasis on fatigue. Treatment methods for Parkinson's disease are outlined focusing with emphasis on exercise as a treatment, leading to the three main aims for the thesis.

1.1 Introduction

Parkinson's disease is a progressive neurological movement disorder, mostly affecting older people (Parkinson's UK 2015). Symptoms suggestive of Parkinson's disease have been described for many centuries, dating back to Egyptian papyrus and Sanskrit texts (Playfer and Hindle 2008). Parkinsons was first distinctively described by James Parkinson in 1817; he described individuals having *'involuntary tremulous motion, with lessened muscular power, in parts not in action and, even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellect being injured'* (Foltynie, Lewis et al. 2003). There are different forms of Parkinsonism including Idiopathic Parkinson's disease; atypical parkinsonian syndromes and other neurodegenerative disorders; secondary or symptomatic causes like drug induced parkinsonism (Playfer and Hindle 2008). Throughout this thesis, the focus will be on Idiopathic Parkinson's disease, shortened to Parkinson's disease.

1.2 Pathology

1.2.1 Normal brain pathways

Most normal movement, voluntary as well as involuntary, is controlled in the basal ganglia in the brain (Kandell 2000). The basal ganglia receive their primary input from the cerebral cortex and send their output to the brain stem and, via the thalamus, back to the prefrontal, premotor, and motor cortices (Kandell 2000). The basal ganglia consist of the striatum, comprising of the caudate nucleus, putamen and the ventral striatum; the globus pallidus, which consist of the and external Globus Pallidus; the subthalamic nucleus; and the substantia nigra, which consists of the pars compacta and the pars reticulate (see Figure 1) (Hall 2016). The striatum receives most of the input into the basal ganglia coming from the

cerebral cortex, thalamus and brain stem (Hall 2016). The neurons from the striatum project to the globus pallidus and substantia nigra, these give most of the output from the basal ganglia. The cells of the internal Globus Pallidus and pars reticulate use γ-aminobutyric acid gamma aminobutyric acid (GABA) as neurotransmitter. GABA is the most common of the inhibitory amino acid central nervous system neurotransmitters. This transmitter produces hyperpolarization by opening either chloride or potassium channels (Martin 2006). The cells of the pars compacta are dopaminergic. In neurons that utilize dopamine as neurotransmitter, the biogenic amine synthetic pathway stops with dopa decarboxylase, the enzyme that synthesizes dopamine. Dopamine is involved in many forebrain circuits associated with emotion, motivation, and reward (Krebs, Weinberg et al. 2012) and it acts on two types of receptors, both of which are linked to adenylate cyclase, cyclic adenosine mono phosphate second messenger systems. Stimulation of D_1 receptors causes an increase in cyclic adenosine monophosphate levels, whereas stimulation of D_2 receptors cause a decrease in cyclic adenosine monophosphate, in the postsynaptic neuron (Shepherd 1994).

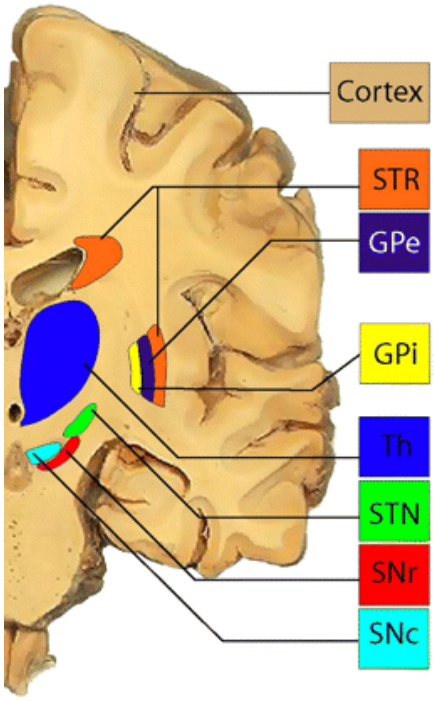

Figure 1: Basal Ganglia

Abbreviatons: STR: striatum; GPe: globus pallidus pars externa; GPi: globus pallidus pars interna; Th: thalamus; subthalamic nucleus; STN: subthalamic nucleus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta (Pereira and Aziz 2006) (reprinted with permission).

Dopamine is an important neurotransmitter in the sympathetic nervous system. Firstly, tyrosine is transported into the sympathetic nerve axon and it is converted to DOPA by tyrosine hydroxylase. Then DOPA is converted into dopamine by DOPA decarboxylase, which is then converted into norepinephrine by dopamine-β-hydroxylase. Norepinephrine is the primary neurotransmitter for postganglionic sympathetic adrenergic nerves (Unglaub Silverthorn 2007).

Opposite to norepinephrine, there is the neurotransmitter acetylcholine that plays an important role in the parasympathetic nervous system. Acetylcholine is a neurotransmitter that is synthesized by binding choline to acetyl coenzyme A (Martin 2006). The binding is produced by choline acetyltransferase. Neurons that contain acetylcholine or choline acetyltransferase are called cholinergic neurons, which are found mostly in the motor system. The chemical binds to acetylcholine receptors which produces an action potential that results in muscle contraction (Martin 2006). Muscle contraction consists of myosin binding to actin, contracting, releasing the actin, and then binding to the next actin in a new cycle (Krans 2010). Finally, the subthalamic nucleus has glutaminergic cells, which are the only excitatory projections of the basal ganglia (Kandell 2000, Hall 2016).

Release of the neurotransmitters described above (dopamine and GABA) are modulated by serotonin receptors (Kandell 2000, Hall 2016).

Movement is controlled via a direct and an indirect pathway (Kandell 2000). The direct pathway in the motor loop starts with an excitatory connection from the cortex cells in the putamen. The putamen cells make inhibitory synapses on neurons in the external globus pallidus, from there to the subthalamic nucleus in a GABA-ergic pathway, and finally from there to the output nuclei in an excitatory glutaminergic projection. From there is an excitatory connection via the thalamus to the motor cortex where the discharge of movement-related cells is facilitated. This circuit is a positive feedback loop; dopamine normally facilitates the direct motor loop by activating cells in the putamen (see Figure 2) (Kandell 2000).

The indirect pathway goes from the cortex to the striatum, then to the external pallidum, then to the subthalamic nucleus (which then projects to the pallidum and to the substantia nigra), and then, through the thalamus, back to the cortex (see Figure 2). So the indirect pathway goes through the subthalamic nucleus, which is bypassed by the direct pathway (Latash 1998). The indirect pathway increases inhibition of the thalamus (Kandell 2000).

Both pathways are affected differently by the dopaminergic projection from the substantia nigra pars compacta to the stratium. Stratial neurons that project in the direct pathway have D1 dopamine receptor that facilitates transmission, while those that project in the indirect pathway have D2 dopamine receptors that reduce transmission. Both have the same net effect and reduce inhibition of the thalamocortical neurons facilitating movements initiated in the cortex (Kandell 2000).

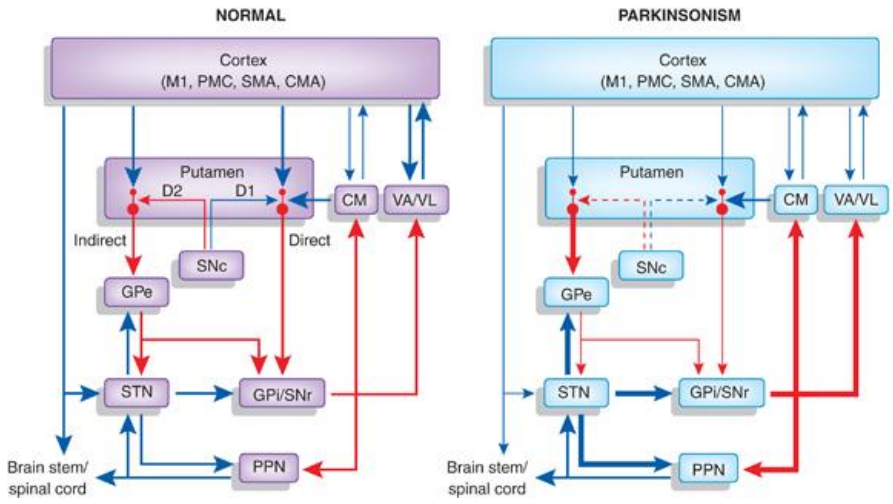

Figure 2: Overview of pathways in the brain for normal and parkinsonism

Red arrows indicate inhibitory connections; blue arrows indicate excitatory connections. The thickness of the arrows corresponds to their presumed activity. Abbreviations: CM, centromedian nucleus of thalamus; CMA, cingulate motor area; D1,D2, dopamine receptor subtypes; M1, primary motor cortex; PMC, premotor cortex, PPN, pendunculopotine nucleus; SMA, supplementary motor area; STN, subthalamic nucleus (Galvan and Wichmann 2008) (reprinted with permission).

1.2.3 Pathways in Parkinson's disease

Parkinson's disease affects both the direct and the indirect pathways. Parkinson's disease occurs when dopaminergic cells in the caudate nucleus, putamen, substantia nigra and globus pallidus degenerate and die, with greater loss in the putamen than in the caudate nucleus (Martin 2006). This results in an increase in activity in the indirect pathway and decreased effect in the direct pathway. Both these changes lead to an increased activity in the interpallidal segment, which results in increased inhibition of thalamocortical and midbrain tegmental neurons which gives hypokinetic features (Kandell 2000). The nigrostratial neurons have a high degree of plasticity, with the residual stratial neurons compensating for the loss of dopamine by increasing their activity (Martin 2006), and symptoms of Parkinson's disease do not start occurring until 60-80% of the dopaminergic

neurons in the brain have degenerated (Grosset 2009). The rate of clinical progression is directly related to the loss of dopamine-producing cells (Boelen 2009).

Besides degeneration of dopaminergic cells, in people with Parkinson's disease, there is degeneration of norepinephrine neurons of the locus coeruleus (Sulzer and Zecca 2000). Norepinephrine is a key neurotransmitter involved in wakefulness and attention (Krebs, Weinberg et al. 2012).

1.3 Aetiology

The exact cause of degeneration of dopaminergic neurons in the brain is still unknown. It is however believed that environmental and genetic factors contribute to the onset of Parkinson's disease (de Lau and Breteler 2006). There is growing evidence that Parkinson's disease may arise from a variety of problems causing damage or death of the dopaminergic neurons (Schapira and Tolosa 2010).

Age is the single most important risk factor for developing Parkinson's disease (Schapira and Jenner 2011). Age may cause an increased vulnerability of dopaminergic neurons to toxic insult because of increasing failure of normal cellular physiological and biochemical processes (Mattson and Magnus 2006). Prevalence rates for Parkinson's disease in epidemiological studies show an exponential increase from one per 1000 in the general population to one in 50 in people 80 and older (Playfer and Hindle 2008). The next important risk is a family history of Parkinson's disease impacting about ten per cent of the cases of Parkinson's disease (de Lau and Breteler 2006). Evidence for a genetic role has come from a number of sources including twin, family, case control and epidemiological studies (Playfer and Hindle 2008). Furthermore, a number of environmental factors, such as pesticides, seem to be associated with an increased risk of developing Parkinson's disease (Swinn 2005). A meta-analysis by Priyadarshi et al. (2000) concluded that the majority of the studies reported consistent elevation in the risk of Parkinson's disease with exposure to pesticides. The combined odd ratio of the studies was 1.94 [95% confidence interval (95% CI) 1.49-2.53] for all the studies indicating that that exposure to pesticides may be a significant risk factor for developing Parkinson's disease (Priyadarshi, Khuder et al. 2000). Post-mortem studies have implicated oxidative damage (Greenamyre and Hastings 2004); antioxidants including vitamin C and E have been examined for a potentially protective role, but there is no consensus yet (Playfer and Hindle 2008, Van Maele-Fabry, Hoet et al. 2012). Morens et al (1995) conducted a systematic review and found consistently an association between cigarettes and lower chance of developing

Parkinson's disease (Morens, Grandinetti et al. 1995). One thing that has repeatedly shown to be protective factor is smoking cigarettes. The first suggested mechanism for this phenomenon is that nicotine causes dopamine release and up-regulation of dopamine receptors, which may mask the early signs of the disease. Furthermore, cigarette smoke contains monoamine oxidase inhibitor B (MAO-B) (one of the drug treatment methods that will be discussed later) (de Lau and Breteler 2006). Coffee drinking has also shown to be associated with a reduced risk of developing Parkinson's disease, the mechanism of this is unknown (Playfer and Hindle 2008, Derkinderen, Shannon et al. 2014).

1.5 Prevalence and Incidence

In industrialised countries Parkinson's disease is present in about 0.3% of the entire population and in about one per cent in the people above 60 years (de Lau and Breteler 2006). Studies in the United Kingdom have shown that Parkinson's disease is more likely to occur in men than in women (PDS 2008). Currently, one in 500 people in the United Kingdom, or 127 000 nationwide, have Parkinson's disease (Parkinson's UK 2015). Furthermore, there is an annual incidence of thirteen per 100 000 (DoH 2005). The number is expected to rise to 162 000 by 2020. Parkinson's Disease cost the National Health Service in 2012/2013 212 million pounds (Parkinson's UK 2013).

In spite of increasing understanding of the pathophysiology and genetics the prognosis of Parkinson's disease remains unclear (Macleod, Taylor et al. 2014). A recent systematic review concluded that Parkinson's disease is associated with increased mortality and a decrease in survival of approximately 5% per year of follow up (Macleod, Taylor et al. 2014). At present there is no known cure (Parkinson's UK).

1.6 Clinical features

Parkinson's disease presents with both motor and non-motor symptoms. The most common features will be discussed below.

1.6.1 Motor symptoms

The main motor symptoms of Parkinson's disease include paucity of movement, rigidity, and tremor (Grosset 2009) affecting gait, mobility (Zampieri, Salarian et al. 2011) and arm function, including difficulties with handwriting (Tresilian, Stelmach et al. 1997, Van Gemmert, Adler et al. 2003). The symptoms will be discussed in more detail below.

Paucity of movement: Paucity of movement consists of slowness of initiation of movement with progressive reduction in speeds and amplitude of repeated movement. It consists of

bradykinesia (slowness of movement), hypokinesia (reduced movement) and akinesia (inability to initiate movement) (Swinn 2005).

Rigidity: Rigidity is the increase in resistance to passive movements around a joint. Rigidity tends to be more evident in flexors, which contributes to a flexed posture (Playfer and Hindle 2008).

Tremor: Tremor is an involuntary rhythmic oscillatory movement of a body part (Playfer and Hindle 2008). There are different types of tremor including postural tremor, which is seen with a sustained posture against gravity; action tremor, which is tremor that is present during voluntary contraction; and kinetic tremor, which occurs during a movement (Playfer and Hindle 2008).

Gait and balance: As described previously the dopaminergic deficit in Parkinson's disease causes reduction in the excitatory drive of the motor cortex which can affect motor unit recruitment and results in muscle weakness. Studies have demonstrated that muscle strength is related to gait (Lima, Scianni et al. 2013). People with Parkinson's disease often walk with a reduced gait speed, shorter stride length, stooped posture and reduced arm swing (Schaafsma, Giladi et al. 2003). Parkinson's disease patients typically walk at 40-60 meters per minute compared to normal 75-90 metres per minute with a reduced stride length of one meter or less compared to 1.2 to 1.5 meters in healthy older people (Playfer and Hindle 2008). Additional issues with gait in people with Parkinson's disease are freezing, which occurs in about half of the people with Parkinson's disease, and possibly associated with that gait hypokenisia and gait festination (Morris, Iansek et al. 2008). Furthermore, people with Parkinson's disease have a reduced balance which increases their risk for falls (Allen, Sherrington et al. 2011).

1.6.2 Non-motor features

Lately, there has been more attention for non-motor symptoms like fatigue, and depression (Leonardi, Raggi et al. 2012). Non-motor symptoms have been suggested to contribute to disability, quality of life, and shortened life expectancy (Chaudhuri, Healy et al. 2006). Below, several non-motor symptoms in people with Parkinson's disease are discussed.

Cognitive and neuropsychiatric symptoms: these symptoms include cognitive impairment, anxiety, apathy, delirium, hallucinations, panic attacks and depression (Chaudhuri, Tolosa et al. 2014). Core symptoms of depression are a depressed mood, loss of pleasure, and feelings of worthlessness or guilt (NHS 2014). Depression is one of the most common non-

motor symptoms and affects up to 50% of people with Parkinson's disease (Dooneief, Mirabello et al. 1992). One large study exploring depression in 1449 people with Parkinson's disease, showed that depression was more common in females than males; in individuals with more advanced stages of Parkinson's disease; and in people with dementia (Riedel, Heuser et al. 2010). Although it is unlikely that depression is a direct result of dopamine depletion in the brain, other changes in neurotransmitter systems that could occur as a consequence of dopamine depletion may be involved in the pathophysiology of depressive symptoms in Parkinson's disease (Playfer and Hindle 2008).

Sleep disorders and dysfunctions: including excessive daytime somnolence, sudden onset of sleep, insomnia, non-rapid eye movement parasomnias, rapid eye movement sleep behaviour disorder, restless leg syndrome, periodic leg movements, and sleep-disordered breathing (Chaudhuri, Tolosa et al. 2014).

Autonomic dysfunction: including bladder urgency, frequency, nocturia, orthostatic hypotension, post-prandial hypotension, sexual dysfunction, erectile dysfunction, and thermoregulatory abnormalities (Chaudhuri, Tolosa et al. 2014).

Gastrointestinal symptoms: including dribbling of saliva, dysphagia, ageusia, constipation, faecal incontinence, nausea, reflux, and vomiting (Chaudhuri, Tolosa et al. 2014).

Other non-motor symptoms: including functional anosmia, visual disturbances, weight gain, weight loss, and fatigue (Chaudhuri, Tolosa et al. 2014). Fatigue is defined as 'a sense of tiredness, lack of energy or total body give out' by the Fatigue Assessment Inventory (Friedman, 2007). Fatigue affects 40% to 56% of patients with Parkinson's disease (Herlofson and Larsen 2003, Friedman, Brown et al. 2007, Okuma, Kamei et al. 2009) which is significantly higher than in age matched controls and age matched geriatric patients (Goulart, Godke et al. 2009). More than half of the people with Parkinson's disease rank fatigue as one of their three most severe symptoms (Friedman and Friedman 1993, Brown, Dittner et al. 2005). Furthermore, a recent review places 'What interventions are effective for reducing or managing unexplained fatigue in people with Parkinson's?' in the top 26 priorities for the management of Parkinson's disease, showing that fatigue is an important issue for people with Parkinson's Disease and needs to be addressed (Deane, Flaherty et al. 2014). Finally, qualitative research shows that woman with Parkinson's disease experience living with fatigue living with a body that serves as a barrier to daily living (Olsson, Stafstrom et al. 2013).

A theory on the origin of fatigue in Parkinson's disease involves the basal ganglia. There are three different ways the basal ganglia may be involved in fatigue. First of all, the dorsolateral prefrontal circuit in the caudate is involved in the dopamine loss seen in Parkinson's disease; secondly, dopamine antagonists induce fatigue and loss of motivation (Chaudhuri and Behan 2000). Some studies observed that levodopa is more effective than placebo in reducing physical fatigue, which suggest that dopamine deficiency may be involved in causing fatigue in Parkinson's disease (Fabbrini, Latorre et al. 2013). However, clinical studies do not find a correlation between fatigue and doses of dopaminergic medications (Fabbrini, Latorre et al. 2013). Finally, disruption of normal basal ganglia derived algorithm of a sequential task processing mechanism would delay the initiation of a task and prevents smooth execution of a task which is a feature that is typical in patients with central fatigue (Chaudhuri and Behan 2000). Previously, several neurotransmitters have been described, including serotonin, dopamine, norepinephrine and GABA. Below, the influence of these neurotransmitters on fatigue will be described. Firstly, it is shown that an increase in serotonin can result in sleep, and it is hypothesized that that an increase in serotonin could also cause fatigue (Foley and Fleshner 2008). Furthermore, it is observed that altered concentrations of dopamine, norepinephrine, and GABA can also influence fatigue (Foley and Fleshner 2008).

Quality of life: the motor symptoms and non-motor symptoms that people with Parkinson's disease experience all contribute to a lower quality of life. The World Health Organization defines quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concern (World Health Organization 1997). Quality of life in Parkinson's disease includes perception of symptoms, level of fitness, self-image, satisfaction with family life, work, the economic situation, the interaction with other people, social support, disease severity, social status, social and living condition (Opara, Brola et al. 2012); quality of life in people with Parkinson's disease is measured by means of questionnaires that address these issues (Opara, Brola et al. 2012). People with Parkinson's disease have a lower quality of life than age related controls (Hariz and Forsgren 2011).

1.7 Diagnosis

There are no biological markers for a definite diagnosis of Parkinson's disease, it is diagnosed on clinical grounds, which results in misdiagnosis. Only 75% of patients with Parkinson's disease at death meet the neuropathological criteria for idiopathic Parkinson's disease (Foltynie, Lewis et al. 2003). Criteria set to improve the accuracy of clinical

diagnosis and accepted as the best clinical practice are the United Kingdom Parkinson's disease Society Brain Bank diagnostic criteria (see appendix 1). Parkinson's disease is diagnosed when bradykinesia is present and either tremor, rigidity or postural instability (National Institute for Health and Clinical Excellence 2006). Furthermore, asymmetric symptom onset and a good response of the symptoms to levodopa are supportive for a diagnosis of Parkinson's disease (de Lau and Breteler 2006). Since levodopa therapy is normally used to treat early symptoms, Parkinson's disease may not be ruled in or out until later in the disease progression (Boelen 2009). Diagnosis of Parkinson's disease could be could be confused with other conditions, such as essential tremor, multiple system atrophy, progressive supranuclear palsy, drug-induced parkinsonism and vascular Parkinson's (Parkinson's UK 2014). A definite diagnosis of Parkinson's disease requires post-mortem confirmation (de Lau and Breteler 2006, National Institute for Health and Clinical Excellence 2006).

1.8 Treatment methods for Parkinson's disease

Different forms of treatment have been suggested for people with Parkinson's disease including drugs, surgery and exercise. Below these different treatments will be discussed.

The main treatment for Parkinson's disease is drug therapy (Parkinson's UK). Drugs are used to treat the symptoms of Parkinson's disease but not the underlying cause. Since symptoms occur as a result of low levels of dopamine, treatment is aimed at restoring dopamine levels to normal (Parkinson's UK). A recent study by the Parkinson's disease MED collaboration group concluded that the overall balance of risks and benefits favours levodopa over levodopa-sparing therapy with better patient related quality of life in the short as well as the long term (Gray, Ives et al. 2014).

There are four main groups of drug therapies: i) drugs that replace dopamine (levodopa); ii) drugs that prevent the breakdown of dopamine (levodopa-sparing therapy): cathechol-*O*-methyltransferase (COMT) and MOA-B inhibitors; iii) drugs that mimic the action of levodopa (dopamine agonists); iv) drugs that block the action of acetylcholine (anticholinergics).

1.8.1 Levodopa

The most effective treatment to date is dopamine replacement drug, levodopa (Gray, Ives et al. 2014). Gray et al. (2014) conducted a large study where they included 1620 patients into a Randomised controlled trial and people were assigned to Levodopa, dopamine

agonists or MOA-B. Results showed that levodopa treatment achieved better scores than the dopamine agonists or MAO-B on the primary Parkinson's disease Questionnaire 39 mobility outcome, and Euroqol-5D generic quality-of-life measures. Furthermore, clinician-rated disease status by Hoehn and Yahr staging was significantly improved (Gray, Ives et al. 2014). Levodopa is the precursor to dopamine, and once it enters the brain it is converted to dopamine by the enzyme dopa-decarboxylase. Dopamine is synthesized in the brain from the amino acid L-tyrosine via the intermediate compound, L-3,4-dihydroxyphenylalanine (L-dopa). Levodopa is often administered in combination with carbidopa or benserazide, which are dopa decarboxylase inhibitors; they allow greater concentrations of levodopa entering the brain (Boelen 2009). Levodopa has a short mode of action because of its short half-life and due to gradually diminishing ability of the presynaptic nerve terminals to store dopamine as the disease progresses. This results in wearing off of the medication and causes ON and OFF phases. Levodopa has side effects including sleep disturbance, vivid dreams, hallucinations, delusions or organic confusional psychosis. Furthermore, levodopa therapy can induce dyskinesias (Fabbrini, Brotchie et al. 2007). Levodopa is often chosen as treatment for fatigue in people with Parkinson's Disease (Lou, Kearns et al. 2003, Schifitto, Friedman et al. 2008) since it restores dopamine levels in the brain and higher dopamine levels are associated with less exhaustion (Foley and Fleshner 2008).

1.8.2 COMT and MOAB inhibitors

Dopamine is inactivated enzymatically by the action of both MOA, an enzyme associated with mitochondria and present in two forms, termed A and B, and COMT, an enzyme localized primarily in glial cells in the brain (Watts and Koller 1997). Inhibition of the COMT enzyme allows the achievement of more stable and sustained plasma levodopa levels, which increases the amount of levodopa that enters the brain. Side effects of this drug are dyskinesia and nausea (Movement Disorder Society 2002, Swinn 2005). MOA-B blocks the metabolism of dopamine which could enhance endogenous dopamine and dopamine from levodopa (Fox, Katzenschlager et al. 2011). Side effects are insomnia, hallucinations and vivid dreams (Swinn 2005). Research has shown that modafinil (the active component in MOA-B) stimulates, norepinephrine, serotonin (5-hydroxytryptamine), and dopamine, making it a treatment method for fatigue (Stocchi 2013, Franssen, Winward et al. 2014).

1.8.3 Dopamine agonists

Dopamine agonists act on pre- and postsynaptic dopamine receptors. Reasons to use dopamine agonists are: direct action; more reliable absorption and transport to the brain than levodopa; longer half-life than levodopa; no generation of free radicals; possible neuroprotective qualities (Movement Disorders Society 2002, Swinn 2005). Side effects are: neuropsychiatric complications; sleep disturbance and excessive daytime somnolence; postural hypotension (Movement Disorders Society 2002, Swinn 2005).

1.8.5 Anticholinergics

Anticholinergics were the first widely accepted treatment for parkinsonism (Movement Disorder Society 2002). Anticholinergics block interstratial cholinergic transmission. This helps to restore the balance of activity between the cholinergic and dopaminergic system which become imbalanced as a result of dopamine loss (Movement Disorder Society 2002). Patients may experience neuropsychiatric side effects (Movement Disorder Society 2002, Swinn 2005).

1.8.6 Surgical treatment

Surgical treatment for Parkinson's disease has been performed since the 1940s and involved ablative procedures of the thalamus and internal globus pallidus. These surgical treatments were replaced by deep brain stimulation in the 1990s (Bronstein, Tagliati et al. 2011). Deep brain stimulation is a treatment especially for people with advanced Parkinson's disease when the disease and the side effects due to medication are severely disabling. The most commonly targeted areas are the motor portions of internal globus pallidus and subthalamic nucleus and the thalamus (Fox, Katzenschlager et al. 2011). Recent trials have found that deep brain stimulation at either target side was found to alleviate parkinsonian motor signs, and to reduce drug-induced side effects (Wichmann and Delong 2011). In patients with advanced Parkinson's disease it improves quality of life. The risk of surgical complications is small, however the stimulation may produce significant side effects including induction of paresthesias, involuntary movements, worsening of gait or speech, gaze deviation or paralysis, and cognitive and mood side effects (Wichmann and Delong 2011).

1.9 Exercise

As described, drug treatment can wear off and comes with side effects; furthermore, neurosurgical treatment comes with obvious risks and limitations. An alternative treatment that possibly slows disease progression down and stimulates movement control that does not induce side effects or has obvious risks and limitations is exercise therapy (Falvo, Schilling et al. 2008).

Exercise is defined as a planned, structured physical activity, which aims to improve one or more aspects of physical fitness (Morris and Shoo 2004). Physical fitness is defined by the American College of Sports Medicine as 'Physical fitness is the ability to perform moderate to vigorous levels of physical activity without undue fatigue and the capability of maintaining such ability throughout life' (ACSM 2005).

Inactivity is known to raise the risk of chronic condition such as cardiovascular diseases, obesity, type-II diabetes, cancer, osteoporosis and fatigue (Berlin, Kop et al. 2006, Pedersen and Saltin 2006). Furthermore, inactivity is associated with reduced aerobic capacity, atrophy and loss of muscle strength (Convertino 1997, Convertino, Bloomfield et al. 1997). It is well-known that exercise has general health benefits including improvement of cardiovascular and cerebrovascular health, reduction of osteoporosis and age related sarcopenia, improvement of psychological affect, and possibly a general anti-inflammatory effect (Ahlskog 2011). It is suggested that on-going vigorous exercise may have a neuroprotective effect as well (Ahlskog 2011).

Research has shown that exercise enhances the synthesis of catecholamines, including norepinephrine and dopamine (Chaouloff, Laude et al. 1987). Furthermore, Fisher et al. (2004) found an increase in expression of dopamine D2 receptor mRNA and down regulation of the dopamine transporter protein within the striatum, changes that are consistent with increased dopaminergic signalling in mice that were exercising on a treadmill five days a week for 30 days (Fisher, Petzinger et al. 2004). One possible mechanism by which exercise may drive activity-dependent neuroplasticity in Parkinson's disease may be through mitigating corticostriatal hyperactivity by modulating dopaminergic signalling, and/or diminishing glutamatergic neurotransmission (Petzinger, Fisher et al. 2010). Furthermore, physical exercise-induced changes in the concentrations of different neurotransmitters, including dopamine, noradrenaline, and serotonin (5-hydroxytryptamine) (Cordeiro, Guimaraes et al. 2014). This mechanism may explain why exercise could be a possible treatment for fatigue.

Exercise can be split up into two major forms, aerobic and anaerobic exercise, that have different effects on health benefits, Parkinson's disease symptoms, and fatigue.

1.9.1 Aerobic exercise

Aerobic exercise is defined as physical exercise of low to high intensity that depends primarily on the aerobic energy-generating process (Plowman and Smith 2008). People who do regular activity have a lower risk of many chronic diseases, such as heart disease, type 2 diabetes, stroke, and some cancers (NHS 2013). Exercise has been shown to improve cognitive function in healthy populations (Guiney and Machado 2013), neurological populations (McDonnell, Smith et al. 2011), and has been shown to prevent age-related cognitive decline (Bherer, Erickson et al. 2013). Furthermore, it has been shown that aerobic exercise improves executive functions (Guiney and Machado 2013) and finally, exercise is often used as a treatment method for depressed mood (Silveira, Moraes et al. 2013). As described above, animal studies have shown that aerobic exercise increases the concentration of dopamine in the striatum of the rat brain (Hattori, Naoi et al. 1994), which represents a possible mechanism of the benefits of aerobic exercise for both Parkinson's disease in general and fatigue specifically. As discussed, people with Parkinson's disease have balance and gait issues and a lower quality of life than age matched healthy individuals (Schaafsma, Giladi et al. 2003, Allen, Sherrington et al. 2011, Hariz and Forsgren 2011). A systematic review and meta-analysis looking into the effects of aerobic exercise on Parkinson's disease included eighteen studies and found a positive effect on the motor actions, balance, and gait, but not quality of life (Shu, Yang et al. 2014). Exercises included walking, treadmill training, aerobic exercise, tai chi, and dance showing a range of aerobic exercises with durations ranging from 20 to 60 minutes. Furthermore, duration of the exercise programmes varied from 3 to 64 weeks (Shu, Yang et al. 2014). As the overall review finds positive effects it would be important to included aerobic exercise into exercise programmes delivered to people with Parkinson's disease; however thought should go into looking at optimal intensity, dose and duration of any programme. Furthermore, another review did find a positive effect of exercise on quality of life (Goodwin, Richards et al. 2008). They included four studies with different exercises, with the programme ranging from six to 26 weeks. Again, as studies with different doses and durations were included, more research is needed into the doses and durations of an optimal exercise programme.

1.9.2 Anaerobic exercise

In strenuous exercise the energy demands can exceed the oxygen supply or its rate of use (Grosset 2009, McArdle, Katch et al. 2010). In this type of exercise (anaerobic exercise), the respiratory chain cannot process all of the hydrogen joined to the nicotinamide adenine dinucleotide (NADH) (McArdle, Katch et al. 2010) and lactate is then produced from the pyruvate faster than the body can process it, causing lactate concentrations to rise. Anaerobic exercise has shown to improve muscle mass, and neuromuscular performance (Taaffe, Duret et al. 1999) in a randomised controlled trial including 53 participants were people were randomly assigned to either high intensity progressive resistance training for 24 weeks or control, which could potentially reduce the risk of falls and fractures in older adults, including people with Parkinson's disease (Taaffe, Duret et al. 1999). Furthermore, muscle weakness, often apparent in people with Parkinson's disease is likely to be associated with fatigue in this population (Falvo, Schilling et al. 2008).

1.9.3 Exercise in Parkinson's disease

A systematic review and meta-analysis by Goodwin et al. (2008) that included fourteen studies and 495 people with Parkinson's disease, concluded that exercise had a positive effect on physical functioning, health related quality of life, strength, balance and gait, but no positive effects on depression and falls (Goodwin, Richards et al. 2008). In this review all studies that researched exercise and an outcome that included physical performance of functioning, falls or health related quality of life; resulting in a variety of exercise studies (in terms of sort of exercise, duration of exercise, disease severity, and number of participants) being researched and pooled together, meaning that results should be interpret with care. A more recent review of Tomlinson et al. (2012) that included 39 randomised controlled trials including 1827 people with Parkinson's disease investigating physiotherapy confirmed the positive effects found in gait, functional mobility and physical functioning in the short term (mean follow up < three months). They did not, however, find a positive result of physiotherapy on quality of life measured by the Parkinson's disease Questionnaire 39 (Tomlinson, Patel et al. 2012). The authors discuss the often inadequate methodological quality and reporting of the trials. Previous studies indicate that there is evidence that if the methodological quality of a study is poor (no allocation concealment; no blinding), larger effects of intervention is reported than in higher quality trials (Egger, Juni et al. 2003). Therefore, it is important to assess methodological quality of each trial. Results from trials with a low methodological quality should be interpret with caution. The authors suggest that larger randomised controlled

trials are needed, particularly focusing on improving trial methodology and reporting, but also looking into longer periods of time (Tomlinson, Patel et al. 2012). Systematic reviews have been done into resistance training as well. One of the systematic reviews provides evidence that progressive resistance exercise can improve strength and several measures of functional ability (Lima, Scianni et al. 2013). The study included only four studies, including 92 participants, indicating that the results need to be interpret with caution due to the small numbers included, and that research into resistance training is scarce (Lima, Scianni et al. 2013) The PEDRO score of the studies ranging between 3 and 8 shows relatively poor methodological quality, which means, as indicated above, that results should be interpret with care. Finally, in the meta-analyses, only post intervention scores were used, discarding any differences between groups at baseline, and two out of four interventions used resistance training in combination with balance training or treadmill walking, meaning that any improvements in functional ability need to be interpret with caution as they might be a result of the treadmill or balance training rather than the resistance training. Another recent systematic review by Uhrbrand et al. (2015) investigating resistance training, endurance training and other intensive training modalities included fifteen studies and suggests that intensive exercise therapy is feasible, safe and beneficial in Parkinson's disease, with strong evidence from a meta-analysis including six studies that resistance training can improve muscle strength (Uhrbrand, Stenager et al. 2015). Although this study claims to be the first systematic review into the effect of intensive exercise therapy there are some drawbacks to the review. Again, all studies investigated exercise programmes with a duration of up to three months, expressing a lack of studies looking into longer term programmes; sample size varied from 15 to 108, indicating that studies with relatively small sample sizes have been included. Studies with small sample sizes, and thus low statistical power, have a reduced change of detecting a true effect, so drawing conclusions from these small studies may be questionable; the PEDRO scores of the studies varied between 4 and 8 with an average of 5.8, again showing relatively poor methodological quality; finally, trials had to be excluded for poor description of intensity, frequency, duration and progression of training, which means that the literature presented here does not included all interventions. Care must be taken with reporting of a trial. A final thing to say is that in the review, conclusions are drawn from between two and six studies. For example, it is described that resistance training may improve quality of life, however, only two studies measures quality of life, and only one of the two studies found a positive effect, indicating that more research is needed into the area to draw definite conclusions. Overall, it seems that more research is needed into intensive

training to draw any definite conclusions and it is of great importance that the reporting of any trials are done using TiDieR guidelines (Hoffmann, Glasziou et al. 2014) so that studies can be assessed, repeated and included in reviews. As the results of intensive training seem to be positive in people with Parkinson's disease, it would be important to include intensive training elements into an exercise programme in order to investigate this further.

A review done by Allen et al (2011) looks into participant characteristics, intervention delivery, retention rate, adherence and adverse events in trials looking into exercise and motor training in people with Parkinson's disease in 53 trials. This review found that overall, trials that assess the effects of exercise and/or motor training, are beneficial in improving walking, balance, muscle strength and the performance of functional tasks in people with mild to moderate Parkinson's disease (Allen, Sherrington et al. 2012). The review discusses some drawbacks of the trials that were included. Firstly, the average intervention duration of all trials was 8.3 weeks (standard deviation was 4.2; range was 2 – 26 weeks) with an average of around 20 hours of training. As Parkinson's disease is a progressive disorder, sustainable interventions are important as a treatment. Although all trials found some benefit of exercise, it is important to research the effects and sustainability of an exercise programme lasting for a longer period of time. Furthermore, 74% of the interventions described involved full-supervision of exercise and/or motor training mostly at universities or hospitals. Again, since Parkinson's disease is a progressive disorder, fully supervised programmes are not likely to be realistic as they are very costly. Effort should be made to investigate the possibility of a low-supervised exercise training in a community setting, to lower burden on the participant (in relation to travel). Furthermore, adherence is an important aspect for clinicians/therapist in the translation of the research to real life (Allen, Sherrington et al. 2012). Adherence was poorly reported, with only 26 studies (49%) of the studies reporting some form of adherence. Care must be taken when designing a trial in how adherence is measured with strategies in place to improve adherence like participant involvement in goal setting and flexibility to allow programs to be modified for individuals (Allen, Sherrington et al. 2012).

There are many studies investigating short term (< three months) exercise interventions. One study running a ten-month trial community base exercise and wellness program for people diagnosed with Parkinson's disease found improvements in ambulation endurance over the ten-month course of their study (Steffen, Petersen et al. 2012). However, in this

study only fifteen people with Parkinson's disease were included, the participants were not randomised, and only ten participants completed the exercise programme indicating that the results found should be explored further in a larger population with a control group.

Overall, there is compelling evidence that exercise and physiotherapy is beneficial for people with Parkinson's disease. However, little research has been done into longer term, sustainable, exercise interventions. Moving forward, it is important to explore the effects of exercise over a longer period (> three months) of time. Furthermore, it is important to ensure methodological quality and good reporting of both the intervention and the results, so data can be used in informing future studies. As described, most studies have been conducted in a specialist setting using intensive supervision. Moving forward, it is important to explore more sustainable exercise interventions.

The mode of delivery of exercise is a relatively unexplored area. In the studies described above most studies deliver exercise in a specialist setting (e.g. hospital, physiotherapy). In order to make exercise for people with neurological conditions, including Parkinson's disease, feasible for a longer period of time, as it is a progressive disorder and will need addressing using exercise indefinitely; low cost, accessible exercise facilities should be present in the community setting.

1.9.4 Exercise for fatigue

Although the perception of worsened fatigue after overtraining may occur as a consequence of afferent inhibition from strained muscles (Andreasen, Stenager et al. 2011), exercise is often chosen as a treatment method for fatigue in other disorders including Chronic Fatigue Syndrome (Whiting, Bagnall et al. 2001, Castell, Kazantzis et al. 2011) and Multiple Sclerosis (Andreasen, Stenager et al. 2011, Pilutti, Greenlee et al. 2013). Andreasen et al (2011) conducted a systematic review looking at the effect of exercise therapy on fatigue in Multiple Sclerosis. In ten studies described in the review the exercise intervention comprised of endurance training of which some demonstrated a substantial effect on fatigue; in three studies, the exercise intervention comprised of resistance training, these studies showed promising results in reducing fatigue; finally, three studies described a combined training with one study showing no effect, one showing an effect, and one showing a trend towards an effect. Overall, the review concludes that exercise therapy has the potential to reduce fatigue in people with Multiple Sclerosis (Andreasen, Stenager et al. 2011).

However, little research has been done into exercise as a treatment method for fatigue in people with Parkinson's disease. A recent study exploring aerobic exercise in 60 people with Parkinson's disease observed that aerobic exercise (three times a week for six months) in the community improved fatigue in people with Parkinson's disease. However, they do state that after adjustment for different training methods and settings, calendar year, and change in levodopa equivalent, the fatigue score changes to non-significant (Uc, Doerschug et al. 2014). Furthermore, a downfall of this study was that they did not have a control group, as both groups of participants received an exercise programme (continues or interval) and in the final analyses, all patients were grouped together. Interestingly, the study found that completers of the intervention were significantly more fatigued than dropouts, which may suggest that an exercise intervention might be more suitable for participants with a certain level of fatigue. Furthermore, a study investigating fifteen people with Parkinson's disease found an effect of high intensity exercise on fatigue as measured by the fatigue severity scale (Kelly, Ford et al. 2014), however this was only a small study and it was not a randomised controlled trial lacking, indicating that further work in a larger group of people including a control group is needed.

1.10 Patient views

Previously, the research agenda has been accused to be mainly led by pharmaceutical and medical devices industries instead of addressing the issues that are important for the patients (Deane, Flaherty et al. 2014). Qualitative research is needed to explore what is important for the patient and for the design of interventions (Deane, Flaherty et al. 2014). Qualitative research has been conducted to explore patients' views on the most bothersome symptoms of Parkinson's disease and on treatment of Parkinson's disease. Patients with Parkinson's disease listed tremors, lack of mobility, pain, imbalance, lack of energy/fatigue, having to give up previously enjoyed activities, dysarthria, and anxiety or depression as most troublesome symptoms (Uebelacker, Epstein-Lubow et al. 2014). Furthermore, a large study was conducted by Deane et al. (2014) in order to identify the top 10 research priorities for the management of Parkinson's disease. Deane et al. identified 94 uncertainties from 4100 responses from patients with Parkinson's disease, carers and health care professionals. They then send these out to 475 participants in order to be prioritised. From the responses a top 26 of uncertainties was presented; one of the uncertainties listed in this top 26 was: 'What interventions are effective for reducing or managing unexplained fatigue in people with Parkinson's?' also indicating that fatigue seems to be an important issue for people with Parkinson's disease.

A previous study (The Long-term Individual Fitness Enablement (LIFE) project) looking at barriers and facilitators of exercise in people with long term neurological conditions revealed that barriers for exercise in people with long term neurological conditions include (Elsworth, Dawes et al. 2009):

- Costs
- Negative personal experiences and attitudes as well as fear and embarrassment of exercising
- Perception that fitness instructors will lack knowledge about their condition and how to help them participate in exercise safely and effectively
- Transportation and access
- Equipment (a lack of equipment suitable for and usable by disabled people)
- A fear of losing balance

Furthermore, the following facilitators were identified (Elsworth, Dawes et al. 2009):

- Positive personal attitudes
- Individually tailored gym programmes
- An exercise place that actively supports people with similar conditions and disabilities
- An exercise programme that considers individual motivators for exercise, not necessarily assuming individuals will be motivated by factors such as weight control, body shape or "keeping fit"

Although barriers concerning community exercise facilities are present, community exercise facilities are widely available in the United Kingdom (Winward 2011); therefore, exploring ways of making community exercise facilities more accessible for people with Parkinson's disease would be an important aspect into the delivery of long term exercise programmes.

The barriers and facilitator found in the first phase of the LIFE study were incorporated in an intervention. A physical activity and support system (PASS) was created addressing practical issues as, how to park, how to find and get to the fitness room, where the toilets and changing areas are and how to meet the fitness professional. Furthermore, a physiotherapist would go through the PASS with the client and would arrange to meet up with the client and local fitness professional, providing knowledge and experience of neurological conditions, advice on how to modify programmes, knowledge of impairments specifically associated with neurological conditions, and an understanding of medications

related to these conditions. All these aspects were incorporated in the second part of the LIFE study; a pilot study exploring the feasibility and acceptability of a community exercise intervention in people with longer-term neurological conditions. Although in this study 99 patients with long term neurological conditions including multiple sclerosis, Parkinson's disease, motor neuron disease, cerebral palsy and a number of neuromuscular conditions were included; people with Parkinson's disease made up the largest group of the study (n= 39). All participants were encouraged to use local gyms to exercise (the number and length of the sessions were determined by the individual). The intervention specifically addressed five key areas: i) access and transport; ii) the fitness instructor; iii) the gym; iv) health professional support; v) how to exercise safely. Results show that on average, patients attended one session per week over twelve weeks resulting in comparable exercise participation to standard GP exercise referral schemes (Elsworth, Winward et al. 2011, Winward 2011). The physiotherapist gave an average of three 1 hour face-to-face and three 5-20 minute phone calls per day (Winward 2011). The study found positive changes in mobility outcomes suggestive of a benefit of moderate effect size.

The study also looked into the effects of this exercise programme on fatigue in the 39 people with Parkinson's disease studied. The study found that participants randomised to the exercise group attended an average of 15 sessions over 12 weeks and no effects of exercise on the Fatigue Severity Scale (self-reported fatigue measure) score was found (Winward, Sackley et al. 2012). A reason for the lack of effect found could be the low attendance, not providing sufficient exercise to induce any change. A study exploring specific prescribed doses and/or motivational approaches is suggested as further research. Following up from this study it would be interesting to explore any longer term effects of the exercise trial with a higher dose of exercise sessions per week using the information on barriers/facilitators in this specific study.

1.11 Aims of the thesis

This chapter described Parkinson's disease and many issues arising with the disease. Fatigue seems to be an important symptom affecting many people with Parkinson's disease. Fatigue may be a direct symptom of Parkinson's disease or secondary due to other complications like depression and due to side effects of medications often prescribed to Parkinson's disease patients, including anti-depressants, anti-hypertensives, and statins (Chaudhuri and Behan 2004). This shows that fatigue is a common and debilitating symptom in people with Parkinson's disease and research is needed not only in the concept of fatigue, but also in possible treatment methods, like exercise. Therefore, this thesis will

aim to explore fatigue and will build results from the LIFE study to investigate exercise as a treatment method for fatigue.

This thesis has three main aims

- To explore fatigue, including a literature review on current treatment methods of fatigue for people with Parkinson's disease.
- To determine baseline characteristics of a group of people with Parkinson's disease and explore fatigue in this group.
- To explore adherence to a six months twice weekly exercise programme and to examine the effects of the exercise on general measures and fatigue after six months.

Chapter 2 Fatigue

Summary

This chapter defines and describes fatigue. It briefly touches on central fatigue and how to measure this. Since intervention studies investigating fatigue in people with Parkinson's disease normally use self-reported questionnaires to measure fatigue, in this chapter different self-reported questionnaires are described. Next, confounding problems that arise with fatigue in people with Parkinson's disease will be discussed. Finally, in order to put this information into context, the ICF-model is used.

2.1 Fatigue defined

Fatigue in Parkinson's disease first appears in literature in the article of J.R. Van Meter (1950). In this article it is stated that 'mental or physical fatigue intensifies the symptoms of Parkinson's disease' (Van Meter 1950). Fatigue was first described as a specific symptom of Parkinson's disease by Hoehn and Yahr (1976). However, its significance has only really been recognised in the last two decades (Fabbrini, Latorre et al. 2013). Despite an increasing number of studies into the subject, its pathophysiology is still unknown (Kluger, Krupp et al. 2013), and there remains a lot of debate into its relationships with other symptoms in people with Parkinson's disease, for example disease severity has both been found related (Herlofson and Larsen 2003, Havlikova, Rosenberger et al. 2008) as well as not related (Friedman and Friedman 1993, van Hilten, Weggeman et al. 1993, Abe, Takanashi et al. 2000, Lou, Kearns et al. 2001, Shulman, Taback et al. 2001) in different studies to fatigue, as will be described later this chapter; as well as measurement techniques, including self-reported measures (Kluger, Krupp et al. 2013) and experimental technologies including transcranial magnetic stimulation (TMS), and FMRI (Abe, Takanashi et al. 2000), all resulting in a range of treatment techniques including drug therapy, cognitive behavioural therapy and exercise therapy (Franssen, Winward et al. 2014). This shows that fatigue needs to be explored further in people with Parkinson's disease in order to inform future treatment techniques.

Although fatigue seems to have a large impact on people with Parkinson's disease, affecting 40% to 56% of all patients (Herlofson and Larsen 2003, Friedman, Brown et al. 2007, Okuma, Kamei et al. 2009), the mechanism of fatigue in people with Parkinson's disease is poorly understood (Kluger, Krupp et al. 2013).

A feeling of constant exhaustion is a characteristic of central fatigue; this feature is often associated with neurological disorders, including Parkinson's disease (Chaudhuri and Behan 2004).

2.1.1 Central fatigue

Central fatigue describes fatigue as the failure to initiate and/or sustain both attentional tasks and physical activities; the subjective sense of fatigue is perceived at a central level (Chaudhuri and Behan 2004). Central fatigue can be present in disorders of the peripheral, autonomic and central nervous system (Chaudhuri and Behan 2004). Brief episodes of fatigue are normal after a period of stress, following loss of sleep, however, sometimes the fatigue is chronic, persistent or relapsing (lasting for >3-6 months), which is extremely common in people with Parkinson's disease (Chaudhuri and Behan 2000).

2.2 Ways to measure fatigue

In the paragraphs below different ways of measuring fatigue will be discussed.

2.2.1 Measuring Central Fatigue

Central fatigue is studied in healthy people and people with neurological disorders by studying central 'abnormalities'. Neurophysiological studies of healthy human subjects using transcranial magnetic stimulation and nerve stimulation reveal changes in motor cortex and spinal excitability. These are associated with fatigability during motor tasks and suggest that deficits in central drive are responsible for a significant percentage of fatigability depending on task demands (Kluger, Krupp et al. 2013).

Neurophysiologic studies of healthy human subjects using TMS and nerve stimulation reveal changes in motor cortex and spinal excitability associated with fatigability during motor tasks and suggest that deficits in central drive are responsible for a significant percentage of fatigue depending on task demands (Kluger, Krupp et al. 2013). Furthermore, Lou et al. (2001) found that the physical fatigue in people with Parkinson's disease is caused by abnormal corticomotor neuron excitability, rather than fatigue by the muscle fibre (Lou, Kearns et al. 2001). Finally, Rothwell et al. (2007), investigated corticospinal excitability after exercise using TMS and found two differences in people with Parkinson's disease compared to healthy patients: no change in the duration of the cortical silent period and no changes in the slope of the input-output curve suggesting an abnormal basal ganglia output to the cortex in people with Parkinson's disease, whereas in healthy controls there was a decrease in corticospinal excitability and an increase in the duration of the cortical silent period after exercise (Khedr, Galal et al. 2007). Studies in

healthy human subjects using TMS and nerve stimulation reveal changes in motor cortex and spinal excitability associated with fatigue during motor tasks. Furthermore, fMRI studies in Parkinson's disease have shown that that metabolic activity is reduced in the supplementary motor area and premotor areas but increased in the primary motor cortex in Parkinson's disease patients (Friedman, Brown et al. 2007). The imaging techniques described above can be expensive, and can only be administered by trained people.

2.2.2 Measuring self-reported fatigue

In most studies investigating ways to treat fatigue both in Parkinson's disease (Abe, Takanashi et al. 2001, Ondo, Fayle et al. 2005, Leentjens, Scholtissen et al. 2006, Mendonca, Menezes et al. 2007, Schifitto, Friedman et al. 2008, Lou, Dimitrova et al. 2009, Ghahari, Leigh Packer et al. 2010, Tyne, Taylor et al. 2010, Ondo, Shinawi et al. 2011, Drijgers, Verhey et al. 2012, Postuma, Lang et al. 2012, Winward, Sackley et al. 2012, Rios Romenets, Creti et al. 2013, Stocchi 2013) as well as in other patient populations like Multiple Sclerosis (Surakka, Romberg et al. 2004, White, McCoy et al. 2004), self-reported questionnaires are used to describe fatigue. Self-reported questionnaires measure fatigue experienced by the patient and is often defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion (Friedman and Friedman 1993, Zwarts, Bleijenberg et al. 2008). Different scales are used in different studies to measure fatigue. A review by Tyson and Brown on fatigue scales in neurological conditions states that none of the by them selected tools met all the criteria required to demonstrate robust psychometrics and utility (Tyson and Brown 2014). A review on Fatigue Rating Scales used for Parkinson's disease discussed nine different scales to measure fatigue (Friedman, Alves et al. 2010), demonstrating the lack of consensus on how to measure fatigue. In this review it was concluded that two scales meet the criteria for the designation of 'recommended' as defined by the Movement Disorders Society for rating fatigue severity: the Fatigue Severity Scale and the Multidimensional Fatigue Inventory (Friedman, Alves et al. 2010). Therefore, these two scales will be discussed in more detail below. Additionally, there is one Parkinson's disease specific fatigue scale, the Parkinson Fatigue Scale, which will also be described.

The Multidimensional Fatigue Inventory: The Multidimensional Fatigue Inventory is a 20-item self-report measure including different dimensions. The scale is short with good psychometric properties (Smets, Garssen et al. 1995). It is shown to have good psychometric properties in non-Parkinson's disease populations (Whitehead 2009), and in one study investigating validity of the scale in people with Parkinson's disease (Elbers, van

Wegen et al. 2012). Disadvantages are that the scale does not define fatigue. Furthermore, discrimination between fatigued and non-fatigued Parkinson's disease patients has not been demonstrated (Friedman, Alves et al. 2010). The scale was considered appropriate for rating fatigue severity by the Movement Disorders Society (Friedman, Alves et al. 2010).

The Parkinson Fatigue Scale: In 2005, Brown et al. developed a Parkinson's disease specific fatigue scale, the Parkinson Fatigue Scale. This scale aimed to distinguish between people with Parkinsonism who considered they had fatigue and those who did not; and between those with problematic and non-problematic levels of fatigue (Brown, Dittner et al. 2005). The scale is a 16-item self-reported questionnaire with response options: strongly disagree, disagree, do not agree or disagree, agree, and strongly agree (Brown, Dittner et al. 2005). Responsiveness to change has not yet been evaluated in Parkinson's disease, furthermore a major disadvantage of this scale is that further studies are needed to evaluate its measurement properties in Parkinson's disease (Friedman, Alves et al. 2010).

Fatigue Severity Scale: The Fatigue Severity Scale is a uni-dimensional questionnaire assessing the effect of fatigue on daily living by use of nine statements which are scored on a seven-point Likert scale ranging from totally disagree (1) to totally agree (7) (Krupp, LaRocca et al. 1989, Elbers, Rietberg et al. 2012). The scale measures physical fatigue, mental fatigue and social aspects, they are not divided in different domains (Friedman, Alves et al. 2010). The items cover motivation; physical function; responsibilities; work, family or social life; exercise; how easily fatigued; frequency of problem; and priority of symptoms (Tyson and Brown 2014). Studies show that this questionnaire has a good internal consistency, and test-retest reliability in different patient groups with neurological disorders (Herlofson and Larsen 2003, Horemans, Nollet et al. 2004) including Parkinson's disease (Hagell, Hoglund et al. 2006, Friedman, Alves et al. 2010). The Fatigue Severity Scale is appropriate to detect changes in fatigue over time (Whitehead 2009). The scale is brief and easy to administer, and it has shown sensitivity to change in previous clinical trials. Disadvantages for the Fatigue Severity Scale include that the scale does not provide a definition of fatigue and only few studies assessed its psychometric properties in Parkinson's disease (Friedman, Alves et al. 2010).The scale was considered appropriate for rating fatigue severity by the Movement Disorder Society (Friedman, Alves et al. 2010). Furthermore, it is the most commonly used scale, making it an attractive scale to use in studies as they can be used meta-analyses (Friedman, Alves et al. 2010).

2.3 Fatigue and confounding problems and fatigue and its relationship to other symptoms of Parkinson's disease

As mentioned before, fatigue has become recognised as an important symptom of Parkinson's disease over the last two decades, resulting in numerous studies into its relationship with other symptoms, including depression, sleepiness, and quality of life. Below, research on these relationships will be discussed.

2.3.1 Fatigue and depression

As described in Chapter 1, depression is very common in people with Parkinson's disease and affects up to 50% of the patients (Dooneief, Mirabello et al. 1992). Fatigue is one of the symptoms included in the criteria for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnoses of anxiety and depressive disorders, in addition to the fundamental affective changes (Lamers, Hickie et al. 2013). Although fatigue is defined in different ways in depressive disorders, fatigue appears to be one of the more important and difficult to treat aspects of depression in general (Friedman, Brown et al. 2007). This shows that that fatigue could be a result of depression in people with Parkinson's disease. A long term study into the relationship between fatigue and depression found that fatigue is related to depression (Alves, Wentzel-Larsen et al. 2004). In this study 233 people with Parkinson's disease were included in 1993 and were followed up for eight years, with 111 people being followed up in 1997 and 78 people in 2001. The study found significant higher depression scores in fatigued patients versus non fatigued patients (Alves, Wentzel-Larsen et al. 2004). However, they did find a high number of fatigued patients that were not depressed (Alves, Wentzel-Larsen et al. 2004). Furthermore, several studies that investigate fatigue in a cohort of Parkinson's disease patients without depression find that fatigue is present in 41-50% of the patients (Karlsen, Larsen et al. 1999, Herlofson and Larsen 2002, Okuma, Kamei et al. 2009). In the study of Karlsen et al. 233 patients with Parkinson's disease were examined and result showed that fatigued patients were more depressed; again, once patients with depression were excluded, the number of patients that were fatigued remained high (43.5%) (Karlsen, Larsen et al. 1999). Herlofson and Larsen looked into fatigue in non-depressed patients with Parkinson's disease and found that in 66 people, 33 people were fatigued, indicating that fatigue is present in non-depressed patients with Parkinson's disease (Herlofson and Larsen 2002). Finally, in the study of Okuma et al. 361 Japanese people with Parkinson's disease were assessed and fatigue was present in 41.8% and a significant higher depression was found in fatigued people (Okuma, Kamei et al. 2009), however, a logistic regression did not find depression as a significant factor in

relation to fatigue (Okuma, Kamei et al. 2009). These results suggest that even though fatigue can be a result of depression in people with Parkinson's disease, it is also an independent symptom, found in people with Parkinson's disease, separate from depression.

2.3.2 Fatigue and sleepiness

Excessive daytime sleepiness is present in 8-50% of patients with Parkinson's Disease (Friedman, Brown et al. 2007). Symptoms of fatigue and sleep dysfunction overlap sufficiently to potentially confound studies of fatigue (Friedman, Brown et al. 2007). Parkinson's disease patients however, manage to distinguish between fatigue and sleepiness. Where sleep will refresh people with sleepiness, people with fatigue remain fatigued after sleep. Studies suggest that fatigue and the degree of sleepiness in Parkinson's disease patients are unrelated (Karlsen, Larsen et al. 1999, Alves, Wentzel-Larsen et al. 2004). Comparable to depression described above, in the study of Karlsen et al. patients with sleepiness were excluded from the cohort, and it was found that 43.5% of the cohort was fatigued, indicating that fatigue is present in people without sleepiness. Similarly, Alves et al. excluded all people with sleepiness from their cohort and found that the prevalence rate of fatigue remained high across all years (32.1% in 1993; 38.9% in 2001), again indicating that fatigue is present in people with Parkinson's disease separate from sleepiness.

2.3.3 Fatigue and disease severity

In a review of fatigue in neurological disorders, it is described that the severity of fatigue is not indicative of the nature or the severity of underlying disease (Chaudhuri and Behan 2004). However, the relation between fatigue and disease severity is debated in the literature. Some studies have found that patients with fatigue had more severe disease status (Herlofson and Larsen 2002, Havlikova, Rosenberger et al. 2008). In the study of Herlofson et al. 66 patients were included and a significant difference was found between fatigued (50% of the patients) and non fatigued patient on the UPDRS III score (Herlofson and Larsen 2002). Havlikova et al. studies 78 people with Parkinson's disease and found a significant correlation between the UPDRS scale and four out of five domains of the multidimensional fatigue inventory (Havlikova, van Dijk et al. 2008). Other studies have found that disease severity did not correlate with fatigue (Friedman and Friedman 1993, van Hilten, Weggeman et al. 1993, Abe, Takanashi et al. 2000, Lou, Kearns et al. 2001, Shulman, Taback et al. 2001). Overall, to date no conclusion can be drawn on the relationship between fatigue and disease severity in people with Parkinson's disease.

2.3.4 Fatigue and Quality of Life

Quality of life is defined by the World Health Organization as a state of complete physical, mental and social well-being (World Health Organization 1997). A variety of studies have investigated the influence of fatigue on quality of life. Herlofson & Larsen (2003) found that severity of fatigue showed a strong correlation with the Parkinson's disease Questionnaire 39 and several domains of the Short Form 36 (SF-36), which are both self-administered questionnaires measuring quality of life. Havlikova et al. (2008) found that fatigue predicted worsening on all quality of life domains as measured by the Parkinson's disease Questionnaire 39 (Havlikova, Rosenberger et al. 2008). Overall, it can be concluded that fatigue has got a negative influence on quality of life in people with Parkinson's disease, demonstrating the importance of addressing fatigue.

2.3.5 Fatigue and physical activity levels

Due to physical activities and mental changes, many people with Parkinson's disease lead a sedentary lifestyle (van Nimwegen, Speelman et al. 2013). Furthermore, a study into exercise and fatigue in 39 people with Parkinson's disease revealed that people who were more fatigued were more likely to be less active (Winward, Sackley et al. 2012). Furthermore, several large cohort studies have shown that fatigue is associated with a more sedentary lifestyle (Friedman, Brown et al. 2007). It is unclear whether physical inactivity is a result of fatigue or whether physical inactivity causes fatigue (Rongen-van Dartel, Repping-Wuts et al. 2014).

2.4 ICF-Model

The issues concerning fatigue that are described above can be put in a model that provides a framework for approaching the questions of what is important to study (Threats 2002). The International Classifaction of Functioning , Disability and Health (ICF) model ICF-model describes a situation of an individual with different health related domains within the context of environmental and personal factors (Davis 2006). Factors in the ICF model are functioning and disability, including body functions and structures, activity and participation, and contextual factors, including environmental and personal factors (Davis 2006). The ICF-model offers a global approach to thinking about health and health-related states. It provides a common language for describing health, functioning and disability (Rosenbaum and Stewart 2004).

All motor, non-motor symptoms arising in people with Parkinson's disease and quality of life are put together by means of the ICF-model with fatigue as the main issue. This gives

an overview on all relations together, shown in Figure 3. The model shows the great complexity around fatigue, by showing that neither fatigue, nor any of the issues that may be involved with fatigue stand on its own.

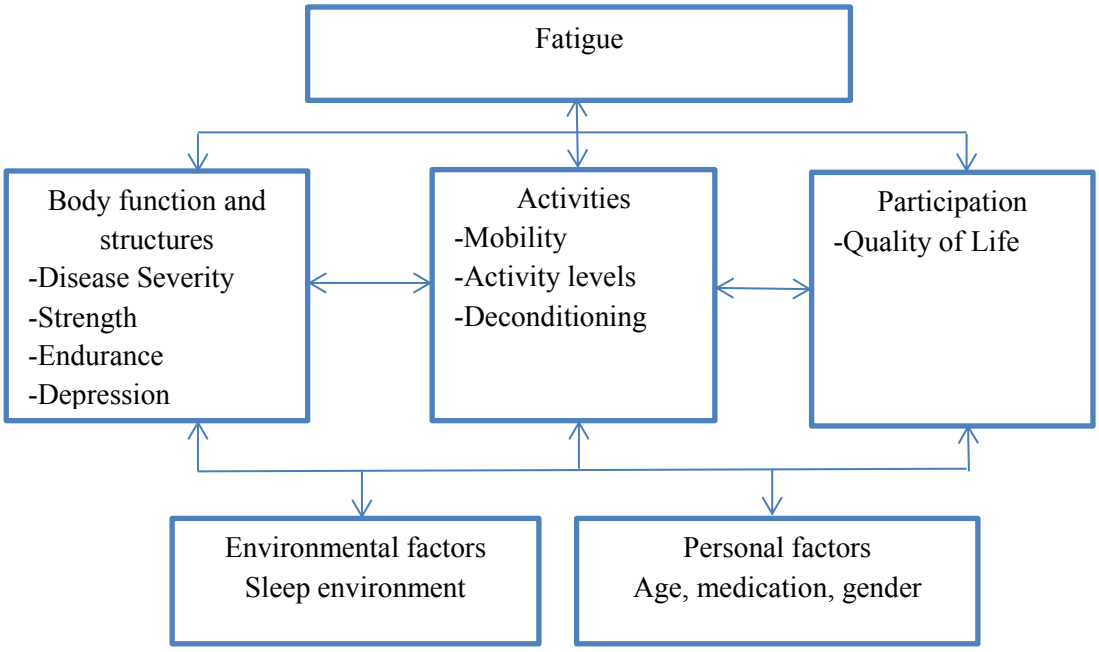

Figure 3: ICF model applied to fatigue in people with Parkinson's disease

2.5 Treatments for fatigue in people with Parkinson's disease

From this chapter it can be concluded that fatigue is a complex phenomenon due to the unknown pathophysiology, the numerous co-factors influencing fatigue, and the numerous methods to measure fatigue. Nonetheless, an increasing number of studies address fatigue and explore different ways of treating fatigue, therefore it is important to get a clear picture of treatment methods in fatigue to find out which methods might be more effective than others. The next chapter will present a systematic review of different treatment methods used to treat fatigue in people with Parkinson's disease.

Chapter 3: Interventions for fatigue in Parkinson's disease: A systematic review and meta-analysis

Summary

This chapter is a systematic review and meta-analysis evaluating the different ways that have been used to treat fatigue in people with Parkinson's disease. A search was conducted of PubMed, Cinahl, Psychinfo, EMBASE, and Web of Knowledge up to November 2013. Fourteen studies with a total of 1890 patients were included in the systematic review, with eleven studies exploring drugs, such as amphetamines, dopamines, caffeine, and memantine. One study explored doxepin and cognitive behavioural therapy; one study focused on cognitive behavioural therapy and one study investigated exercise as a treatment method for fatigue. Methodological quality was assessed using the PEDro scale. For meta-analyses, studies were weighted on variance. Effect sizes were calculated with 95% confidence interval (CI); overall effect was presented by means of a Z-score; heterogeneity was investigated using the I2. Three articles (investigating amphetamines) were appropriate for meta-analysis,which was performed according to scales used: Multidimensional Fatigue Inventory: mean difference, –6.13 (95%CI: –14.63-2.37, Z 5 1.41, P 5 0.16; I2 5 0); Fatigue Severity Scale: mean difference, –4.00 (95%CI: –8.72-0.72, Z 5 1.66, P 5 0.10; I2 5 0), indicating that further research to develop treatment methods for fatigue in people with Parkinson's disease is necessary.

3.1 Introduction

Studies show that non motor symptoms may have an impact on the lives of patients with Parkinson's disease (Herlofson and Larsen 2002), contributing to disability, reduced quality of life, and shortened life expectancy (Chaudhuri, Healy et al. 2006). One of the factors reducing quality of life in people with Parkinson's disease is fatigue (Herlofson and Larsen 2002, Havlikova, van Dijk et al. 2008, Miwa and Miwa 2011). Fatigue appears to be a common and disabling symptom for people with Parkinson's disease affecting all aspects of life including activities of daily living, work and social activities, and is often overlooked (Herlofson and Larsen 2003, Winward, Sackley et al. 2012).

Fatigue affects up to 58% of all people with Parkinson's disease (Alves, Wentzel-Larsen et al. 2004, Friedman, Alves et al. 2010), and more than half rank it as one of their three worst symptoms (Garber and Friedman 2003). The aetiology and pathophysiology of fatigue in Parkinson's disease remains unclear . Considering the impact of increased fatigue levels in this population, evidence for treatments to reduce its impact will provide

useful information to inform evidence based clinical practice and guide rehabilitation programmes.

As described in the previous chapter, fatigue can be measured in different ways. Since studies into fatigue in people with Parkinson's disease generally use self-administered questionnaires, the focus in the chapter will be on subjective fatigue as measured by questionnaires.

Evidence for treatment effects is limited (Seppi, Weintraub et al. 2011). A recent non–motor symptom review by Seppi et al. (2011) included evidence for treating fatigue in Parkinson's disease. The review included only three studies and concluded that evidence was insufficient for the use of the pharmacological treatments, methylphenidate and modafinil, for fatigue (Seppi, Weintraub et al. 2011). The review found looked into the effects of methylphenidate and modafinil on fatigue in people with Parkinson's disease (Seppi, Weintraub et al. 2011). The included study with regards to methylphenidate was a randomised controlled trial in 36 people looking into the effects of methylphenidate as a treatment method for fatigue and found a positive effect of the drug on fatigue scores (Mendonca, Menezes et al. 2007). The review found two randomised controlled trials looking into modafinil as a treatment method. One study, including 19 fatigued people with Parkinson's disease did not find an improvement over time using modafinil (Lou, Dimitrova et al. 2009); the other study, including 13 patients with fatigue received either modafinil or placebo for nine weeks and found no effects on fatigue (Tyne, Taylor et al. 2010). The small number of studies included in this review shows that more research into fatigue in people with Parkinson's disease is needed. However, the literature has to be explored further to investigate whether any additional trials have investigated fatigue, either as a main outcome, or a secondary outcome. Overall, there are a number of different treatment methods for fatigue in people with Parkinson's disease investigated including drug treatment (as described above) (Seppi, Weintraub et al. 2011), and exercise training (Winward, Sackley et al. 2012); however, there is no clear consensus to guide clinicians.

3.1.1 Aim of this systematic review and meta-analysis

The aim of this systematic review was to conduct a review and meta-analysis in people with Parkinson's disease investigating any interventions addressing fatigue comparing to any control group in a randomised controlled setting, with self-reported fatigue as an outcome measure, in order to establish the evidence of effectiveness of the treatment methods.

3.2 Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines (appendix 2) (Moher, Liberati et al. 2009), no review protocol was published.

3.2.1 Literature search

In order to reduce the chance that relevant papers will be discarded, two people (CW, MF) independently searched the electronic databases Pubmed, Psychinfo, Cinahl, Embase and Web of Knowledge for articles published from the inception of each database up to and including November 2013. An example of a search strategy can be found in appendix 3. References found in the retrieved articles where checked and on-going trials were identified via www.clinicaltrials.gov. The search included the following key words: Parkinson's disease, parkinsonian disorders, Parkinson's, fatigue. Only articles published in English and Dutch were included. Authors were not contacted to establish additional studies.

3.2.2 Study selection

Two people (CW and MF) independently evaluated titles and abstracts to determine eligibility. Full text was then obtained and reviewed to decide whether the inclusion criteria were met. In the case of lack of consensus a third reviewer's (HD) input was sought. Studies were only included in the review if all criteria were met; Inclusion criteria were: (a) population described by authors as 'Parkinson's disease' (patients of all ages and any duration of Parkinson's disease were included; studies were included if they focused just on people with Parkinson's disease, or if people with Parkinson's disease were included and data on this subgroup was provided, in order to ensure all patients with Parkinson's disease were included in the current review); (b) the study was a randomised controlled trial (to limit bias and improve reliability and accuracy of conclusions (Akobeng 2005)); (c) to ensure inclusion of enough papers, studies were included in which there was a comparison of any intervention aiming at reducing fatigue with another intervention or control state, any length of study and length of follow up were included; (d) a validated fatigue specific measure was used, either as a separate questionnaire, or as a specific fatigue subscale of a larger questionnaire, (e) the study was double blind, or where this was not possible, single blind to ensure strong methodological quality. Studies intended to be double blind, but failed to be so, were excluded from the review.

Studies were excluded if: (a) fatigue was not mentioned in the abstract; (b) explicitly stated that the population was a Parkinson related disorder and not idiopathic Parkinson's disease, (c) data after a crossover of patients were not used to avoid a carry-over effect.

Studies were included in a meta-analysis if usable data were available (i.e. number of participants and mean (SD) scores).

3.2.3 Data extraction

A spread sheet was created, piloted and then applied to abstract the relevant data from the included articles. Four data extractors assessed the papers and extracted data from eligible studies. The extracted data were compared to establish reliability and mistakes were rectified and disagreements were discussed.

Data extracted were: (1) characteristics of the trial's participants including information on number of participants, participants age, disease duration, drugs taken, sponsor, and inclusion and exclusion criteria; (2) characteristics of intervention including amount, duration, number of drop-outs; (3) type of outcome measure (including fatigue specific measure with its outcomes (confidence interval, mean, standard deviation, and p-value) at baseline and after the intervention); adverse events; remarks as necessary. If data was not available in the publication, the authors were contacted to provide data. One author provided the team with data, other authors did not respond.

3.2.4 Risk of bias

Bias at study level was assessed using the PEDro scale (The George Institute for Global Health 2012). On this scale items are scored 0 for absent, 1 for present and a score out of eleven is obtained (The George Institute for Global Health 2012). Two authors (CW and MF) used the PEDro scale, one of the authors (CW) also authored of one of the included studies, therefore MF scored this study. Only studies scoring excellent methodological quality were included in any meta-analyses. Any disagreements on scoring were discussed with a third reviewer (HD). Potential publication bias was investigated using funnel plots.

3.2.5 Data synthesis and analysis

The primary outcome measure was the difference in fatigue score on any used self-reported fatigue measure.

Studies investigating similar interventions (e.g. using drugs from the same group) were eligible for meta-analysis. Meta-analysis was performed using RevMan V 5.1 (Review Manager (RevMan)) [Computer program]. Version 5.1. Copenhagen: The Nordic

Cochrane Centre, The Cochrane Collaboration, 2011) (Cochrane 2011). A significance level of p=0.05 was set.

In the meta-analyses, data from similar studies were pooled together. The meta-analyses were performed by computing mean differences using a random effect model. In this model inter-study treatment effect variance is estimated (DerSimonian and Kacker 2007). This model, was used since it is assumed that there is not one true effect size shared by all studies (caused by differences in study population, interventions received, and follow up length) (Borenstein 2007, Riley, Higgins et al. 2011). When different scales were used to measure the same outcome, standardised mean differences were calculated. Studies were weighed on variance, the less variance, the bigger the weighting (Collaboration 2002). Effect sizes were calculated with 95% confidence interval, overall effect was presented by means of a Z-score (which can be thought of as describing the data in standard deviation units) (Freemantle and Geddes 1998). Heterogeneity, a measure of how much of the variability in treatment effect estimates is due to real study differences, and how much was due to change, was investigated with the I^2 statistic (Higgins, Thompson et al. 2003). Pooled analyses with a substantial (more than 50%) heterogeneity were not reported. In order to investigate comparable outcomes where possible, subgroup analyses were done separately for uni-dimensional and multi-dimensional fatigue questionnaires where mean differences were calculated.

3.3 Results

A total of 14 studies (total number of participants = 1,890) were included in the review. In total 972 studies were identified through database searches. No unpublished relevant studies satisfied the criteria for inclusion. Two studies included (Rascol, Fitzer-Attas et al. 2011, Stocchi 2013) the same dataset; therefore, one dataset was used (See Figure 4).

Three studies investigating amphetamines were eligible for meta-analysis.

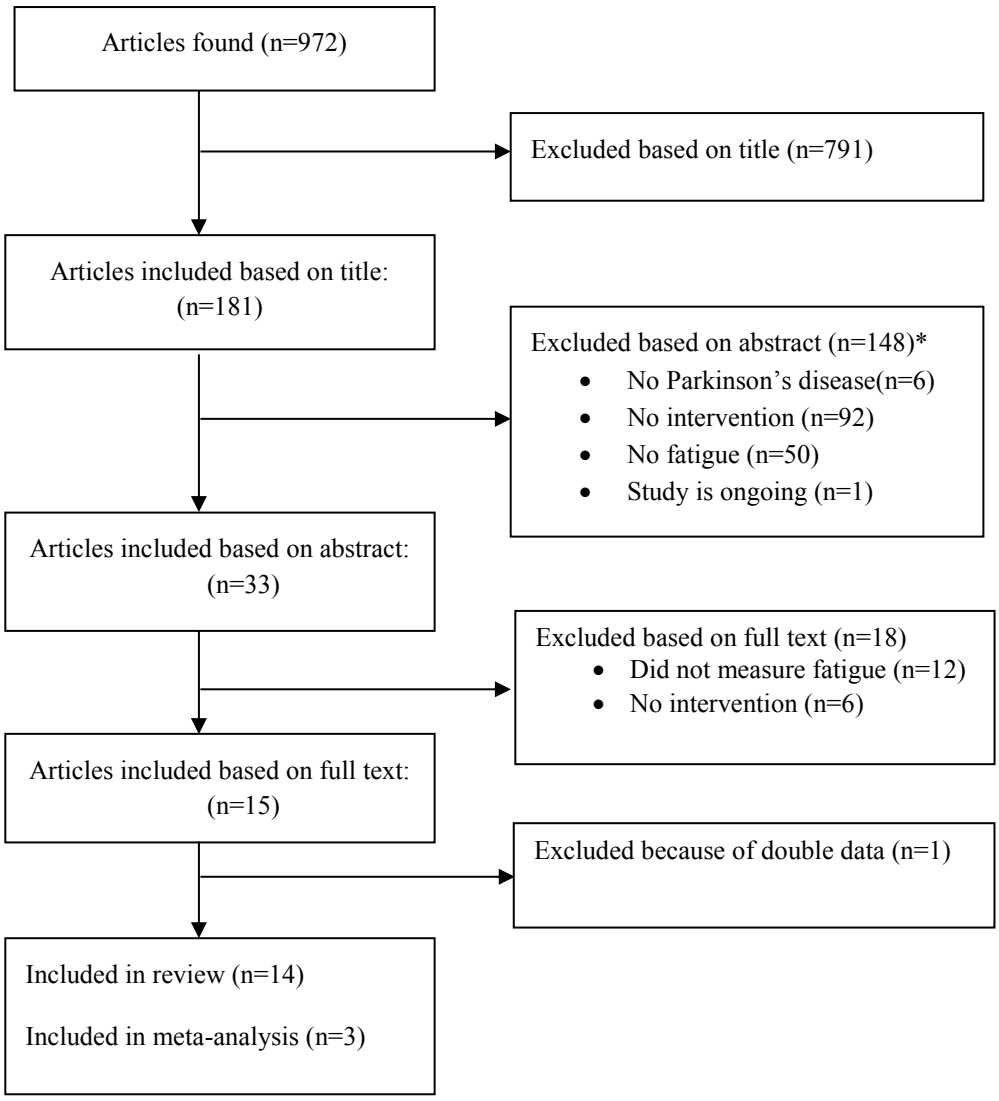

Figure 4: PRISMA flow diagram

Flow diagram showing the database search for interventions to treat fatigue in people with Parkinson's disease.

* Studies may be excluded for more then one reason.

3.3.1 Study characteristics

All 14 studies selected for the review were studies published in English. From the 14 studies found, 11 used a pharmacological treatment (Abe, Takanashi et al. 2001, Ondo, Fayle et al. 2005, Leentjens, Scholtissen et al. 2006, Mendonca, Menezes et al. 2007, Schifitto, Friedman et al. 2008, Lou, Dimitrova et al. 2009, Tyne, Taylor et al. 2010, Ondo, Shinawi et al. 2011, Drijgers, Verhey et al. 2012, Rios Romenets, Creti et al. 2013, Stocchi 2013), one used an online self-management intervention (Ghahari, Leigh Packer et al. 2010), one used a caffeine treatment (Postuma, Lang et al. 2012) and one used an exercise intervention (Winward, Sackley et al. 2012). Drugs and hormones used were Pergolide (n=1) (Abe, Takanashi et al. 2001), pramipexole (n=1) (Drijgers, Verhey et al. 2012), acute tryptophan depletion (n=1) (Leentjens, Scholtissen et al. 2006), modafinil (n=3) (Ondo, Fayle et al. 2005, Lou, Dimitrova et al. 2009, Tyne, Taylor et al. 2010), methylphenidate (n=1) (Mendonca, Menezes et al. 2007), memantine (n=1) (Ondo, Shinawi et al. 2011), rasagiline (n=1) (Stocchi 2013), carbidopa-levodopa (n=1) (Schifitto, Friedman et al. 2008), doxepin (n=1) (Rios Romenets, Creti et al. 2013). The study size varied from eight to 1176. The age in the studies ranged from 50 to 82. Disease duration varied from 5 months to 9.1 years. Drugs taken, but not investigated, were: dopaminergics, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase (MAO-B) inhibitor, and anticholerinergics. Outcome measures used were Fatigue Severity Questionnaire (n=1) (Abe, Takanashi et al. 2001), Profile of Mood States (fatigue subscale) (n=2) (Leentjens, Scholtissen et al. 2006, Drijgers, Verhey et al. 2012), fatigue impact scale (n=1) (Ghahari, Leigh Packer et al. 2010), Parkinson's Fatigue Scale (n=1) (Stocchi 2013), Multidimensional Fatigue Inventory (n=2) (Mendonca, Menezes et al. 2007, Lou, Dimitrova et al. 2009), Fatigue Severity Scale (n=8) (Ondo, Fayle et al. 2005, Mendonca, Menezes et al. 2007, Schifitto, Friedman et al. 2008, Tyne, Taylor et al. 2010, Ondo, Shinawi et al. 2011, Postuma, Lang et al. 2012, Winward, Sackley et al. 2012, Rios Romenets, Creti et al. 2013) (see Table 1).

Table 1: Basic characteristics of included studies

Author	Year	N	Intervention		Outcome measure used	Intervention period	PEDro score	Disease Duration (in years)		Drugs taken
			Active	Control				Active	Control	
Abe, K., M. Takanashi, et al.	2001	41	Pergolide Mesilate 990 ± 357 µg/day	Bromocriptine* 7.9 ± 2.5 mg/day	Fatigue severity questionnaire	5 weeks	6	6.0	6.3	Dopaminergics
Drijgers, R.L., Verhey, F.R.J., et al.	2012	25	Pramipexole 500 µg OR Methylphenidate 10 mg	Placebo	Profile of mood status; fatigue subscale	1.5 hours	11	5.0**		Dopaminergics; COMT inhibitor; MAO-B inhibitor; anticholerinergics
Ghahari, S., T. Leigh Packer, et al.	2010	6	Fatigue self-management programme OR Information only	No intervention	Fatigue impact scale	7 weeks	8	No data		
Leentjens, A. F., B. Scholtissen, et al.	2006	15	Acute tryptophan depletion 75 g amino-acid mixture 3g/100g tryptophan, was left out	Placebo 75 g amino-acid mixture, tryptophan was not left out	Profile of mood status	6 hours	11	No data		NMDA agonist; dopamine agonist;
Lou, J. S., D. M. Dimitrova, et al.	2009	19	Modafinil 100 mg twice a day	Placebo	Multidimensional fatigue inventory	2 months	11	4	8	dopamine agonists; carbidopa/levodopa; COMT inhibitor
Mendonca, D. A., K. Menezes, et al.	2007	36	Methylphenidate 10 mg 3 times a day	Placebo	Fatigue severity scale; multidimensional fatigue inventory	6 weeks	11	3.5	9.1	dopaminergics

Table 1 (continued): Basic characteristics of included studies

Author	Year	N	Intervention		Outcome measure used	Intervention period	PEDro score	Disease (in years)		Duration	Drugs taken
			Active	Control				Active		Control	
Ondo, W. G., R. Fayle, et al.	2005	40	Modafinil Up to 200 mg twice a day	Placebo	Fatigue Severity Scale	4 weeks	11	6.5		7.0	Dopaminergics
Ondo, W. G., Shinawi, L. et al.	2011		Memantine 20 mg/day	Placebo	Fatigue Severity Scale	8 weeks	11	No data			Dopaminergics
Postuma, R.B, Lang, A.E. et al.	2012	61	Caffeine Up to 200mg twice a day	Placebo	Fatigue Severity Scale	6 weeks	11	8.0		7.8	Dopaminergics
Rios Romenets, S., Creti, L.	2013		Cognitive behavioural therapy/ bright light therapy OR Doxepin 10mg/day	Placebo	Fatigue Severity Scale	6 weeks	9	5.2 OR 5.2		4.8	dopaminergics
Schifitto, G. J. H. Friedman, et al.	2008	361	Carbidopa-levodopa 37.5/150mg OR Carbidopa-levodopa 75/300mg OR Cabidopa-levodopa 150/600mg	Placebo	Fatigue Severity Scale	40 weeks	11	.5		.5	No medication
Stocchi et al.	2013	1105	Rasagiline 1mg/day OR Rasagiline 2 mg/day	Delayed start intervention	Parkinson fatigue scale	72 weeks	11	<18 months			No medication

Table 1 (continued): Basic characteristics of included studies

Author	Year	N	Intervention		Outcome measure used	Intervention period	PEDro score	Disease (in years)	Duration	Drugs taken
			Active	Control				Active	Control	
Tyne, H. L., J. Taylor, et al.	2010	13	Modafinil Up to 400 mg/day	Placebo	Fatigue severity scale	9 weeks	11	No data		Dopaminergics; dopamine agonists
Winward, C., C. Sackley, et al.	2012	39	Exercise	Delayed start exercise	Fatigue severity scale	12 weeks	9	5.7	5.9	Dopaminergics; dopamine agonists

*: both groups received an active (but different) intervention. **: data not available for separate groups

3.3.2 Methodological quality and bias

Ten studies (Ondo, Fayle et al. 2005, Leentjens, Scholtissen et al. 2006, Mendonca, Menezes et al. 2007, Schifitto, Friedman et al. 2008, Lou, Dimitrova et al. 2009, Tyne, Taylor et al. 2010, Ondo, Shinawi et al. 2011, Drijgers, Verhey et al. 2012, Postuma, Lang et al. 2012, Stocchi 2013) were of excellent methodological quality as scored by the PEDro scale (11/11). Three studies (Ghahari, Leigh Packer et al. 2010, Winward, Sackley et al. 2012, Rios Romenets, Creti et al. 2013) were of good methodological quality (8/11; 9/11; 9/11). These studies did not achieve an excellent PEDro score due to an inability to blind the participants and therapists (Winward, Sackley et al. 2012) the assessors and therapists (Rios Romenets, Creti et al. 2013), or the assessors, therapists and participants (Ghahari, Leigh Packer et al. 2010). The study of Abe et al. (2001) (Abe, Takanashi et al. 2001) was of fair methodological quality and scored 6/11 on the PEDro scale with points 2,3, and 5-7 missing; however, not all information necessary for scoring was provided in the article. Funnel plots should have data points from a sufficient number of trials to be able to demonstrate publication bias (The Cochrane Collaboration 2011). Since only a limited number of trials were found, no tests were done for publication bias.

3.3.3 Outcomes

An overview of the outcomes of the studies can be found in Table 2. Studies investigating multiple arms are included in the table more than once. Abe et al. (2001) found a significant effect of taking pergolide mesilate compared to bromocriptine. Drijgers et al. (2012) found a significant effect of treatment with pramipexole vs placebo and pramipexole vs methylphenidate. Lou et al. (2009) found a significant effect of modafinil over placebo. Medonca et al. (2006) found a significant result two fatigue scales when comparing methylphenidate to placebo. Rios Romenets et al. (2013) also found a significant effect for their treatment group with doxepin vs placebo on fatigue, no significant effect was found for the Cognitive Behavioural Therapy and light therapy. Finally, Stocchi et al. (2013) found a significant effect for taking rasagiline vs placebo.Ghahari et al. (2010); Leentes et al. (2006); Ondo et al. (2005); Ondo et al. (2010); Postuma et al. (2013); Schifitto et al. (2011); Tyne et al (2010); and Winward et al. (2012) did not find any significant differences between the experimental group and the control group in treatment of fatigue (see Table 2).

Table 2: Outcomes studies

Study	Intervention	Pre Control Mean (SD)	Pre Experimental Mean (SD)	Post Control Mean (SD)	Post Experimental Mean (SD)	p-value
Abe, K., Tahanashi, M. et al. (2001)	Pergolide mesilate vs placebo	4.8 (0.9)	5.1 (0.7)	4.7 (0.8)	4.4 (0.55)	<0.05
Drijgers, R.L., Verhey, F.R.J. et al. (2012) M	Pramipexole vs placebo	78.0 (10.0)	75.6 (11.6)	70.7 (13.9)	62.6 (16.3)	<0.05
Drijgers, R.L., Verhey, F.R.J. et al. (2012) M	Pramipexole vs mehtylphenidate	77.1 (10.1)	75.6 (11.6)	73.0 (13.4)	62.6 (16.3)	<0.05
Ghahari, S., Leigh Packer, T. et al. (2010)	Behavioural program vs control	83.5 (46.0)	77.3 (47.2)	81.5 (71.4)	72.3 (45.6)	>0.05
Leentjens, A. F., Scholtissen, B. et al. (2006)	Acute tryptophan depletion vs placebo	59 (14.0)	58 (13.7)	56 (15.2)	65 (15.4)	>0.05
Lou, J.S., Dimitrova, D.M. et al. (2009)	Modfinil vs placebo	63.5 (4.8)	55.8 (5.1)	61.0 (4.8)	54.5 (5.12)	<0.05
Medonca, D.A., Menezes, K. et al. (2007) (FSS) M	Methylphenidate vs placebo	45.1 (6.5)	43.8 (6.7)	43.2 (8.4)	37.3 (9.5)	<0.05
Medonca, D.A., Menezes, K. et al. (2007) (MFI) M	Methylphenidate vs placebo	51.7 (16.1)	51.0 (10.8)	48.5 (16.5)	42.6 (15.6)	<0.05
Ondo, W.G., Fayle, R. et al. (2005)	Modfinil vs placebo	36.8 (12.8)	37.6 (14.1)	37.8 (10.8)	36.8 (12.7)	>0.05
Ondo, W. G., Shinawi, L. et al. (2010)	Memantine vs placebo	37.2 (14.3)	37.6 (14.2)	35.7 (16.9)	37.4 (17.7)	>0.05
Postuma, R. B., Lang, A.E. et al. (2013)	Caffeine vs placebo				-2.85 (-7.73,2.06)*	>0.05

Table 2 (continued): Outcomes studies

Study	Intervention	Pre Control Mean (SD)	Pre Experimental Mean (SD)	Post Control Mean (SD)	Post Experimental Mean (SD)	p-value
Rios Romenets, S., Creti, L. (2013)	Doxepin vs placebo			0 (5.8)**	-17.7 (14.3)**	<0.05
Stocchi, F. et al. (2013) M	Rasagiline 1mg vs placebo			0.17 (0.03)**	0.03 (0.04)**	>0.05
Stocchi, F. et al. (2013) M	Rasagiline 2 mg vs placebo			0.17 (0.03)**	-0.02 (0.04)**	>0.05
Schifitto, G., Friedman J.H. et al (2011) M	Levodopa 150 mg vs placebo			0.75 (1.39)**	0.30 (1.08)**	>0.05
Schifitto, G., Friedman J.H. et al (2011) M	Levodopa 300 mg vs placebo			0.75 (1.39)**	0.36 (1.11)**	>0.05
Schifitto, G., Friedman J.H. et al (2011) M	Levodopa 600 mg vs placebo			0.75 (1.39)**	0.33 (1.04)**	>0.05
Tyne, H. L., Taylor, J. et al. (2010)	Modafinil vs placebo	5.4 (3)***	6.1 (2)***	5.1 (3)***	5.7 (3)***	>0.05
Winward, C., Sackley, C. et al. (2012)	Exercise vs control	4.15 (1.49)	3.9 (1.41)	3.72 (1.46)	3.5 (1.30)	>0.05

*Reported as mean and 95% confidence interval; **Reported as change score baseline vs end score; ***Medium (range) instead of Mean (SD)

Abbreviations: SD: Standard Deviation; FSS: Fatigue Severity Scale; MFI: Multidimensional Fatigue Inventory; M: indicates multiple arm trials which appear more than once in the table

3.3.4 Adverse events

All studies investigating amphetamines report adverse events. Leentjes et al. (2006) mention that six people experienced nausea. In the study of Lou et al. (2009) three subjects in the experimental group drop out due to blood in urine, memory loss and loss of balance, frequent urination, soft stool and flatulence, and early wakefulness. Medonca et al (2007) describe that three people in each group dropped out due to adverse events. In the experimental group complaints were backache, difficulty sleeping, feeling more bradykinetic, being mildly short of breath and feeling dizzy. Furthermore, a side effects questionnaire (including 20 side effects) was completed. Six people in experimental group mentioned side effects; five people in the placebo group mentioned side effects. In Ondo et al. (2005) adverse events in the modafinil group were a dry mouth (n=1), dizziness (n=1), back pain (n=1), nausea and anxiety (n=1). Adverse events in the placebo group were hypotension (n=1), renal calcinosis (n=1) and blurred vision (n=1). In Ondo et al. (2011) four people in the memantine group dropped out due to shoulder pain (n=1), lethargy (n=1), dyskinesia (n=1), nausea/confusion (n=1), anxiety (n=1); further adverse events in the experimental group were: sedation (n=2), confusion (n=1), pain (n=1), obsessive thinking (n=1), lethargy (n=1), and dyskinesia (n=1); finally, adverse events in the placebo group were nausea (n=3), dizziness (n=2), nervousness (n=1), hypertension (n=1), limb numbness (n=1), anxiety (n=1), weight loss (n=1), and jerking (n=1). Drijgers et al. (2012) were the only study using dopamine agonists who mentioned adverse events. Two participants dropped out due to dizziness, panic and nausea; the other studies (Abe et al (2001); Schifitto et al (2008); Stocchi et al. (2013)) did not mention any adverse events. Gahari et al (2010) and Winward et al (2012) did not report any adverse events. As the interventions using drugs exhibit more adverse events than the online management and exercise programmes, non-drug interventions could be a better choice as treatment for fatigue in people with Parkinson's disease. However, it must be noted, that although the adverse events were not reported in the studies, adverse events may have occurred. A review investigating exercise trials in people with Parkinson's disease remark that adverse events are not often reported in trials (Goodwin, Richards et al. 2008). In future, authors should adhere to the TIDieR guidelines in order to be able to draw clear conclusions on safety of exercise trials.

3.3.5 Meta-analysis

In the amphetamine group three studies were included (Lou et al (2009); Medonca et al. (2007); Ondo et al. (2005)). Two different fatigue scales were used (Multidimensional Fatigue Inventory, multi-dimensional; and Fatigue Severity Scale, uni-dimensional).The whole group included 45 people in the experimental group and 45 in the control group. Two separate analyses were done on the whole group. In the first analysis Lou et al.; Ondo et al.; and data from Medonca et al. on the Multidimensional Fatigue Inventory were included. The mean difference was -0.25 with a confidence interval of -0.67 to 0.16, the I^2 was 0 % and the z score of the overall effect was 1.20 (p=0.23) (see Figure 5). In the second analysis, data from Lou et al; Ondo et al; and data from Medonca et al. on the Fatigue Severity Scale were included. Here, the mean difference was -0.36 with a confidence interval of -0.78 to 0.06, the I^2 was 0% and the z score of the overall effect was 1.67 (p=0.09) (see Figure 6).

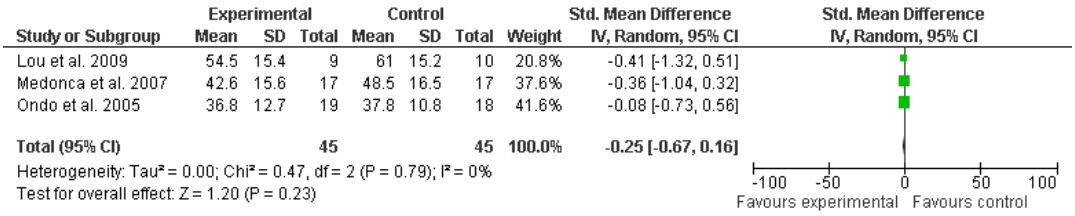

Figure 5: Forest plot amphetamines
(Medonca Multidimensional Fatigue Inventory)

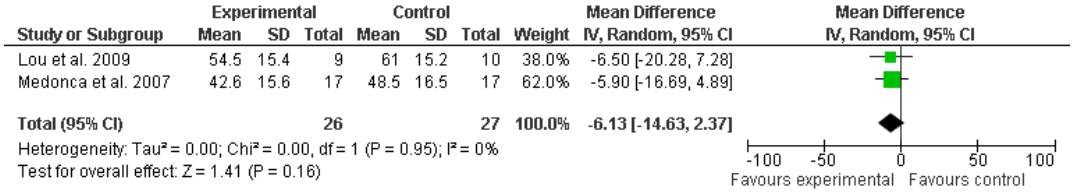

Figure 6: Forest plot subgroup analysis amphetamines Multidimensional Fatigue Inventory

Furthermore, sub analyses on the two different fatigue scales were undertaken. For the analysis of the Multidimensional Fatigue Inventory Lou et al. (2009) & Medonca et al. (2007) were combined; there were 26 people were in the experimental group, 27 in the control group. The mean difference was -6.13 with a confidence interval of -14.63 to 2.37, the I^2 was 0% and the z score of the overall effect was 1.41 (p=0.16) (see Figure 7).

For the analysis of the Fatigue Severity Scale Ondo et al. (2005) and Medonca et al. (2007) were combined; there were 36 people in the experimental group and 35 people in the control group. The mean difference and confidence interval was -4.00 (-8.72, 0.72). I^2 was 0% and the Z score of the overall effect was 1.66 (p=0.10) (see Figure 8).

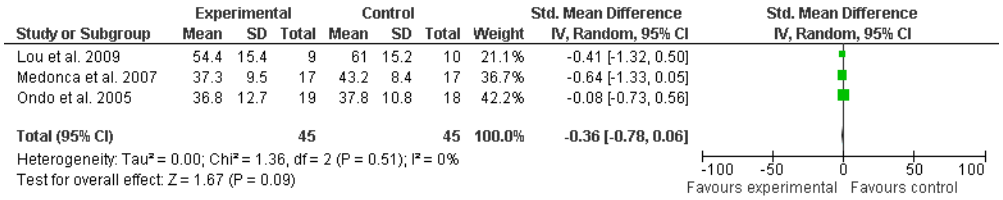

Figure 7: Forest plot amphetamines

(Medonca Fatigue Severity Scale data)

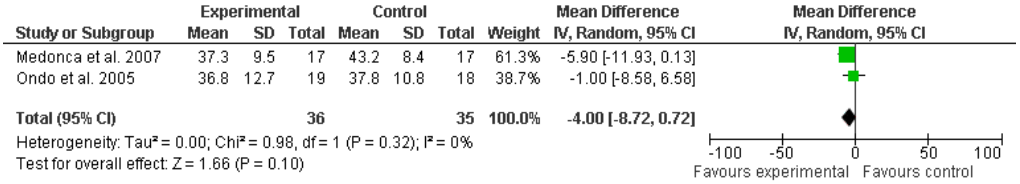

Figure 8: Forest plot subgroup analysis amphetamines Fatigue Severity Scale

3.4 Discussion

Individually the studies of Medonca et al. (amphetamines), Abe et al., Drijgers et al. (2012), Rios Romenets et al., and Stocchi (2014) (dopamine) showed a treatment effect (Mendonca, Menezes et al. 2007, Drijgers, Verhey et al. 2012, Rios Romenets, Creti et al. 2013, Stocchi 2013). No non-pharmacological studies showed a treatment effect. Because of heterogeneity (in outcome measures, different drugs and dosages, and duration of studies), data from the dopamine studies could not be pooled. When data from studies investigating amphetamines were pooled, no treatment effect was shown. This review adds additional research evidence to Seppi et al. (2011) and has resulted in the inclusion of a further eleven articles with a meta-analysis.

In general the medications used were well tolerated. If adverse events were reported it was stated that no differences were found in adverse events between the treatment group and the placebo group, which indicates that the used methods were safe to use. No adverse events were reported in the exercise study of Winward et al (2012), but adverse events are often inadequately reported (Goodwin, Richards et al. 2008, Allen, Sherrington et al.

2012). Apart from Drijgers et al. (2012) the studies on dopamine agonists do not report their adverse events. A review on treatments of Parkinson's disease states that well reported adverse events using dopamine agonists are nausea, vomiting, hypotension and psychosis (Movement Disorders Society 2002, Movement Disorders Society 2002). Overall, studies investigating drugs to treat fatigue, seem to find a number of adverse events, whereas the studies of Gahari et al. and Winward et al. investigating respectively an online self-management programme, and an exercise programme did not find report any adverse events. A review on exercise in people with Parkinson's disease stated that adverse events are generally not reported in the exercise studies (Goodwin, Richards et al. 2008), meaning that they either do not happen, or are not reported, which has to be explored further in order to draw any conclusions on safety of exercise trials.

Different mechanisms for treating fatigue are proposed. Studies directly addressing fatigue include treatment with pergolide mesilate (Abe, Takanashi et al. 2001), an online self-management programme (Ghahari, Leigh Packer et al. 2010), modafinil (Lou, Dimitrova et al. 2009, Tyne, Taylor et al. 2010), methylphenidate (Mendonca, Menezes et al. 2007), levodopa (Schifitto, Friedman et al. 2008) and exercise (Winward, Sackley et al. 2012). Different mechanisms are behind these choices of treatment methods. Three studies did not explain an underlying mechanism (Schifitto, Friedman et al. 2008, Tyne, Taylor et al. 2010, Winward, Sackley et al. 2012). Other studies described their method in detail. Abe et al (2001) describes a mechanism where patients with fatigue have shown reduced glucose metabolism or reduced isotope uptake, which may be addressed by dopamine which can improve frontal lobe function and may improve fatigue in that way (Abe, Takanashi et al. 2001). Schifitto et al. 2008 used a similar treatment method, so it can be concluded that a similar hypothesis underlies their intervention. Since glucose metabolism is the process through which glucose is oxidized to carbon dioxide and water as a metabolic fuel (i.e. to provide energy) (McArdle 2010), a reduction in glucose metabolism may explain fatigue. Furthermore, glucose is the main fuel for the brain (McArdle, Katch et al. 2010) indicating that fatigue in people with Parkinson's disease could have a central origin. Lou et al. (2009) describe that modafinil is a central nervous stimulant whose mechanism is associated with an activation of the tuberomamillary nucleus and orexin-containing neurons (Lou, Dimitrova et al. 2009). Tyne et al. (2010), also use modafinil to treat fatigue, so it can be expected that the same hypothesis underlies their research. Finally, Medonca et

al. (2007) explain that methylphenidate is a central nervous stimulant and is an antagonist of dopamine and norepinephrine transporters on the presynaptic neuronal cell membrane. Reduced reuptake results in an increase in extracellular levels of both neurotransmitters (Mendonca, Menezes et al. 2007). Although, Winward et al. (2012) do not describe a reasoning for using exercise as a treatment method for fatigue in people with Parkinson's disease, it can be hypothesised that they choose this method as it was previously found that exercise has the potential to induce a positive effect on fatigue in people with Multiple Sclerosis (Andreasen, Stenager et al. 2011, Latimer-Cheung, Pilutti et al. 2013), and animal models imply that exercise might be effective in treating fatigue in people with Parkinson's disease (Friedman, Brown et al. 2007).Other treatment methods focused on treatment of excessive daytime sleepiness (Ondo, Fayle et al. 2005), insomnia (Rios Romenets, Creti et al. 2013), depression (Leentjens, Scholtissen et al. 2006) or general treatment of Parkinson's disease (Ondo, Shinawi et al. 2011, Rascol, Fitzer-Attas et al. 2011, Drijgers, Verhey et al. 2012, Postuma, Lang et al. 2012). The different explanations of fatigue in people with Parkinson's disease, and the many ways to treat fatigue, shows there is no consensus yet on what fatigue is and how it should be treated. Therefore, more research is necessary into the mechanisms behind fatigue, and treatment of fatigue in people with Parkinson's disease.

Apart from the study of Schifito et al (2008) and Stocchi (2013), participants in all other studies continued to take their routine medication. As described, drugs such as dopamine agonists could influence fatigue, and mono-amine oxidase inhibitor can have amphetamine-like effects, which may introduce bias; results should therefore be interpreted with care.

The difficulty in defining fatigue is one reason for the multitude of measures (Friedman, Alves et al. 2010) and there is little evidence to guide which measurement instrument to use (Friedman, Brown et al. 2007). Although the scales in the included studies used validated scales, different scales measure different aspects of fatigue (Aaronson, Teel et al. 1999), therefore caution is needed when pooling data together. Further research and agreement is needed on evaluating the best method of measuring fatigue in people with Parkinson's disease in order to have a standardized measure for this phenomenon. In this review however, the majority of the studies (eight) explored fatigue using the fatigue

severity scale. Indeed, literature indicates that the fatigue severity scale is the most used scale to explore fatigue in chronic diseases .

It should be noted that a number of studies had to be excluded from the review because validated fatigue measurement tools had not been used, and/or other parameters including sleep could not be separated out from measurement of fatigue, thereby limiting findings (Adler and Thorpy 2005, Ray Chaudhuri, Martinez-Martin et al. 2013). This is an important finding as at first glance the literature appears to be rich with studies investigating the impact of interventions on fatigue. This limitation due to inadequate case definition and a reliable, validated measure appears to severely limit advancement of understanding in this area.

Ten out of the fourteen included studies show an excellent methodological quality as scored by the PEDro scale, although the study of Abe et al. (2006) only showed a fair methodological quality. This study was included in the meta-analysis and therefore caution is necessary when interpreting of the results. However, it is worth mentioning Abe at al. is the oldest study found in this review and it has been shown that methodological quality of studies has improved over the last decade (Moseley, Herbert et al. 2002). One of the studies included in the review (Winward, Sackley et al. 2012) was written by authors of this review (CW, HD, DW), however, the PEDro scoring was done by one of the authors that was not involved in that particular study (MF).

One final problem in translating findings from studies on people with Parkinson's disease is the diagnosis of Parkinson's disease (Tolosa, Wenning et al. 2006). This difficulty in diagnosis contributes to the fact that the results in this systematic review need to be interpreted with caution. A commonly used diagnosis of idiopathic Parkinson's disease is provided by the brain bank clinical diagnostic criteria (Hughes, Daniel et al. 1992). However, only a limited number of studies used this criterion in their inclusion criteria (Hughes, Daniel et al. 1992, Alves, Wentzel-Larsen et al. 2004, Adler and Thorpy 2005, Ondo, Fayle et al. 2005, Lou, Dimitrova et al. 2009, Ghahari, Leigh Packer et al. 2010, Tyne, Taylor et al. 2010, Ray Chaudhuri, Martinez-Martin et al. 2013). Studies should try to include people diagnosed with idiopathic Parkinson's disease to increase heterogeneity of the study sample.

3.5 Limitations

There are some limitations to this review and meta-analysis. First of all, the selection was limited to studies in English and Dutch which may have caused language bias with potentially relevant studies published in other languages being missed. Second, although the authors excluded measures of physical fatigue, previous research states the overlap between mental fatigue and physical fatigue may not be clear on rating scales, additionally sleep may be a confounding factor as well (Friedman, Alves et al. 2010). All this taken together shows that it is hard to define and measure fatigue and this may have created problems with including studies in the current review. Finally, different fatigue scales were used in different studies, so results from the meta-analysis should be interpreted carefully. Moving forward, it would be important to use one standard fatigue scale to make it possible to pool findings. As discussed earlier, the fatigue severity scale is the most used fatigue scale making it a favourable choice of measure in future research.

3.6 Conclusion

Different methods of treating fatigue in people with Parkinson's disease are currently being used. Drug therapy is the most common way of treating fatigue in Parkinson's disease. After analysis, no significant effects were found on treatment of fatigue in people with Parkinson's disease with either amphetamines or dopamine agonists. This shows that more research is necessary into treatment methods of fatigue in people with Parkinson's disease. Consensus into determining the best way to measure fatigue in people with Parkinson's disease would further improve research in this area.

The review showed that most interventional studies focus on mood, depression and sleepiness, only one intervention looked into relationships between physical activity, exercise tolerance and self-reported fatigue even though there is evidence to believe that exercise is likely to diminish fatigue. The question whether exercise is a possible treatment for fatigue in people with Parkinson's disease has not been explored thoroughly enough to provide a definite answer. Although Winward et al. 2012 did not find a positive relationship between exercise and fatigue in people with Parkinson's disease, the authors indicate that the lack of finding could be attributed to the low levels of attendance (on average once a week) and they suggest that future studies should explore the effect of specific doses of prescribed exercise (Winward, Sackley et al. 2012). Only one exercise

study was found directed at treating fatigue in people with Parkinson's disease showing the field is relatively unexplored, and more research into exercise type, dosage, and duration could add to providing a clearer picture on the effects of exercise on fatigue in people with Parkinson's disease.

As discussed previously fatigue is a complex phenomenon due to the unknown pathophysiology, the numerous co-factors influencing fatigue, and the numerous methods to measure fatigue; it would be important to first explore fatigue further in relation to physical activity and exercise tolerance in order to explore the possibilities of an exercise intervention to treat fatigue in people with Parkinson's disease.

The next Chapter will explore relationships between self-reported fatigue and physical activity and exercise tolerance.

Chapter 4: Fatigue, baseline correlations

Summary

First, as a sub-study, the day to day reliability of the activity monitor (GeneActiv) was assessed. For this sub-study, 30 patients were included and results show that there is no difference in activity between the days of the week. Furthermore, this chapter is a cross sectional study investigating associations between self-reported fatigue and a set of measures including: disease severity, quality of life, mobility, physical activity, and exercise capacity. For the cross-sectional study, 89 patients were included. Significant Pearson correlations were found between the self-reported fatigue and self-reported fatigue during the exercise tolerance test (RPEbreath (r=-0.282; p=0.024)); (RPElegs r=-0.261; p=0.033)); respiratory exchange rate (r=-0.309; p=0.002) and GENEActiv light activity (-0.209; p=0.049). The possible correlation between and self-reported fatigue exercise capacity may implicate that if exercise capacity (measured as respiratory exchange ratio) is improved by for example an exercise programme, self-reported fatigue may be improved as well.

4.1. Introduction

As described previously, fatigue is a major issue in people with Parkinson's disease. Despite the high prevalence of fatigue, the systematic review and meta-analysis (Chapter 3) concluded that currently there is no effective way of treating fatigue in people with Parkinson's disease (Franssen, Winward et al. 2014), supporting the need to better understand this symptom in order to develop effective interventions.

Although fatigue in relation to psychometrics has been well studied and described in people with Parkinson's disease including quality of life (Havlikova, Rosenberger et al. 2008, Elbers, van Wegen et al. 2014), sleepiness (Karlsen, Larsen et al. 1999, Alves, Wentzel-Larsen et al. 2004, Friedman, Brown et al. 2007), and depression (Karlsen, Larsen et al. 1999, Alves, Wentzel-Larsen et al. 2004, Okuma, Kamei et al. 2009) as described in Chapter 2. Fatigue and quality of life seem to be correlated as shown in the study of Herlofson and Larsen, where 66 participants were included and fatigue related to a lower quality of life as well as in the study of Elbers et al. in which 153 participants were included and results showed that participants that experienced more fatigue, reported lower levels of quality of life. It must be noted however, that the authors showed that the

relationship between fatigue and quality of life was confounded by depression and anxiety. Studies suggest that fatigue and the degree of sleepiness in Parkinson's disease patients are unrelated (Karlsen, Larsen et al. 1999, Alves, Wentzel-Larsen et al. 2004). In the study of Karlsen et al. patients with sleepiness were excluded from the cohort of participants, and it was found that 43.5% of the cohort was fatigued, indicating that fatigue is present in people without sleepiness. Similarly, Alves et al. excluded all people with sleepiness from their cohort and found that the prevalence rate of fatigue remained high across all years (32.1% in 1993; 38.9% in 2001), again indicating that fatigue is present in people with Parkinson's disease separate from sleepiness. Finally, although depression seems to be related to fatigue, studies show that non-depressed participants still show a high percentage of fatigue. A long term study into the relationship between fatigue and depression found that fatigue is related to depression (Alves, Wentzel-Larsen et al. 2004). In this study 233 people with Parkinson's disease were included in 1993 and were followed up for eight years, with 111 people being followed up in 1997 and 78 people in 2001. The study found significant higher depression scores in fatigued patients versus non fatigued patients (Alves, Wentzel-Larsen et al. 2004). However, they did find a high number of fatigued patients that were not depressed (Alves, Wentzel-Larsen et al. 2004). Furthermore, , several studies that investigate fatigue in a cohort of Parkinson's disease patients without depression find that fatigue is present in 41-50% of the patients (Karlsen, Larsen et al. 1999, Herlofson and Larsen 2002, Okuma, Kamei et al. 2009). In the study of Karlsen et al. 233 patients with Parkinson's disease were examined and result showed that fatigued patients were more depressed; again, once patients with depression were excluded, the number of patients that were fatigued remained high (43.5%) (Karlsen, Larsen et al. 1999). Herlofson and Larsen looked into fatigue in non-depressed patients with Parkinson's disease and found that in 66 people, 33 people were fatigued, indicating that fatigue is present in non-depressed patients with Parkinson's disease (Herlofson and Larsen 2002). Finally, in the study of Okuma et al. 361 Japanese people with Parkinson's disease were assessed and fatigue was present in 41.8% and a significant higher depression was found in fatigued people (Okuma, Kamei et al. 2009), however, a logistic regression did not find depression as a significant factor in relation to fatigue (Okuma, Kamei et al. 2009). However, fatigue in relation to measures of physical performance has been studied less.

In Chapter 2, the possible relation between fatigue and disease severity is described. Some studies have found that patients with self-reported fatigue had more severe disease status (Herlofson and Larsen 2002, Havlikova, Rosenberger et al. 2008), where other studies have found that disease severity did not correlate with fatigue (Friedman and Friedman 1993, van Hilten, Weggeman et al. 1993, Abe, Takanashi et al. 2000, Lou, Kearns et al. 2001, Shulman, Taback et al. 2001) as described in Chapter 2. Because it is still unclear what the relation between self-reported fatigue and disease severity is, more research is required; since there is more research leaning towards a relationship between the two, it is expected that a self-reported fatigue and disease severity will correlate. As described previously in Chapter 2, it is expected that self-reported fatigue correlates to self-reported quality of life (Herlofson and Larsen 2003, Havlikova, Rosenberger et al. 2008).

Research into fatigue in relation to mobility, physical activity and exercise tolerance in people with Parkinson's disease is scarce. Research in stroke has shown that mobility is likely not to be related to self-reported fatigue (Michael, Allen et al. 2006). Furthermore, previous research in a small sample size indicated that fatigue is related to both exercise tolerance and physical activity (Garber and Friedman 2003). In the study of Garber and Friedman, only 37 patients with Parkinson's disease were assessed on disease severity, fatigue, functional capacity, physical activity, and mobility. They found increased levels of fatigue were associated with decreased levels of leisure physical activity, lower frequency of vigorous physical activity, less time spent moving about performing daily tasks each day, lower diastolic blood pressure and VO_{2max}, and longer Up and Go performance time (Garber and Friedman 2003). In this study only a small sample size was included which can be an issue in cross sectional studies which may not represent the general group (Mann 2003). Furthermore, they used a questionnaire to assess physical activity. Questionnaires assessing physical activity have been shown to have limitations in terms of their reliability and validity, activity monitors could give a more accurate indication of physical activity (Prince, Adamo et al. 2008). A study using a larger sample size, could give more generalizable results; furthermore, using activity monitors could give a more accurate indication of physical activity, than using just questionnaires.

To date, it is unclear whether it is possible to improve self-reported fatigue in people with Parkinson's disease. In order to better understand relationships between self-reported

fatigue and exercise this chapter aims to explore the correlations between self-reported fatigue and physical measures including disease severity, aerobic capacity and mobility that can be improved using an exercise programme.

Although cross sectional studies are limited by the fact that they are carried out at one time point and give no indication of the sequence of events, they can investigate associations between risk factors and the outcome of interest (Levin 2006). The sample and response rate determine how well results can be generalised to the population as a whole (Levin 2006).

4.1.1 Aims

- to explore relationships between self-reported fatigue and activity levels in people with Parkinson's disease;
- to explore relationships between self-reported fatigue and exercise tolerance in people with Parkinson's disease

4.2 Methods

4.2.1 Participants

A cross sectional study was conducted. Patients with idiopathic Parkinson's disease were recruited between December 2011 and August 2013 as part of a single-blinded Randomised Controlled Trial (Clinical Trial Gov number: NCT01439022; Research Ethics Committee reference: 11/SC/0267; funding: National Institute for Health Research). (Participant flow and drop out throughout the whole trial will be described in Chapter 5). Recruitment of participants was facilitated by the National Institute for Health Research Clinical Research network: The Dementias and neurodegeneration research network. Possible participants were approached by means of promotion by the neurologist and Parkinson's nurses; at local Parkinson's meetings; and by means of invitation letters from GP surgeries. Inclusion criteria for the study were: (i) diagnosis of idiopathic Parkinson's disease (as defined by the United Kingdom Parkinson's disease Society Brain Bank clinical diagnostic criteria (see appendix 1) (Hughes, Daniel et al. 1992)); (ii) able to walk ≥100 meters. Exclusion criteria were: (i) dementia; (ii) history of additional prior neurological condition; (iii) severe depression or psychosis or a mental state that would preclude consistent active involvement with the study over its duration; (iv) cardiac

precautions that would prevent the subject from completing the full battery of outcome measures; (v) any known contraindication to exercise; (vi) reduced cognitive function of any cause (MMSE < 23); (vii) an orthopaedic condition that limited independent walking. After agreeing to take part in the study, participants came to the laboratory for one visit, where the main assessor took written informed consent prior to participation of all participants, in accordance to the Declaration of Helsinki. Participants' medication was continued as normal and was recorded.

4.2.2 Measures

4.2.2.1 Fatigue

In order to establish fatigue, that is listed as the health condition in the ICF-model described in Figure 3, a self-reported fatigue measure was chosen. Measures of self-reported fatigue have been described in Chapter 2. For this study, the Fatigue Severity Scales (FSS) was chosen as outcome measure to assess subjective fatigue (see appendix 4) over the The Multidimensional Fatigue Inventory and the Parkinson's Fatigue scale as the scale is brief and easy to administer; it has shown sensitivity to change in previous clinical trials; and it is most commonly used to assess fatigue in people with Parkinson's disease (Fabbrini, Latorre et al. 2013). The items cover motivation; physical function; responsibilities; work, family or social life; exercise; how easily fatigued; frequency of problem; and priority of symptoms (Krupp, LaRocca et al. 1989).

4.2.2.2 Disease severity

In order to establish the level of severity of Parkinson's disease of the participants, disease severity, that is described in the ICF-model under body function and structures, was measured. For assessing the disease severity and progression in Parkinson's disease patients two scales are commonly used: the Movement Disorder Sponsored Unified Parkinson Disease Rating Scale (MDS-UPDRS) (see appendix 5) and the Hoehn and Yahr scale (Dibble, Cavanaugh et al. 2010). The Hoehn and Yahr scale is widely utilized and accepted (Goetz, Poewe et al. 2004) and included in the MDS-UPDRS. The MDS-UPDRS is shown to be a valid and reliable questionnaire (Winter, von Campenhausen et al. 2011). It focuses on impairments associated with Parkinson's disease (Dibble, Cavanaugh et al. 2010). The MDS-UPDRS is the most widely used clinical rating scale for Parkinson's disease and it is provided with clear and detailed descriptions of methods for data

acquisition (Goetz, Tilley et al. 2008). The questionnaire contains four parts: part I mainly includes participation as described in the ICF-model and covers non-motor experiences of daily living, the first six questions are administered by the researcher; the other questions are self-administered. Part II covers activities as listed in the ICF model and concerns motor experiences of daily living and is completely self-administered. Part III, that covers body function and structures as listed in the ICF-model, is a motor examination and part four includes questions about motor complications, both sections (three and four) are administered by the researcher (Goetz 2011). Each question has 5 response possibilities: 0 (normal); 1 (slight); 2 (mild); 3 (moderate); and 4 (severe). The time required to complete all parts of the questionnaire is approximately 40 minutes. The scale ranges from 0 to 132 and the lower the score, the less disability. The scale has a floor, but no ceiling effect (Goetz, Tilley et al. 2008). The scale has shown to have excellent factor validity if all parts are considered separately (Goetz, Tilley et al. 2008). Throughout this thesis, part III of the MDS-UPDRS will be analysed and discussed. Part III of the MDS-UPDRS was selected because it focuses on motor symptoms which are likely to change with an exercise intervention (Ridgel, Vitek et al. 2009, Uc, Doerschug et al. 2014). Furthermore, this part of the MDS-UPDRS was chosen over the Hoehn and Yahr scale because the Hoehn and Yahr scale measures unilateral versus bilateral signs and presence or absence of gait balance impairments. Therefore, an increment in the Hoehn and Yahr scale does not necessarily represent a higher degree of overall motor dysfunction (Goetz, Poewe et al. 2004). Furthermore, the Hoehn and Yahr scale seems relatively insensitive to treatment induced change, especially in the lower categories (Goetz, Poewe et al. 2004), which is the target population of this study.

4.2.2.3 Two minute walk test

A walk test was used as an indicator of the functional ability of the participants. Mobility is falls under activities in the ICF-model. Walk tests can be administered as a means of evaluating functional status and to monitor the effectiveness of an intervention (Solway, Brooks et al. 2001). The 12-minute walk test (12MWT) was originally developed to assess physical fitness in healthy young men (Brooks, Parsons et al. 2004). It is a useful and reproducible measure of exercise tolerance (Butland, Pang et al. 1982). More recently, shorter versions of this test, the six- and two-minute walk test (6MWT; 2MWT), have been developed (Butland, Pang et al. 1982). In all tests participants walk between two markers

on a measured trail, and try to cover as much ground as possible in a set time frame (e.g. two, six or twelve minutes) (Brooks, Parsons et al. 2004). In other patient populations and in Parkinson's disease, the 2MWT is shown to be a reliable, feasible and efficient measure (Light, Behrman et al. 1997, Brooks, Hunter et al. 2002, Brooks, Parsons et al. 2004). A recent systematic review described the psychometric properties of the 2MWT and found that the 2MWT could be a valid walk-test for individuals with neurological conditions by correlating the 2MWT with the 6MWT, 12MWT, 10 meter walk test, the SF-36 and the modified Barthel Index (Pin 2014). In this research the 2MWT was chosen as a measure of functional ability.

4.2.2.4 Quality of life

Quality of life, as described under participation in the ICF-model, was measured using a self-administered questionnaire, the short form 36 (SF-36) (appendix 6). The SF-36 is widely used (Leonardi, Raggi et al. 2012) and the validity of this questionnaire has been tested repeatedly (Dibble, Cavanaugh et al. 2010). The SF-36 gives information on eight different domains (Jenkinson, Layte et al. 1997). These domains are: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health (Ware 2014). The SF-36 has been recommended for use in Parkinson's disease (Martinez-Martin, Jeukens-Visser et al. 2011). Compared to healthy participants, people with Parkinson's disease generally report far greater levels of disability in terms of functioning and well-being (Jenkinson, Peto et al. 1995). (Martinez-Martin, Jeukens-Visser et al. 2011). Other quality of life questionnaires that are frequently used include the EuroQol 5D 5L and the Parkinson's disease specific one Parkinson's Disease Quest 39. The EuroQol 5D 5L is brief and easy to administer, however it is not likely to detect change (Marra, Woolcott et al. 2005). Generic quality of life scale might overlook important specific aspect that could be influenced by having Parkinson's disease (Jenkinson, Fitzpatrick et al. 1997). There are Parkinson's disease specific questionnaires that measure quality of life, including the Parkinson's Disease Quest 39, however, generic scales have a large amount of reference data, are widely available and utilized in many Parkinson's disease studies (Martinez-Martin, Jeukens-Visser et al. 2011).

4.2.2.5 Physical Activity Questionnaire in the Elderly

To monitor physical activity levels in the participants (described under activities in the ICF-model), a physical activity questionnaire was used. The Physical Activity Questionnaire in the Elderly (PASE) (appendix 7) is a questionnaire which looks at leisure time, household and work-related activities and physical activity recall over the last week. It is an easily scored, quick to tool to assess physical activity in an elderly population (Schuit, Schouten et al. 1997). The overall score ranges from 0 to 400 or more, with a higher score indicating more activity. Studies have shown that this questionnaire is reliable and valid (Washburn, Smith et al. 1993, Liu, Buffart et al. 2011). Also test-retest reliability was shown to be good (Liu, Buffart et al. 2011). A downside of the PASE is that the questionnaire may overestimate women's physical activity as compared to men since women normally have a greater engagement in heavy housework and taking care of others (Schuit, Schouten et al. 1997) (appendix 7). There are currently no Parkinson's disease specific questionnaires to measure physical activity levels. Other questionnaires used in studies in people with Parkinson's disease are for example the Yale Physical Activity survey (Garber and Friedman 2003, Delikanaki-Skaribas, Trail et al. 2009, Nocera, Amano et al. 2013) and Godin Leisure Activity Questionnaire (Garber and Friedman 2003, Nocera, Amano et al. 2013). Although the Yale Physical Activity Survey showed good correlations with VO_{2max}, but accuracy in assessing low-intensity activities, activities likely to be conducted by people with Parkinson's disease, is not established (Bonnefoy, Normand et al. 2001). Furthermore, both the Yale Physical Activity Survey and the Yale Physical Activity survey are both not specifically tailored to elderly people, which is likely to be the core group of participants in this study, whereas the PASE is specifically designed for an elderly population.

4.2.2.6 Activity monitor (GENEActiv)

Another measure to establish physical activity patterns (described under activities in the ICF-model) is an activity monitor. The GENEActiv is a wrist worn activity monitor. The GENEActiv, was worn by the participants around the wrist for seven days following an assessment. The GENEAactiv is a triaxial acceleration sensor which is lightweight, waterproof. It sampled at 100Hz for seven days. The participants sent the monitor back in a pre-stamped, addressed envelope. The data was then downloaded from the device onto the computer and transformed into a 60-second epoch excel file. An Excel Macro was

designed by GENEActiv (GENEActiv 2014) which generated minutes per day spent sedentary, performing light, moderate or vigorous activities (Welch, Bassett et al. 2014). The file that was collected from the participants was run through this Macro to calculate a total weekly activity count. Finally, one outcome was calculated by averaging the data across the days.

4.2.2.7 Exercise tolerance

Exercise tolerance, which falls under body function and structures in the ICF-model, is described by means of aerobic capacity. Aerobic capacity of the participants was determined using a modified Sjostrand cycle ergometer test (Sjostrand 1947). Participants were thoroughly screened before the fitness test including the Physical Activity Readiness Questionnaire (appendix 8) (Glendhill 2002) and blood pressure measurement (ACSM 2009), and a 12-lead Electrocardiogram. Electrocardiograms were assessed following a set of criteria, any values found in the electrocardiograms that were outside the set parameters were run past the study neurologist. Following advice from the neurologist, the participants were either asked to perform the cycle ergometer test, or their general practitioner (GP) was asked to give advice on the participant performing the ergometer test. Exclusion criteria for the exercise test were: systolic blood pressure > 180 mmHg; diastolic blood pressure > 100 mmHg; a known heart murmur, stents fitted, and advice from the GP not to do the exercise test. Prior to testing sessions, participants were asked to refrain from the consumption of alcohol, cigarettes, food, caffeine and to avoid exercise for a period of three hours. Each participant received a full description of the exercise test procedure and was familiarised with Borg's rating of perceived exertion (RPE) CR10 Scale (0-10) using a set text (see appendix 9) (Borg 1998). Saddle heights were adjusted to accommodate knee flexion (170° to 175°). Feet were supported in the pedals by toe clips, and straps.

All participants underwent an incremental cycle ergometer exercise test (Lode Excalibur Sport, Gronigen, Netherlands) of two minute stages, after an initial one minute of unloaded cycling. Workload was progressed based on the modified Sjostrand protocol (increasing workload initially by 50 Watts and then by 25 Watts). The test ended at volitional exhaustion or if the participant was unable to maintain a cadence of 50 rpm. The criteria for true maximal effort included a plateau in $\dot{V}O_2$ max; maximal heart rate $\geq$ 95% of age

predicted maximum; and respiratory exchange ratio >1.06 (Winter 2007). Verbal encouragement was given throughout.

Pulmonary gas exchange was measured breath-by-breath using an automated metabolic analysis system (Cortex Metalyzer, Leipzig Germany). The system was calibrated prior to each test in accordance to manufacturer's instructions. All participants wore a face mask covering the nose and mouth connected to a low-resistance volume transducer (Triple V, Hoechberg, Germany). Heart rate was recorded continuously throughout the testing protocol using short-range telemetry (Polar S810, Finland). The respiratory exchange ratio is the radio of carbon dioxide (VCO_2) output over oxygen (VO_2) uptake (Cooper and Storer 2001) and maximum respiratory exchange ratio was averaged over the last 30 seconds of the test. End exercise respiratory exchange ratio can be used to represent objective maximal effort (Cooper and Storer 2001). Trained people show lower respiratory exchange ratios than untrained people for a given workforce (Ramos-Jiménez, Hernández-Torres et al. 2008).

4.2.2.8 Self-reported fatigue during exercise tolerance

As a marker of single-activity self-reported fatigue, the CR10 rating of perceived exertion scale was used to measure leg fatigue and breathlessness at the end of each stage, which previously has been done in Multiple Sclerosis (Dawes, Collett et al. 2014). The original rate of perceived exertion scale was a 15-point scale from 6 to 20 reflecting the range of heart rate in a healthy group of young subjects during maximal exercise on a cycle ergometer. The ratio scales method showed that the perception of exertion grew with the physical work load (Borg 1990). The CR10 rate of perceived exertion is a category ratio scale from 1 to 10 with 1 being no effort and 10 being maximal effort (Borg 1998) and it has shown reasonable validity, sensitivity and reliability as a subjective measure in the healthy population. Although reliability in Parkinson's disease has not been researched specifically, the scale is found to be valid in other clinical populations like in people with chronic lower back pain (Dawes, Barker et al. 2005). It is easy to use because of its simplicity. It enables determination of both relative and absolute subjective levels (Noble and Robertson 1996). To standardise the procedure and improve accuracy of the rate of perceived exertion scale it was important that participants understood both the verbal

anchors and the numerical value. The following instructions were given to each participant (ACSM 2014):

"_____(name), during the exercise test we want you to pay close attention to how hard the exercise is. In particular we want to know how hard you are breathing, and the sensations that you are feeling in your legs. I'll be asking you to select a number from this scale from 1 to 10. Each number represents the amount of effort that you can feel in your breathing or legs. The words are there to help you choose a number. Try not to underestimate or overestimate your feelings of exertion. So, while you are resting, looking at the scale, how would you describe your breathing now? (Pause) And using the same scale, how would you describe the feelings in your legs?

4.2.2.9 Other measures

All measures described above were collected as part of a larger randomised controlled trial (Clinical Trial Gov number: NCT01439022; Ethics number: 11/SC/02/67). This trial included other measures not described and discussed in this thesis.

4.2.3 Data handling and analyses

Data were analysed using IBM SPSS Statistics 22. Descriptive statistics (means and standard deviations) were generated to describe the characteristics of the participants.

4.2.3.1 GENEActiv day to day reliability

The GENEActiv devices were given to the participants on different days of the week; hence the start day was different for different participants. Furthermore, data collected from the GENEAactiv devices did not always contain data of six full days. In order to establish whether incomplete data (ie. if data collection of less than six days occurred) could be used, it was investigated whether there were systematic differences in day of the week in the number of minutes per activity. Furthermore, it was necessary to consider possible differences between different days of the week included in this dataset since previous research suggests there may be differences in activities during weekdays compared to weekend days (Jago, Anderson et al. 2005, Treuth, Catellier et al. 2007, Corder, Craggs et al. 2013). In a subgroup of the participants, day to day variability in the GENEActiv data was investigated. For this, averages of each activity of each day (all data captured by the GENEActiv was included if there was three days or more worth of data)

were compared in 30 subjects to establish whether there was a difference in activity between the days. A one-way-ANOVA was performed to establish any differences.

Previous research has shown that a minimum of 3-4 days is required to achieve 80% reliability, which was the proportion of total variance accounted for by inter-individual sources (Matthews, Ainsworth et al. 2002). Therefore, it was decided that it was valid to average at least three days, regardless of when the days were in the week, as overall outcome measure for the GENEActiv in case no differences were found in the ANOVA.

4.2.3.2 Correlations

Associations were explored using Pearson correlation coefficients. Subjective fatigue (Fatigue Severity Scale) was plotted against the other fatigue measures as a scatterplot to examine for systematic bias, random error and heteroscedasticity. Significance was set as $p>0.05$.

4.4 Results

4.4.1 GENEActiv day-to-day reliability

Table 3 presents an overview of the average total number of minutes per day per activity (sedentary, light, moderate and vigorous). The ANOVA revealed no significant difference between days for each activity.

Table 3: Overview of average minutes per day spent sedentary; doing light, moderate or vigorous activity as measured by the GENEActiv and p-values for comparisons per day

	Sedentary Mean (SD) Minutes	**Light Mean (SD) Minutes**	**Moderate Mean (SD) Minutes**	**Vigorous Mean (SD) Minutes**
Monday (n=31)	777 (117)	81 (55)	80 (71)	1 (4)
Tuesday (n=25)	755 (131)	93 (57)	98 (79)	1 (2)
Wednesday (n=28)	773 (156)	92 (56)	92 (85)	3 (10)
Thursday (n=17)	752 (154)	86 (49)	85 (66)	1 (3)
Friday (n=25)	736 (113)	93 (55)	101 (68)	2 (4)
Saturday (n=30)	795 (145)	91 (57)	74 (65)	1 (1)
Sunday (n=31)	771 (123)	81 (63)	72 (59)	1 (4)
p-value ANOVA	0.772	0.947	0.653	0.621

Abbreviations: SD: Standard Deviation.

4.4.2 Demographics

In total 105 participants were included in the study (the power calculation for the trial will be provided in Chapter 5). Eighty three participants were able to participate following in- and exclusion criteria as described under heading 4.2.2.7. Table 4 gives an overview of the baseline descriptive statistics of all 105 participants (apart from heart rate (n=83)).

Table 4: Baseline descriptive statistics (n=105)

Variable	Mean (SD)	Range
Gender	Male =61	
Age (Years)	66.9 (7.8)	39-86
Years of PD	5.0 (4.1)	0-18.0
UPDRS III (range 0-132)	18 (10)	0-57
2 MWT (meters)	141 (24)	66-221
SF-36 PH (range 0-100)	63 (18)	21-92
SF-36 MH (range 0-100)	70 (17)	28-93
Heart rate (bpm)	129 (24)	39-183

Abbreviations: SD: Standard Deviation; PD: Parkinson's disease; UPDRS III: Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale section three; SF-36: Short Form 36; PH: Physical Health; MH: Mental Health.

Of all 105 participants sixty-nine participants were on dopamine medication; 23 participants took dopamine agonists; one participant took glutamate agonists; two participants took anticholinergics; six people were one Monamine Oxidase Type B inhibitor (MOAB) medication and six people were not on drugs to treat Parkinson's disease. Sixty-nine participants were prescribed one Parkinson's disease specific drug were the other 30 participants on Parkinson's disease drugs took a mixture of several Parkinson's disease drugs. Furthermore, 45 participants were taking both Parkinson's disease as well as non-Parkinson's disease drugs and three people did not take any Parkinson's disease specific medication but did take other drugs.

Non Parkinson's disease drugs included anti-depressants (n=12); anti-hypertensives (n=27); cholesterol lowering drugs (n=17); bowel and urinary tract medication (n=28); anti-sickness drugs (n=5); drugs for thyroid disorder (n=8); drugs for bi-polar disorder (n=1); drugs for pancreatic insufficiency (n=1); drugs for tachycardia (n=1); drugs for stomach ulcers (n=2); drugs for insomnia (n=1); drugs for diabetes (n=3); drugs for arthritis (n=1); drugs for gout (n=2); drugs for migraine (n=1); and drugs for chronic obstructive pulmonary disease (n=1). Table 5 gives an overview of mean and standard deviation (SD) of self-reported fatigue; physical activity and exercise tolerance.

Table 5: Measures of fatigue, physical activity and exercise tolerance showing mean, standard deviation (SD) and range of the scale

Variable	Mean (SD)	Range
FSS (range: 1-7) (n=105)	3.8 (1.4)	1.1-7
GENEActiv sedentary (minutes) (n=89)	766 (139)	346-1134
GENEActiv light (minutes) (n=89)	88 (43)	16-238
GENEActiv moderate (minutes) (n=89)	90 (80)	5-424
GENEActiv vigorous (minutes) (n=89)	4 (17)	0-147
RER (range: 0.85-1.5) (n=82)	1.2 (0.1)	0.9-1.4
RPE breath (range: 0-10) (n=83)	6 (2)	0-10
RPE legs (range (0-10) (n=82)	7 (2)	2-10
$\dot{V}O_2$ **(ml*kg*min^{-1}) (n=83)**	23 (7)	9-43

*Abbreviations: SD: Standard Deviation; FSS: Fatigue Severity Scales; RER: Respiratory Exchange Ratio; RPE: Rate of Perceived Exertion.

4.4.3 Correlations

Table 6 displays Pearson correlations between self-reported fatigue measures of physical activity and exercise tolerance. Significant Pearson correlations (small to moderate effect sizes) were found between the self-reported fatigue (Fatigue Severity Scale) and self-reported fatigue during the exercise tolerance test (fatigue severity scale and rate of perceived exertion for breathing (r=-0.282; p=0.024)); fatigue severity scale and rate of perceived exertion for the legs (r=-0.261; p=0.033); maximum respiratory exchange ratio (r=-0.309; p=0.002) (see Figure 9). Furthermore, a significant Pearson correlation was found between self-reported fatigue and GENEActiv light activity (-0.209; p=0.049).

Table 6**:** Pearson correlations with self-reported fatigue (Fatigue Severity Scale)

Variable	FSS Pearson r	p-value
GENEActiv sedentary (n=89)	0.040	0.710
GENEActiv light activity (n=89)	-0.209*	0.049
GENEActiv moderate activity (n=89)	-0.121	0.258
RER (n=83)	-0.309	0.051
RPE breath (n=82)	-0.282*	0.010
RPE legs (n=82)	-0.261*	0.018
$\dot{V}O_2$ (ml*kg*min^{-1})	-0.179	0.076

*Pearson r is significant (p<0.05); abbreviations: FSS: Fatigue Severity Scale; RER: Respiratory Exchange Ratio; RPE: Rate of Perceived Exertion

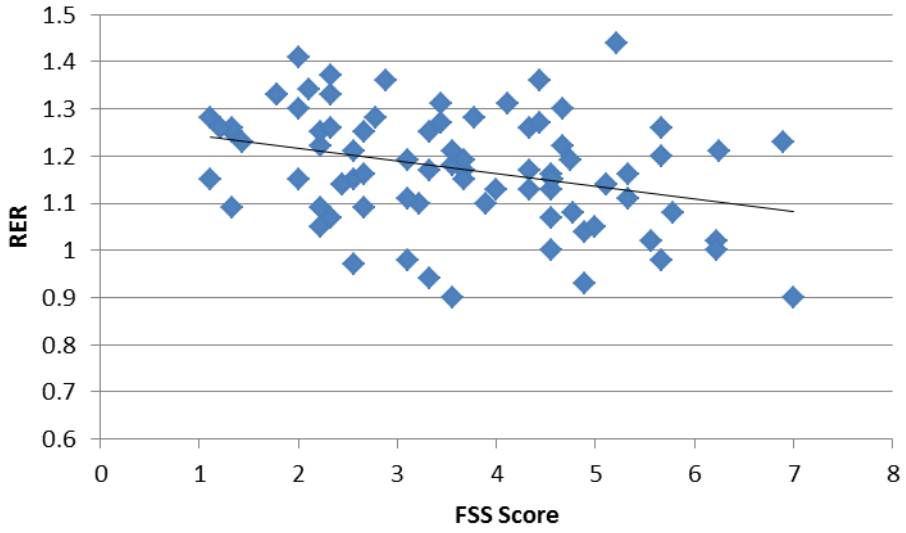

Figure 9: Strongest Pearson correlation: Fatigue Severity Scale and the Respiratory Exchange Ratio (r=-0.309; p=0.004)

No significant correlations were found between self-reported fatigue (Fatigue Severity Scale) and VO_2max (r=-0.179; p=0.076) and self- reported fatigue and sedentary time and moderate activity (r=-0.121; p=0.258) as measured by the GENEActiv (see Table 6).

4.5 Discussion

In current research fatigue in Parkinson's disease is mostly measured using self-reported questionnaires. This study found that 41% of participants was fatigued (Fatigue Severity Scale score>4), which is slightly lower than most studies (Herlofson and Larsen 2003, Okuma, Kamei et al. 2009, Friedman, Abrantes et al. 2011) but still shows fatigue is present in a large portion of the participants, hence this shows that fatigue is an important issue to address. A possible explanation for the relatively low number of people classified as fatigued in this study is that the participants in this study were recruited as part of a larger randomised controlled trial where exercise was investigated. It is possible that recruitment bias has been a problem here. As mentioned, in cross sectional studies it is important to have a representative sample (Levin 2006), which may not be the case here as participants were recruited for an exercise study, possibly resulting in a skewed sample of participants. Research has often found that participants that are recruited for general and physical activity studies differ from the general population (van Heuvelen, Hochstenbach et al. 2005, Martinson, Crain et al. 2010).

4.5.1 Relationships between self-reported fatigue and activity levels

Different correlations were found between self-reported fatigue (as measured by the Fatigue Severity Scale) and activity levels (as measured by the GENEActiv). Whilst there was a correlation between fatigue and light activity, no other correlations were found. People that were more fatigued performed less light activity; however, they were not necessarily more sedentary or performing less moderate activities. This suggests that regardless of their fatigue, people with Parkinson's disease do not seem to do more or less activity. Previous research has found inconclusive results regarding the relationship between fatigue and physical activity. Where one study investigating the effects of physical activity levels in people with Parkinson's disease found no correlation between the two, another study investigation looking into fatigue and activity levels found that people with more severe self-reported fatigue were more sedentary (Garber and Friedman 2003, Rocha dos Santos, Barbieri et al. 2014). It may be important to split physical activity into different components, in order to better establish what people with Parkinson's disease do during a day, and what influence this has on fatigue and vice versa.

4.5.2 Relationships between self-reported fatigue and exercise tolerance

Results from this study from the peak recordings of both rate of perceived exertion and respiratory exchange ratio suggest that participants had a normal exercise response and relationship between objective and subjective measures during it. A true maximal aerobic capacity (VO_2 max) is defined as a maximal heart rate (HR_{max}) > 85% of age-adjusted predicted HR_{max} and a respiratory exchange ratio > 1.10 (Katzel, Sorkin et al. 2011). Only 37 participants reached an age predicted HR_{max} of >85% and a respiratory exchange ratio of >1.10. Medications such as β-blockers will affect some physical test results (ACSM 2014), therefore, rate of perceived exertion was taken into account as well. Rate of perceived exertion at the end of the test was on average 7 (rate of perceived exertion for the legs) and 6 (rate of perceived exertion for breathing) out of 10 suggesting that neither leg fatigue nor breathlessness were the reason for terminating the acute exercise intervention. As only four people performing the exercise test were on β-blockers, no further analyses have been done to look into the effects of β-blockers on the data. This data is in line with other neurological populations and suggests that either motivation or an inability to move was the limiting factor during an endurance test (Weiser, Kinsman et al. 1973, Noble and Robertson 1996, Dawes, Collett et al. 2014). This study found a negative correlation between self-reported fatigue and the respiratory exchange ratio, indicating that people that report lower fatigue were able to work harder than people that reported higher levels of fatigue. There is one previous study that investigated the correlation of self-reported fatigue (using the Fatigue Severity Scale) and exercise tolerance in patients with Parkinson's disease in 37 subjects (Garber and Friedman 2003). Garber et al (2003) hypothesized that people who are more fatigued have poorer functional capacity which their findings confirmed (Garber and Friedman 2003). The current study was conducted in a much larger sample size which allows for a better generalisability.

This study found that self-reported fatigue measured during exercise tolerance (measured as rate of perceived exertion) and self-reported fatigue over a longer period of time (as measured by the Fatigue Severity Scale) correlated well. Furthermore, exercise tolerance and self-reported fatigue (as measured by the Fatigue Severity Scale) correlated with one another. Since previous research has shown that it is possible to increase aerobic capacity (Bergen, Toole et al. 2002, Uc, Doerschug et al. 2014) and respiratory exchange ratio (Friedlander, Casazza et al. 1997, Bergman and Brooks 1999) in people with Parkinson's

disease and exercise tolerance and self-reported fatigue may be related, it is plausible that an increase in exercise tolerance could lead to a possible decrease in self-reported fatigue. Furthermore, previously it has been discussed that fatigue could be related to depression, and quality of life and a lower physical activity. Previous research has shown that aerobic exercise could improve depression (Daley 2008), and increase quality of life (Goodwin, Richards et al. 2008), which could have a positive effect on self-reported fatigue.

4.5.3 Limitations

There are some limitations to the study. Firstly, confounding factors of fatigue like depression and sleep disorder are not specifically addressed by separate questionnaires, however, previous studies show that fatigue is present regardless of the presence of depression and sleep disorders (van Hilten, Weggeman et al. 1993, Karlsen, Larsen et al. 1999, Herlofson and Larsen 2002, Alves, Wentzel-Larsen et al. 2004, Herlofson, Ongre et al. 2012). Secondly, there is still no universally accepted measure of fatigue in people with Parkinson's disease. The Fatigue Severity Scale is, however, used in several studies of people with Parkinson's disease (Alves, Wentzel-Larsen et al. 2004, Tyne, Taylor et al. 2010, Valko, Waldvogel et al. 2010, Elbers, Rietberg et al. 2012). Finally, patients recruited for this study were part of a larger exercise study. It is likely that the sample described here is not a representative sample as participants were recruited for a specific purpose, which was a trial investigating exercise, and it is highly likely that the participants were either already doing exercises, or were interested in doing exercise, which may not represent all patients with Parkinson's disease. Furthermore, only people with Parkinson's disease that were able to walk on their own for at least 100 meters were included, which only represent a group of people with Parkinson's disease.

Finally, as discussed in Chapter 3, different drugs can have an influence on fatigue in people with Parkinson's disease. For example, Abe et al (2001) describes a mechanism where patients with fatigue have shown reduced glucose metabolism or reduced isotope uptake, which may be addressed by dopamine which can improve frontal lobe function and may improve fatigue in that way (Abe, Takanashi et al. 2001). Although drugs could have an influence on fatigue, no further analyses have been done into any differences between participants on and participants not on drugs, the main reason being that only two participants were not taking any medication at all. In future studies, it would be interesting

to look at the different effects of drugs on the relationship between fatigue and exercise parameters.

4.5.4 Conclusion

Both the current study, as well as outcomes from previous studies regarding the Fatigue Severity Scale, seem to correlate with measures for aerobic capacity (Garber and Friedman 2003). However, in the current study, respiratory exchange ratio was described as a factor of fatigue which represents how hard people relatively work (Cooper and Storer 2001), rather than just presenting aerobic capacity. This may be an important factor in developing treatment programmes for treating fatigue in people with Parkinson's disease. The possible correlation between the respiratory exchange rate and t self-reported fatigue may implicate that if respiratory exchange ratio is improved (lower respiratory exchange ratio at the same workload) (Jeukendrup, Mensink et al. 1997, Bergman and Brooks 1999, Ramos-Jiménez, Hernández-Torres et al. 2008) by for example an exercise programme, as previously shown in studies (Friedlander, Casazza et al. 1997, Bergman and Brooks 1999), self-reported fatigue could be improved as well.

The next chapter will explore the effects of an exercise programme on fatigue and other measures in people with Parkinson's disease to address the question whether an improvement in fitness could diminish fatigue.

Chapter 5 Randomised controlled trial investigating exercise as a treatment for fatigue in people with Parkinson's disease

Summary

The previous chapter indicated that exercise may improve fatigue in people with Parkinson's disease. This chapter is a randomised controlled trial looking into the effects of exercise on fatigue in people with Parkinson's disease. In the trial, 105 people were included and allocated to either an exercise programme (twice a week for six months; n=54) or a control intervention (handwriting exercises twice a week for six months; n=51). The main finding was that the exercise programme showed an improvement in the UPDRS (Cohen's d = 0.25). No strong effect of the exercise programme on fatigue was detected (Cohen's d = 0.17). Finally, high adherence (twenty-four participants attended at least 76% of all prescribed sessions) and few adverse events showed that the exercise programme is feasible.

5.1 Introduction

Following on from the previous chapter were a correlation was found between respiratory exchange rate and self-reported fatigue, this chapter will build on these results and will explore the effects of an exercise programme to treat fatigue in people with Parkinson's disease.

5.1.1 Exercise for fatigue

In the literature, studies investigating treatment methods for fatigue measure fatigue using self-reported questionnaires. Exercise as a treatment method for this self-reported fatigue was described in Chapter 1. In summary, exercise is often chosen as a treatment method for fatigue in other disorders such as Multiple Sclerosis (Andreasen, Stenager et al. 2011, Pilutti, Greenlee et al. 2013). Findings from studies on exercise, including yoga, aerobic exercise, strength exercise, to improve fatigue in Multiple Sclerosis have shown that exercise may have a small influence on reducing fatigue (Oken, Kishiyama et al. 2004, Surakka, Romberg et al. 2004, Pilutti, Greenlee et al. 2013). However, little research has explored the impact of exercise as a treatment method for fatigue in people with Parkinson's disease.

5.1.2 Exercise for fatigue in Parkinson's disease

In Chapter 1 the possible benefits of both aerobic and anaerobic exercise on Parkinson's disease and fatigue have been described. In brief, animal studies have shown that aerobic exercise increases the concentration of dopamine in the striatum of the rat brain (Hattori, Naoi et al. 1994), which represents a possible mechanism of the benefits of exercise for both symptoms of Parkinson's disease in general and fatigue specifically. Previous studies have also shown that forty minutes of active assisted cycling can increase aerobic capacity (Ridgel, Peacock et al. 2012). Furthermore, a study by Hass *et al.* (2007) concluded that 24 sessions of whole body resistance training improved muscular fitness in people with Parkinson's disease (Hass, Collins et al. 2007). Therefore, an exercise programme including both aerobic and anaerobic exercise may be beneficial for treating fatigue in people with Parkinson's disease.

In Parkinson's disease there is little research into exercise as a treatment method for self-reported fatigue. One exercise study that investigated the effects of exercise on self-reported fatigue was conducted by Winward and colleagues (Winward, Sackley et al. 2012). The current was part of a larger study, the Long-Term Individual Fitness Enablement (LIFE) project, run by the same group that developed the study described in this thesis. In the study, participants with long-term neurological conditions were asked to exercise in a gym-based setting and were instructed to do exercises following current guidance (five aerobic sessions and two strength sessions per week) (Elsworth, Winward et al. 2011). 39 participants with Parkinson's disease were included (control group n=19; intervention group n=20). The study found that in the intervention group a mean of 15 exercise sessions were attended with 55% attending 1 or more times per week (Winward, Sackley et al. 2012). The intervention group was further divided into fatigued (Fatigue Severity Score >4) and non-fatigued participants and only two people out of eight classified as fatigue managed to attend the exercise programme once a week. The study found no effects of a twelve week exercise programme on the Fatigue Severity Scale score (Winward, Sackley et al. 2012), which may be explained by the low attendance; however, reasons of low attendance have not been discussed in the paper. In a more recent study exploring aerobic exercise in the community, people with Parkinson's disease, 60 patients were asked to exercise three times a week for 45 minutes over six months. The study observed that aerobic exercise in the community improved self-reported fatigue in people

with Parkinson's disease (Uc, Doerschug et al. 2014). An interesting finding in this study was that there were difference in fatigue level at the start between completers of the intervention and dropouts out the intervention, with the completers being significant more fatigued at baseline. This may imply that there is a good chance for improvement of the level of fatigue in this group. Overall, more research is needed to establish whether exercise could be a treatment method for fatigue in people with Parkinson's disease and whether it may be effective in people with a certain level of fatigue.

As described in Chapter 4, a higher aerobic capacity correlates significantly with lower self-reported fatigue. This may imply that an improvement in aerobic capacity may lead to an improvement in self-reported fatigue. Previous studies, including a systematic review including fifteen studies looking at resistance training, endurance training and other intensive training modalities in Parkinson's disease found an improvement in aerobic capacity following an exercise programme (Bergen, Toole et al. 2002, Ridgel, Vitek et al. 2009, Uhrbrand, Stenager et al. 2015), therefore it is expected that an exercise programme will increase aerobic capacity which in turn may improve self-reported fatigue.

5.1.3 Duration of exercise programme

A systematic review and meta-analysis including fourteen paper researching of exercise programmes of up to twelve weeks (Goodwin, Richards et al. 2008, Allen, Sherrington et al. 2012), showed that exercise is beneficial with regards to physical functioning, health-related quality of life, strength, balance and gait speed for people with Parkinson's Disease (Goodwin, Richards et al. 2008). Previous work conducted within this group involved a twelve week community based exercise programme in people with long-term neurological conditions. In this trial, participants went to Inclusive Exercise Initiative gyms that offer an inclusive exercise environment, an accessible fitness facility, equipment designed and tested for use by people with disabilities, and fitness staff with expertise in exercise prescription. Participants had to self-direct their exercises to meet their own fitness goals for twelve weeks (Elsworth, Winward et al. 2011). The study found positive results in attendance and suggested a future study looking at long-term effects up to at least six months to confirm any benefit (Elsworth, Winward et al. 2011). One recent study by Schenkman et al (2012) investigating a 16 months exercise trial, followed up 96 participants out of 121 participants at 16 months (79.3% retention rate) which suggests that

a longer-term programme is feasible. The programme compared three interventions. The first intervention consisted of a supervised flexibility/balance/function exercise group. The second group was a supervised aerobic exercise group. Both groups received supervised exercise three days a week for four months; in month five, supervision was tapered and after that they received one supervised session per month. Finally, there was a control group that exercised under supervision during an initial session and then once a month for 16 months. The participants were asked to keep an exercise diary that was reviewed once a month. Their programme lacked a non-exercising control group, but saw no reduction in UPDRS score in both their exercise groups, which one would normally expect in Parkinson's disease due to the progressiveness of the disorder (Schenkman, Hall et al. 2012). Since the benefits of longer term exercise programmes have not been established thoroughly, a six months exercise intervention was developed.

5.1.4 Community exercise

In spite of the well-known benefits of exercise in people with Parkinson's disease it is apparent that there are barriers to participation. Previous research, as described in Chapter 1, has shown that people with disabilities have identified the following barriers for exercise, including community exercise (Elsworth, Dawes et al. 2009):

- Costs
- Negative personal experiences and attitudes as well as fear and embarrassment of exercising
- Perception that fitness instructors will lack knowledge about their condition and how to help them participate in exercise safely and effectively
- Transportation and access
- Equipment (a lack of equipment suitable for and usable by disabled people)
- A fear of losing balance

Furthermore, the following facilitators were identified (Elsworth, Dawes et al. 2009):

- Positive personal attitudes
- Individually tailored gym programmes
- An exercise place that actively supports people with similar conditions and disabilities

- An exercise programme that considers individual motivators for exercise, not necessarily assuming individuals will be motivated by factors such as weight control, body shape or "keeping fit"

The barriers and facilitators described were taken into account when developing the current exercise programme. The programme had to be low-cost, accessible, tailored to the individual, and nearby their home.

Although barriers concerning community exercise facilities are present, community exercise facilities are widely available in the United Kingdom (Elsworth, Winward et al. 2011, Winward 2011). A pilot study exploring the feasibility and acceptability of a community exercise intervention in people with longer-term neurological conditions found that adherence to a twelve week programme was good with participant attending an average of 15 exercise sessions over twelve weeks (Elsworth, Winward et al. 2011, Winward 2011). Therefore, it is expected that a 24 week community based programme in people with Parkinson's disease will show similar results in terms of adherence.

The study also found that participants required on average three physiotherapy support sessions in a twelve week period (Winward 2011), therefore the programme was developed with participants receiving support once a month from an exercise expert.

The aim for the control group was not to provide exercises in a gym setting, but to provide the same support that the participants in the exercise group received (Boutron, Moher et al. 2008). Therefore, the participants in the control group received the same number of support sessions as the participants in the exercise group received.

The components described above were incorporated into an intervention consisting of a randomised controlled trial investigating a community based six months exercise programme.

5.1.4 Aims

- To investigate the effects of a community based six months exercise programme on fatigue in people with Parkinson's disease using an randomised controlled trial
- To explore the adherence to and safety of a community based six months exercise programme in people with Parkinson's disease
- To explore what baseline characteristics could predict adherence to the programme.

- To explore whether participants who attended more sessions of the implemented exercise programme benefitted from larger potential benefits.

5.2 Methods

The study as described below is set up as an external randomised controlled pilot trial.

Since the study is set up as a randomised trial, CONSORT guidelines for reporting randomised trials (see appendix 10) were followed in reporting the trial and the results (Schulz, Altman et al. 2010) (divided over this chapter and the previous chapter).

The intervention is described following TiDier guidelines (see appendix 11) (Hoffmann, Glasziou et al. 2014). The TiDier guidelines have been implemented to improve the completeness of reporting and the replicability of interventions (Hoffmann, Glasziou et al. 2014). Below, the rationale of the components of the trial is described.

This study was a phase II single blind pilot randomised controlled trial. Participants, including in- and exclusion criteria were described in Chapter 4. No changes were made to the methods after commencement of the trial.

5.2.1 Power calculation

As a pilot trial no formal power calculation has been used to direct the sample size, however data from short term exercise studies of the primary outcome measure (of the trial this thesis is based on; the two minute walk test) suggest that effect sizes from changes in motor symptoms observed in the two minute walk test of 0.3 can be expected for exercise one time per week to 0.8 for three times per week, with clinically meaningful change in the elderly of twelve meters or an effect size of 0.55. Thus it is likely that 80 subjects in total would be sufficient to detect an effect size of 0.55 with a power of 80% and alpha of 0.05. Allowing for attrition, in 99 participants there were five people dropping out during a twelve week intervention, thus it was expected that in six months 100 people would allow for attrition.

5.2.2 Randomisation and assessments

The participants were assessed at baseline and then at three (halfway through the intervention), six (at the end of the intervention) and twelve months. Participants recruited to the study were allocated the next available study number by the blinded assessor. The study number related to a computer-generated randomization list drawn up by the Oxford Clinical Trials Unit (Nuffield Department of Primary Care Health Sciences, Oxford University), that randomised individuals (1:1) into either intervention (exercise) or control

(handwriting) groups. The Oxford Clinical Trials Unit used minimisation techniques for randomisation to allow for balancing medication and gender at baseline were used. The list was held by the principal investigator who informed the physiotherapist and exercise professional supporting the intervention of group allocation. The project's physiotherapist, exercise expert and the participants were not blinded to group allocation. Group allocation was concealed from the assessor until the end of the study.

All assessments were conducted at the Movement Science Lab (Oxford Brookes University) by the same blinded assessor, and patients were reminded throughout the trial that the assessor was blinded to the allocated intervention.

5.2.3 Interventions

When and how much: The intervention took place twice a week over a period of six months with each session lasting 60 minutes. Both groups were asked to continue other daily activities as they usually would, including any exercise which was part of their routing before the start of the trial. After the six month assessment no further instruction on exercise (or hand writing practice) was given. Both groups were instructed to perform daily activities as they usual would; including any exercises that were part of their routine before the start of the trial.

5.2.3.1 Experimental Group

Where: The gym-based exercise sessions were delivered in exercise facilities, in Oxfordshire and Berkshire, under the supervision of an exercise expert. Participants were able to choose participating facilities nearby their home to minimise travel burden (which has been identified as a barrier in previous research (Elsworth, Dawes et al. 2009)).

How and who provided: The projects' physiotherapist attended the initial session and ensured that the exercises were appropriate throughout the exercise programme. This first session was also aimed at putting the participant at ease; to get them familiar with the gym; and to introduce them to the staff normally present in the gym, which were identified as barriers for people with neurological illnesses to exercise in a gym facility (Elsworth, Winward et al. 2011). Other staff members working in the gym were fully informed about the study prior to any participants beginning the intervention. Exercise prescription was provided by an exercise professional (registry of exercise professional's level 4 qualification in exercise for long term neurological conditions). The project physiotherapist

ensured that safe exercise prescription was achieved at all times and ensured that any medical/medication issues were best addressed. The participants could contact the projects' exercise expert if anything unusual happened or when they needed more assistance.

When and how much: The exercise programme totalled 48, 60 minutes sessions over a 24 week period (2 times a week).

What: An exercise programme combining aerobic components (as discussed in Chapter 1, aerobic exercises may be beneficial in improving balance, gait, physical function, and quality of life in individuals with Parkinson's disease (Hackney and Earhart 2009, Canning, Allen et al. 2012, Li, Harmer et al. 2012), and anaerobic exercise (as discussed in Chapter 1 resistance training (anaerobic exercise) is the only form of exercise that increases muscle size and strength (ACSM 2014). Anaerobic exercise has shown to improve muscle mass, neuromuscular performance (Taaffe, Duret et al. 1999) which could potentially reduce the risk of falls and fractures in older adults, including people with Parkinson's disease (Falvo, Schilling et al. 2008).

At the start of each session, each participant performed 30 minutes of aerobic training and was able to choose from a treadmill, bicycle ergometer, cross-trainer or rowing ergometer, if the equipment was available. After an initial warm up of 10 minutes, the participant was instructed to exercise so that their heart rate was maintained in an aerobic training zone for 20 minutes (55-85 percentage age predicted maximal heart rate) following prescription guidelines (ACSM 2009) rather than using the exercise tolerance data to determine exercise intensity. Speed and resistance were manipulated to maintain the participant's heart rate within an aerobic zone (medication affecting heart rate was considered). Participants recorded the type of equipment used and actual duration, as well as rating of perceived exertion (RPE, CR10 scale) (Borg 1998) and heart rate in their diaries.

After the aerobic exercise, there were 30 minutes of anaerobic training. Strength was trained on resistance equipment, performed at an initial resistance so ten repetitions could be performed. Leg extension was performed on a seated leg press and squats performed using a chair. Functional core stability/mobility was trained during upper limb training. Upper limb/trunk exercises included: Double arm pull-down, a double arm lateral raise and single arm rotation performed seated, or standing as able.

Tailoring: At the monthly support session, exercise intensities and progression were monitored. The interventions were personalised and progressed according to the following protocols. At the initial session the exercise professional or physiotherapist set the exercise intensity so that the participants achieved 55-85 percentage age predicted maximal heart rate (ACSM 2009), for the duration of the aerobic training, participants were then taught to manipulate speed or resistance in order to maintain the exercise intensity. Exercise tolerance data could be used to assess exercise intensity, however it was decided to keep to the ACSM guidelines. For the anaerobic exercises, initial resistance was selected so ten repetitions could be performed. The exercise professional or physiotherapist instructed the participants that when two full sets of ten could be performed at a given resistance, within two minutes, to increase resistance. This would lead to a resultant decrease in repetitions and then the protocol would be repeated.

How well: In order to be able to define adherence to the programme participants were provided with an exercise booklet to fill out (see appendix 12). For aerobic exercise, time (in minutes) and machine were noted down. Furthermore, rate of perceived exertion and heart rate were recorded in the exercise booklet. For the anaerobic training, the volume of work done was reported by noting down the resistance weight and the number of repetitions.

All travel and gym costs were met by the study.

5.2.3.2 Control Group

Patient and public involvement was used to create an effective control group where people would adhere to a certain programme. Possibilities of an active control group were explored during user group meetings where people with Parkinson's disease identified handwriting as a major issue. A programme aimed at handwriting could engage people and would create an active control group without implementing exercise.

What and where: The control group received a hand writing programme based on the Parkinson's Disease Society's guidance information sheet for handwriting (PDS 2008). Participants were provided with a handwriting programme to complete at their home (in Oxfordshire or Berkshire), 60 minutes twice weekly for six months.

Who provided and how: The control group were monitored and supported by an exercise expert. They would get a first visit with the exercise expert and were provided with four booklets each containing two 60 minute handwriting sessions. The exercise expert would explain what was expected from the participant (filling out one booklet per week, containing two sessions of 60 minutes of handwriting exercises) and the exercise expert would go through the first book with the participant to ensure they knew how to complete the work books. They would then be visited by the exercise expert every month to be provided with a new set of booklets and they could contact the exercise expert or physiotherapist if they needed more advice or had any concerns.

When and how much: The handwriting program also totalled 48 sessions over a 24 week period (2x a week). The 60minute session consisted of the following, Warm up exercises for both hands (wriggling figures, making a fist, touching figure with thumb, circling wrists, shrugging shoulders and stretching hands), then a variety of writing activities (eg copying shapes, writing pangrams, writing a post card, filling in a form) and finished with hand exercises (rolling putty, using pegs, placing sticks in a jar, and ball drop and catch). Writing activities varied from work book to work book in order to maintain interest.

Tailoring: There was no formal tailoring or progression, as all participants in the handwriting group followed the same work books. However, participant could monitor their own performance using 'The quick brown fox jumps over the lazy dog' pangram which was performed every session and feedback was given by the exercise expert or physiotherapist at the monthly support sessions.

How well: As with the exercise group, diaries were used by participants in the control group to record their practice.

5.2.4 Measures

Measures have been described in Chapter 4. No changes in outcome measures were made after commencement of the trial. Below, the measures used are listed.

Primary outcome measure:

Self-reported fatigue was assessed using the Fatigue Severity Scale (FSS) (Krupp, LaRocca et al. 1989)

Secondary outcome measures:

Disease severity was measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (UPDRS-III) (Winter, von Campenhausen et al. 2011).

To measure mobility, the two-minute walk test (2MWT) was conducted in which participants were asked to walk at a normal comfortable speed on a track of 16 meters for two minutes; the distance covered was measured (Brooks, Parsons et al. 2004).

The Short Form 36 (SF-36) was used to measure quality of life (Ware 2014).

In order to assess activity levels of the participants, the Physical Activity Scale for the Elderly (PASE) was conducted (Schuit, Schouten et al. 1997). For seven days following an assessment the participants wore an accelerometer (GENEActiv) (Welch, Bassett et al. 2014) on their wrist for a week. Outcome scores reflecting sedentary activity, light activity and moderate activity were calculated by averaging the data across the days of data collection (Welch, Bassett et al. 2014, Pavey, Gomersall et al. 2015).

Aerobic capacity of the participants, by averaging VO_2 over the highest 30 seconds of the test. Maximum respiratory exchange ratio was calculated from the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$; averaged over the last 30 seconds of the test. The CR10 Rating of Perceived Exertion scale was used to measure leg fatigue and breathlessness at the end of each stage, which previously has been done in Multiple Sclerosis (Dawes, Collett et al. 2014).

5.2.5 Data handling and analyses

Data were analysed using IBM SPSS Statistics 22. In order to investigate any changes over time all people were included in an intention to treat analysis.

5.2.5.1 Demographics

Mean and standard deviation (SD) were calculated for both groups the exercise group and the control group at baseline as well as twelve and twenty-four weeks after the commencement of the trial. Two tailed Independent t-tests were performed to establish any differences in primary and secondary outcomes between the exercise group and control group at baseline.

5.2.5.2 Effects of the intervention

The effects of the intervention were expressed over time (baseline versus 24 weeks) between the groups as Cohen's D and 95% confidence interval. Significance was established if the 95% confidence interval does not cross 0. The Cohen's D was calculated using a linear mixed model. A linear mixed model was used instead of an ANOVA's and a regression model because of the advantage that all data collected can be used, and missing data does not result in exclusion of complete subjects (Seltman 2014).

5.2.5.3 Adherence and safety

Feasibility of the intervention was measured in terms of adherence and adverse events. Adherence in the exercise group was determined by counting the number of sessions participants had undertaken during the intervention. For the exercise intervention a session would count as going to the gym and attempting to perform the aerobic exercises, the anaerobic exercises, or both. Besides number of sessions the participants attended in the gym, sub-analyses were performed on the time spent on aerobic exercise (in minutes), and whether or not they performed anaerobic exercise (yes/no per exercise).

Adherence of the control group was determined by counting the number of sessions participants had completed in their booklet. A session was counted as completed if over 50% of the session was completed.

The exercise expert in collaboration with the physiotherapist would ask the participants whether or not any adverse events and serious adverse events had taken place in between visits. Furthermore, any other adverse events and serious adverse events that became apparent during any contact with a participant were recorded throughout the trial.

5.2.5.4 Progression of exercises

To assess anaerobic exercise progression over time the average volume (kilograms times repetitions) of all participants was calculated per session. Progression was then presented as change score from baseline. Aerobic exercise progression is not measured as intensity did not have to be reported in the exercise diary.

5.2.5.5 Predictors of adherence

Outcomes from baseline measures as described in Chapter 4 (Chapter 4: Table 4 and Table 5) were correlated with number of gym sessions attended.

5.2.5.6 Sub-analyses of the effects of intervention

In order to investigate the relationship between attended gym sessions and the outcomes of the exercise programme, a sub analysis was performed of participants that were randomised into the exercise group. All participants who were non-compliant (defined as attending '0' or '1' session) were assigned a number of '0' sessions. Pearson's correlations were performed between number of sessions attended and change data. Change data was defined as: Change data = 24 weeks assessment – baseline assessment.

Finally, the effects of the intervention were expressed over time (baseline versus 24 weeks) within the exercise group as Cohen's D and 95% confidence interval. Significance was established if the 95% confidence interval does not cross 0.

5.2.6 Correlations at 6 months

Finally, significant correlations found in Chapter 4 regarding self-reported fatigue and physical activity, exercise tolerance and fatigue reported during exercise tolerance were explored after the intervention using Pearson's correlations.

5. 3 Results

5.3.1 Participant flow and dropout

The flow diagram in Figure 10 shows the flow of participants through the study.

A total of 170 people expressed an initial interest in the study. 107 people were screened for eligibility and 105 people were included in the study. 54 participants were allocated to the exercise group; 51 patients were allocated to the control group.

Eighty-six people were followed up on after twelve weeks, resulting in a retention rate of 82%. Reasons for loss to follow up were: i) too ill to attend further sessions (n=3); ii) re-diagnosed (dementia n=1; multiple system atrophy n=1); iii) withdrew consent (n=8); reasons: medical reasons (n=4); too busy (n=3); not interested anymore (n=1)); iv) unavailable to come in on time (i.e. twelve weeks after the start ± two weeks) (n=4); v); vii) passed away (n=1).

91 people were followed up on after 24 weeks resulting in a retention rate of 87% (compared to the baseline appointment). Reasons for loss to follow up were: i) too ill to come in (n=3); ii) re-diagnosed (dementia n=1; multiple system atrophy n=1); iii)

withdrew consent (n=8); vi) passed away (n=1). These were the same reasons as the reasons for loss to follow up at twelve weeks.

5.3.2 Demographics

Descriptive statistics are presented in Table 7. In the table, numbers found at three months are included, however, as exercise interventions lasting three months have been explored previously, this thesis focuses at the outcomes at six months, which has not been explored much, and therefore, further analyses were performed comparing data from the baseline and six months into the trial.

All variables except from the 2MWT were similar at baseline between the two intervention groups.

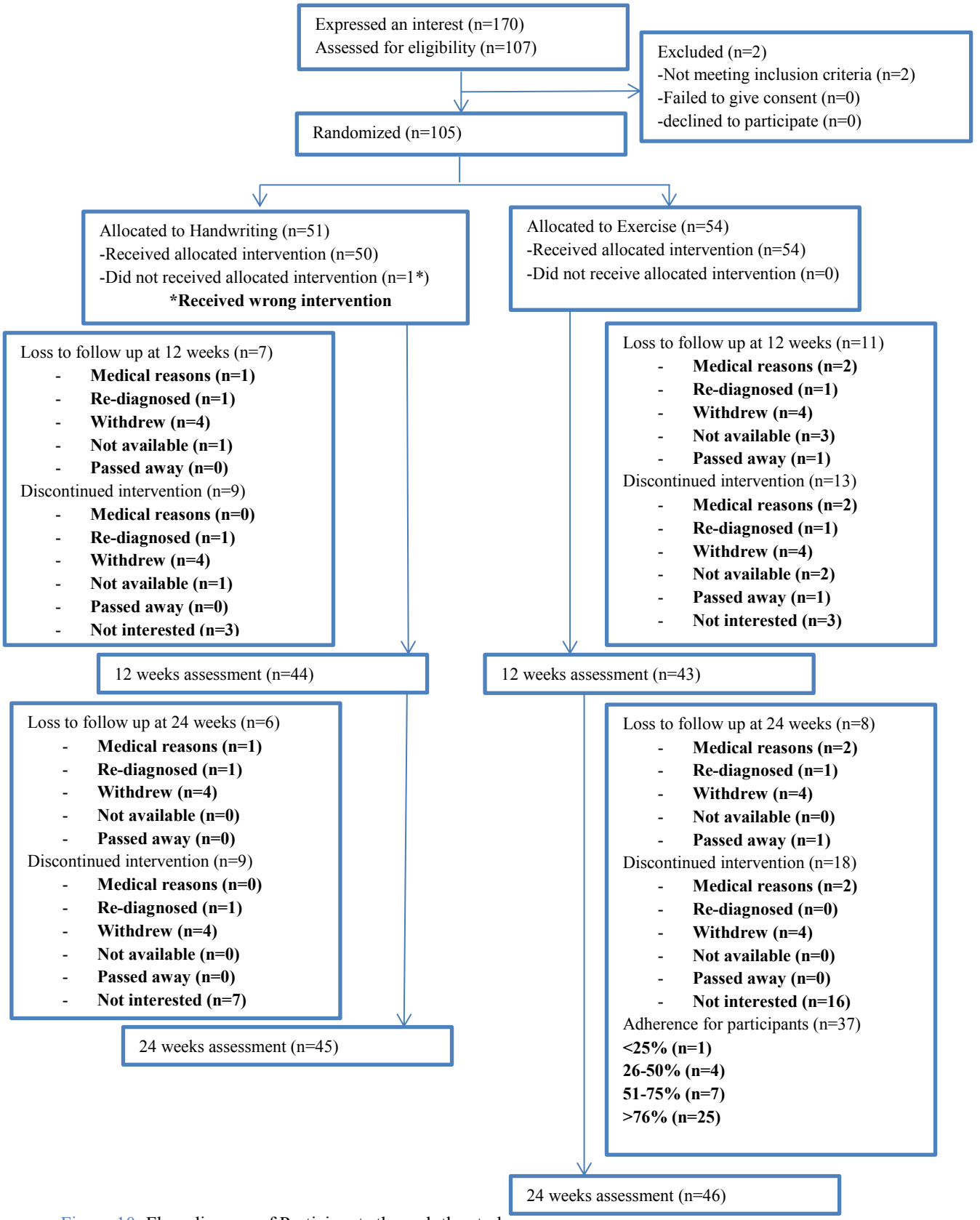

Figure 10: Flow diagram of Participants through the study

Table 7: Descriptive statistics: Mean and Standard Deviation (SD) for assessment 1, 2 and 3 for both groups (exercise and control).

p-values are reported for differences at assessment one between the exercise and control group as determined by t-test.

Variable	Assessment	Exercise Mean (SD)	Control Mean (SD)	p-value (difference at baseline)
Age	1	66 (9)	68 (7)	0.254
Years since diagnosis	1	4.8 (4.1)	5.3 (4.1)	0.547
Weight	1	76.9 (16.6) (n=54)	78.1 (14.1) (n=51)	0.693
	2	77.2 (15.6) (n=42)	76.6 (14.6) (n=44)	
	3	76.8 (15.8) (n=45)	76.5 (15.0) (n=45)	
UPDRS part III	1	17 (10) (n=54)	19 (10) (n=51)	0.214
	2	14 (10) (n=42)	18 (10) (n=44)	
	3	14 (9) (n=45)	19 (9) (n=45)	
2 Minute Walk Test	1	146.5 (23.9) (n=54)	137.0 (22.7) (n=51)	0.041
(metres)	2	152.6 (21.3) (n=42)	135.6 (25.9) (n=44)	
	3	147.8 (30.6) (n=45)	138.0 (25.0) (n=45)	
SF-36	1	70 (18) (54)	68 (17) (n=51)	0.579
Mental Health	2	73 (16) (n=43)	70 (16) (n=44)	
	3	70 (18) (n=46)	66 (19) (n=45)	
SF-36	1	64 (18) (n=54)	61 (19) (n=51)	0.384
Physical Health	2	66 (17) (n=43)	61 (19) (n=44)	
	3	64 (18) (n=46)	60 (21) (n=45)	
PASE	1	66 (35) (n=40)	64 (33) (n=48)	0.803
	2	76 (43) (n=32)	77 (31) (n=39)	
	3	78 (41) (n=39)	74 (40) (n=33)	

Abbreviations: UPDRS part III: Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; SF-36: Short Form 36; PASE: Physical Activity Scale for the Elderly. Assessment 1: baseline assessment; Assessment 2: 12 weeks assessment; Assessment 3: 24 weeks assessment.

Mean and SD for all fatigue measures for the three assessments for both the exercise group and the control group are presented in Table 8.

Table 8: Measures of fatigue, physical activity and exercise tolerance

Mean and Standard Deviation (SD) for assessment 1, 2 and 3 for both groups (exercise and control). P-values are reported for differences at assessment one between the exercise and control group as determined by a t-test.

Variable	Assessment	Exercise Mean (SD)	Control Mean (SD)	p-value
FSS	1	3.6 (1.4) (n=54)	3.9 (1.4) (n=51)	0.239
	2	3.5 (1.4) (n=44)	3.4 (1.4) (n=44)	
	3	3.3 (1.5) (n=46)	3.5 (1.5) (n=45)	
GA: Sedentary (Minutes)	1	762 (156) (n=45)	770 (121) (n=44)	0.768
	2	745 (147) (n=37)	789 (139) (n=35)	
	3	760 (142) (n=34)	784 (153) (n=35)	
GA: light (Minutes)	1	86 (42) (n=45)	90 (72) (n=44)	0.695
	2	80 (40) (n=37)	84 (47) (n=35)	
	3	74 (36) (n=34)	79 (74) (n=35)	
GA: moderate (Minutes)	1	92 (88) (n=45)	87 (72) (n=44)	0.759
	2	83 (80) (n=37)	78 (68) (n=35)	
	3	73 (57) (n=34)	79 (74) (n=35)	
$\dot{V}O_2$	1	21.3 (7.2) (n=43)	20.6 (7.1) (n=39)	0.779
	2	21.1 (6.6) (n=34)	20.2 (6.8) (n=32)	
	3	21.4 (5.8) (n=31)	20.4 (7.7) (n=31)	
RER	1	1.18 (0.10) (n=43)	1.17 (0.14) (n=39)	0.633
	2	1.23 (0.10) (n=34)	1.18 (0.14) (n=32)	
	3	1.19 (0.09) (n=31)	1.19 (0.14) (n=31)	
RPElegs	1	7 (3) (n=43)	7 (2) (n=39)	0.928
	2	8 (2) (n=34)	7 (2) (n=32)	
	3	8 (2) (n=31)	8 (2) (n=31)	
RPEbreath	1	6 (2) (n=43)	7 (2) (n=39)	0.972
	2	7 (2) (n=34)	7 (2) (n=32)	
	3	7 (2) (n=31)	7 (2) (n=31)	

Abbreviations: FSS: Fatigue Severity Scale; GA: GENEActiv; $\dot{V}O_2$: Ratio of Oxygen consumption; RER: respiratory exchange ratio; RPElegs: Rate of perceived exertion for the legs; RPEbreath: Rate of perceived exertion for the breathing. Assessment 1: baseline assessment; Assessment 2: 12 weeks assessment; Assessment 3: 24 weeks assessment.

5.3.3 Effects of the intervention

Effect sizes are reported in Table 9. Cohen suggested that d=0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size. The data shows

small effects sizes for the 2 MWT (d=0.25) and for the MDS-UPDRS part III (d=0.27), all other effect sizes were smaller than 0.2.

Table 9: Effect sizes over time of the difference (assessment 1 and assessment 3) between the groups (exercise and handwriting) (n: see table 8)

Variable	Cohen's d	95% confidence interval
2 MWT	0.27*	0.04 – 0.51
UPDRS-III	0.25*	0.02 – 0.49
SF-36 Mental Health	0.12	-0.11 – 0.36
SF-36 Physical Health	0.07	-0.16 – 0.30
PASE	0.06	-0.16 – 0.28

* significant (95% confidence interval does not cross 0).

Abbreviations: 2 MWT: 2 minute walk test; UPDRS III: Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; SF36: Short Form 36; Phys: Physical; Men: Mental; PASE: Physical Activity Scale for the Elderly.

Effect sizes for the fatigue measures are reported in Table 10. All effect sizes were smaller than 0.2. Effect size for the Fatigue Severity Scale (d=0.17) approached 0.2.

Table 10: Effect sizes over time (assessment 1 and assessment 3) between the two groups (exercise and handwriting) for the fatigue, physical activity and exercise tolerance (n: see table 8).

Variable	Cohen's d	95% confidence interval
FSS	0.17	-0.19 – 0.41
$\dot{V}O_2$	0.08	-0.11 – 0.27
RER	0.10	-0.12 – 0.32
GENEActiv Sedentary	0.07	-0.15 – 0.29
GENEActiv Light	0.09	-0.13 – 0.31
GENEActiv Moderate	0.01	-0.21 – 0.23

Abbreviations: FSS: Fatigue Severity Scale; $\dot{V}O_2$: Ratio of Oxygen consumption; RER: Respiratory Exchange Ratio

5.3.4 Progression in the exercise programme

Figure 11 shows average progression over time of the exercises per session. All exercises show a positive trend towards progression over the number of sessions.

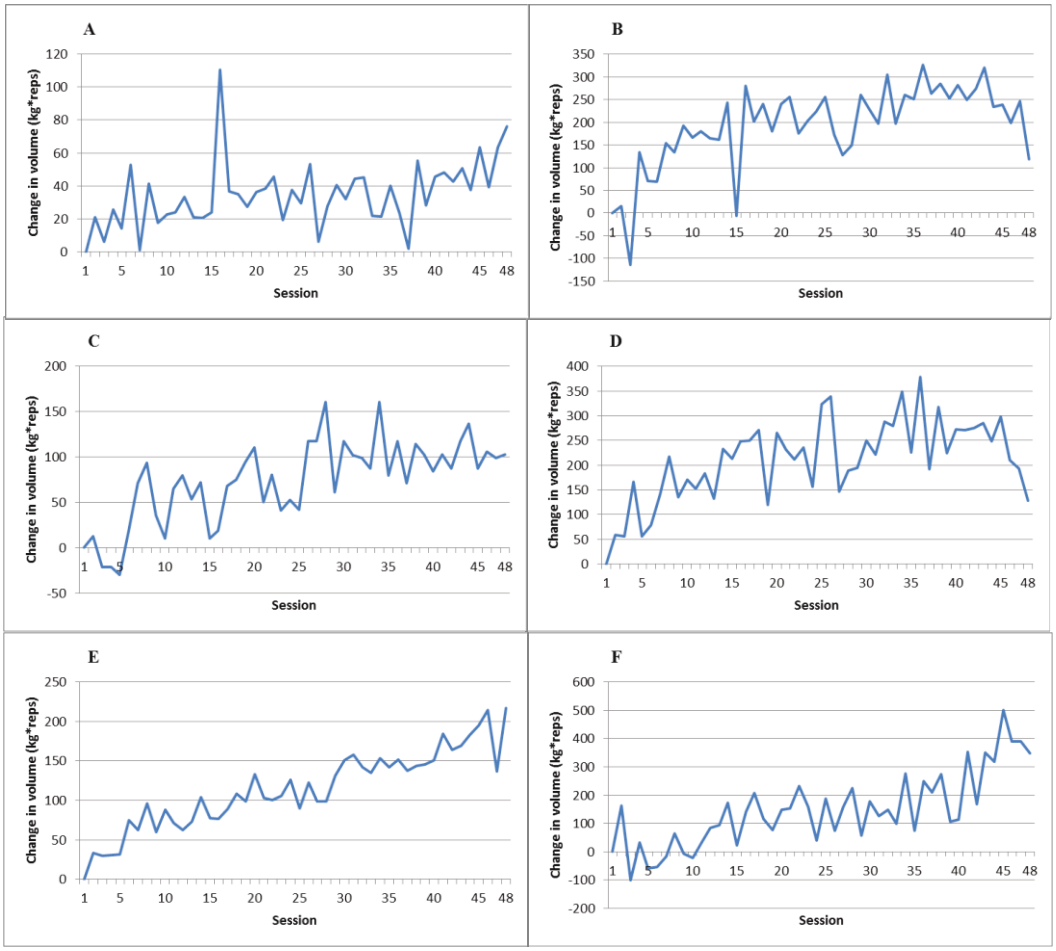

Figure 11: Progression of exercise (as expressed in kilograms times repetitions) over time (n=37)

A: Arm Press; B: Double Arm Pull Down; C: Leg Extension; D: Rotational Woodchop; E: Sit to Stand; F: Leg Press

*abbreviations: kg = kilograms; reps = repetitions

5.3.5 Adherence to exercise

In total, 54 participants were allocated to the exercise group. Out of these, two participants withdrew due to medical reasons (one participant was hospitalized for three weeks and was too frail to do the intervention; one participant was depressed); one participant withdrew because they were no longer interested in taking part; one participant was re-diagnosed with Lewy-body dementia, which is stated as an exclusion criteria; and one participant died very early on in the intervention. Furthermore, participants were classified as non-compliant if they attended none or only the initial session. In total nine participants were classified as non-compliant. Finally, three participants did participate in the programme, but lost their booklet; their data were treated as missing data. In total, 37 participants

adhered to some extend to the exercise programme. These 37 participants (68%) attended an average of 37 (SD=10) of 48 sessions. The minimum number of sessions attended was nine and the maximum was 47 sessions. One participant attended fewer than 25% of the sessions; four participants attended between 26% and 50%; eight participants attended between 51% and 75%; and 24 participants attended over 75% of the prescribed exercise sessions.

During the attended sessions participants completed an average of 30 minutes (SD = 3 minutes) of the 30 minutes prescribed aerobic exercise. Regarding anaerobic exercises, participants performed the leg press on average 33 sessions; leg extension nine sessions; sit-to-stand 31 session; double arm pull down 35 session; rotation wood chop 29 session; and arm raise 34 sessions out of 48 session.

5.3.6 Adherence to control programme

In total 51 participants were randomised into the control group. Of these participants, twelve participants were non-compliant. One person completed 25% of the sessions; four participants completed between 26 and 50% of the sessions; six participants completed between 51 and 75% of the sessions; and 28 participants completed at least 76% of the prescribed sessions.

5.3.7 Adverse events

In total, eight adverse events were reported in the exercise group. Only two adverse events were related to the intervention. One participant suffered from an abnormal heart rate response during the intervention; one participant felt faint during exercise which was later classified by the consultant as orthostatic hypotension. The latter participant did continue the intervention. As a result of adverse events two participants allocated to the exercise group withdrew consent before starting the intervention period. One of them suffered a severe fall which led to three weeks hospitalization; the other person withdrew because of severe depression. One participant died early on in the intervention period due to unrelated issues. Three participants suffered falls unrelated to the exercise intervention. One person broke their leg unrelated to the intervention.

5.3.8 Parameters relating to adherence to exercise sessions

The following descriptive measures positively related (Pearson r) to the number of sessions participants attended: 2MWT (r=0.370; p=0.008); SF-36 Physical Health (r=0.415; p=0.003). However, the following descriptive measures did not relate to the number of sessions attended: UPDRS III (r=-0.106; p=0.466); SF-36 Mental Health (r=0.221; p=0.126); and PASE (r=0.214; p=0.203) (see Table 11).

Table 11: Pearson Correlations with number of sessions attended to baseline characteristics

	Pearson r	p-value
UPDRS III (n=50)	-0.106	0.466
2MWT (n=50)	0.370	0.008
SF36 Physical Health (n=49)	0.415	0.003
SF36 Mental Health (n=49)	0.221	0.126
PASE	0.214	0.203

Abbreviations: 2MWT: 2 minute walk test; UPDRS III: Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; SF36: Short Form 36; PASE: Physical Activity Scale for the Elderly.

The number of sessions attended related with $\dot{V}O_2$ (r=0.387; p=0.014). The correlation between number of session attended and self-reported fatigue levels (FSS) approached significance (r=-0.278; p=0.051). The following descriptive measures did not relate to the number of sessions attended: respiratory exchange ratio (r=0.002; p=0.988); and baseline activity levels as monitored by all outcomes of the GENEActiv (sedentary: r=-0.530; p=0.740; light: r=0.010; p=0.951; moderate: r=0.027; 0.868) (see Table 12).

Table 12: Pearson correlations with number of sessions attended and physical activity and exercise tolerance.

	Pearson r	p-value
FSS (n=50)	-0.278	0.051
GENEActiv sedentary (n=41)	-0.530	0.740
GENEActiv light (n=41)	0.010	0.951
GENEActiv moderate (n=41)	0.027	0.868
$\dot{V}O_2$ (n=40)	0.387	0.014
RER (n=40)	0.002	0.988

Abbreviations: FSS: Fatigue Severity Scale; $\dot{V}O_2$: Ratio of Oxygen consumption; RER: Respiratory Exchange Ratio

5.3.9 Sub-analyses of participants in the exercise group

In the sub-analyses, all participants randomised to the exercise group (n=54) were included. These data show small effects sizes in UPDRS part III (Cohen's d=0.24; 95%

confidence interval 0.03-0.45). Effect sizes for SF-36 physical health (Cohen's d=0.17; 95% confidence interval -0.04-0.38); and PASE (Cohen's d=0.17; 95 % confidence interval -0.02-0.37) approached 0.2 (see Table 13).

Table 13: Effect sizes over time (baseline assessment and 24 weeks assessment) in the exercise group (n=54)

Variable	Cohen's d	95% confidence interval
UPDRS III	0.24	0.03 – 0.45
2 MWT	0.10	-0.11 – 0.31
SF-36 Mental Health	0.09	-0.12 – 0.29
SF-36 Physical Health	0.17	-0.04 – 0.38
PASE	0.17	-0.02 – 0.37

Abbreviations: 2MWT: 2 minute walk test; UPDRS III: Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; SF36: Short Form 36; Phys: Physical; Men: Mental; PASE: Physical Activity Scale for the Elderly.

For fatigue, small effect sizes were found in light activity (d=0.3); and moderate activity (d=0.27) (see Table 14).

Table 14: Effect sizes for fatigue, physical activity and exercise tolerance over time (baseline assessment and 24 weeks assessment) in the exercise group (n=54)

Variable	Cohen's d	95% confidence interval
FSS	0.14	-0.06 – 0.35
$\dot{V}O_2$	0.08	-0.11 – 0.27
RER	0.08	-0.11 – 0.27
Sedentary	0.14	-0.05 – 0.33
Light	0.30	0.10 – 0.49
Moderate	0.27	0.08 – 0.47

Abbreviations: FSS: Fatigue Severity Scale; $\dot{V}O_2$: Ratio of Oxygen consumption ; RER: Respiratory Exchange Ratio

Furthermore, in this subgroup, analyses were performed to explore whether or not participants that adhered well to the programme experienced greater benefits compared to the participants that did not adhere well to the programme. Correlations of the number of sessions and the above mentioned measures are presented in Table 15; two examples of the correlations are shown in Figure 12 (number of attended sessions plotted against change score of the UPDRS part III) and Figure 13 (number of attended sessions plotted against change score of the FSS). There was no significant correlation between number of sessions attended and any of the measures explored.

Table 15: Pearson correlation coefficients between the number of attended sessions and the change score between assessment one and assessment three in the exercise group.

Variable	Number of sessions attended	
	Pearson r	P-value
UPDRS III (n=42)	0.022	0.891
2MWT (n=42)	0.235	0.134
SF36 mental health (n=43)	0.236	0.128
SF36 physical health (n=43)	0.048	0.759

Abbreviations: 2MWT: two minute walk test; UPDRS III: Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; SF36: Short Form 36; FSS: Fatigue Severity Scale; RER: Respiratory Exchange Ratio.

Table 16: Pearson correlation coefficients between the number of attended sessions and the fatigue change scores between assessment one and assessment three in the exercise group.

Variable	Number of sessions attended	
	Pearson r	P-value
FSS (n=43)	-0.019	0.901
GENEActiv sedentary activity (n=26)	0.129	0.530
GENEActiv light activity (n=26)	-0.167	0.414
GENEActiv moderate activity (n=26)	-0.243	0.231
$\dot{V}O_2$ **(n=29)**	-0.298	0.116
RER (n=29)	0.015	0.939

Abbreviations: FSS: Fatigue Severity Scale; $\dot{V}O_2$: Ratio of Oxygen consumption; RER: Respiratory Exchange Ratio

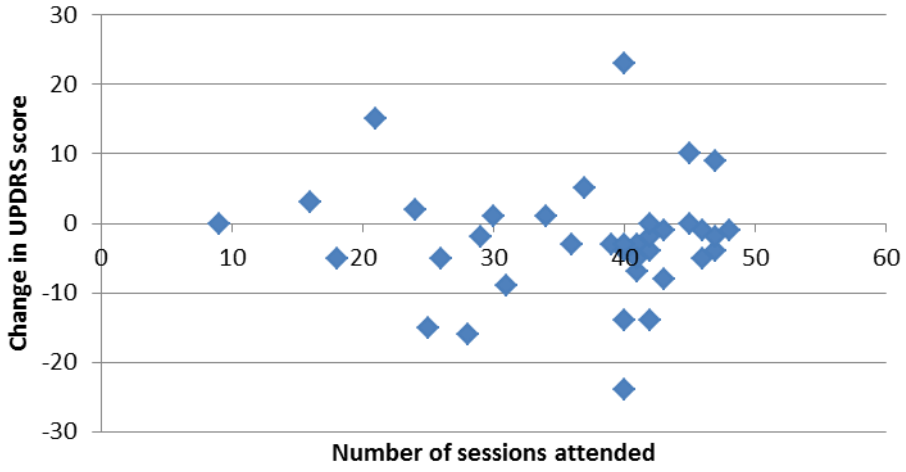

Figure 12: Scatterplot of the number of session attended and the change in the UPDRS part III (Movement Disorders Society Unified Parkinson's Disease Rating Scale part III) score from baseline assessment to the 24 weeks assessment. Abbreviations: UPDRS = Unified Parkinson's Disease Rating Scale

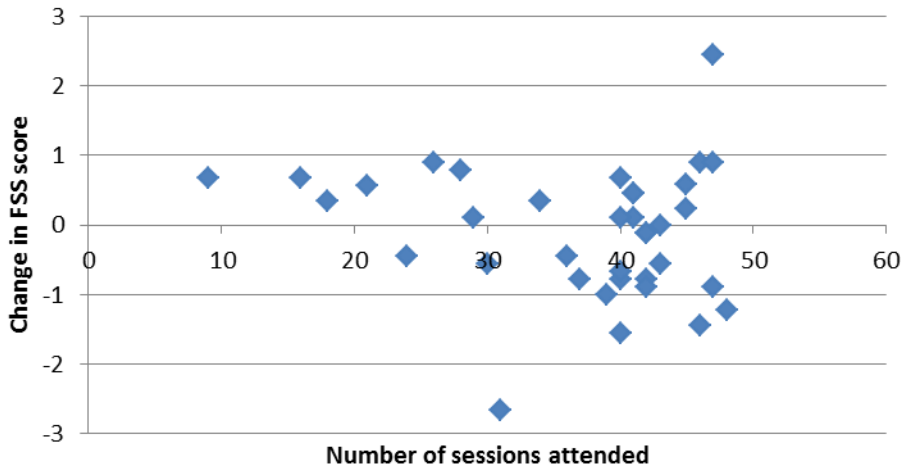

Figure 13: Scatterplot showing the number of session attended and the change in the Fatigue Severity Scale from baseline assessment to the 24 weeks assessment. Abbreviations: FSS = Fatigue Severity Scale

5.3.9 Correlations at 6 months

No significant correlations were found correlations between self-reported fatigue (Fatigue Severity Scale) and measures of physical activity (GENEActiv light), exercise tolerance (Respiratory Exchange Ratio), and self-reported fatigue during exercise tolerance (Rate of Perceived Exertion) (see Table 17).

Table 17: Pearson's correlations between self-reported fatigue (Fatigue Severity Scale) and physical activity and exercise tolerance

Variable	FSS Pearson r	p-value
GENEActiv light activity (n=89)	0.123	0.366
RER (n=83)	-0.006	0.963
RPE breath (n=82)	-0.186	0.135
RPE legs (n=82)	-0.083	0.505

Abbreviations: FSS: Fatigue Severity Scale; RER: Respiratory Exchange Ratio; RPE: Rate of Perceived Exertion

5.4 Discussion

The scores for self-reported fatigue decreased in both the exercise and the control group after the intervention period. A possible explanation for this finding is that simply having an organised occupation (i.e. 'something' to do), in combination with the attention of an exercise expert is sufficient to reduce fatigue.

5.4.1 Effects of the exercise intervention

The main finding in of this study is that the exercise programme produced a small improvement in disease severity in the exercise group compared to the control group. This is in line with other exercise studies that find improvement in the MDS-UPDRS III (Comella, Stebbins et al. 1994, Ridgel, Vitek et al. 2009, Sage and Almeida 2009). Even though the current study was community based with a smaller number of sessions per week than in the other studies mentioned, there was still a small improvement in the MDS-UPDRS III indicating that this programme might benefit disease severity.

Small effect sizes were found over time in the exercise group for both light and moderate activity as measured by the GENEActiv. As can be seen in Table 7, these effect sizes show that people in the exercise group are likely to be less active over the week. This result may be different from what expected, since participants go to the gym, and it is expected that this would result in more activity during the day. However, previous research has shown that there is a compensatory decline in energy expenditure following imposition of physical activity (Epstein and Wing 1980, Goran and Poehlman 1992, Rowland 1998).

The initial analysis showed a small improvement in the 2MWT in the group receiving the exercise intervention, but further analyses showed that the groups were different at baseline and the 2MWT did not show an improvement over time as shown in the absence of an effect size in the exercise group over time. Other studies investigating the effects of exercise on mobility did find an increase in 2MWT (Lauhoff, Murphy et al. 2013) or 6MWT (Duncan and Earhart 2012, Shulman, Katzel et al. 2013, Kretschmer, Irina et al. 2014). A possible explanation for small improvement in the 2MWT in the exercise group is that at baseline, the participants performed at a level similar to the general older population (Bohannon, Wang et al. 2014); therefore, it is likely that there was little room for improvement, which would explain the lack of detectable improvement over time.

This study found no positive increase in the exercise group in $\dot{V}O_2$ or respiratory exchange ratio. This is in contrast to other studies (Bergen, Toole et al. 2002). A possible explanation for this finding is similar to that of the 2MWT in that the $\dot{V}O_2$ and respiratory exchange ratio were similar to the general older population to begin with. Furthermore, 68% of the

patients attended some of the programme. Since 32% did not attend any exercise sessions, this might have influenced overall findings.

Finally, results show that, when all participants were combined, a progression of exercise (expressed as kilograms multiplied by repetitions) is seen. Progression of exercise may indicate that the body's physiological capacities have expanded (ACSM 2014). The progression seen in the exercises indicate that exercise could induce an improvement of physiological capacities over time in people with Parkinson's disease. Intensity was not reported in the exercise diary, therefore, aerobic exercise progression is not discussed in this study. In future studies, intensity should be recorded, so progression of aerobic exercise can be reported. If a positive increase in the exercise group in $\dot{V}O_2$ or respiratory exchange ratio had been found, this could have been an indicator of aerobic exercise progression, however, no positive increase was found, meaning no conclusions can be drawn with regards to aerobic exercise progression.

5.4.2 Feasibility

This programme provides evidence of the feasibility of a low cost exercise programme that people are likely to adhere to. Part of that important information is adherence to the programme (Allen, Sherrington et al. 2012). This is one of the first studies implementing a longer term exercise programme in people with Parkinson's disease. Although overall, fifteen participants were non-compliant, 24 participants attended at least 76% of all prescribed sessions. These fifteen people were all non-compliant and attended none, or just the very first session. This finding shows, that non-compliance can be predicted early on. This shows that it is feasible to implement the programme in the community. One thing to take into account when discussing the adherence to this programme is that participants for this study were recruited specifically for an exercise study. Hence, people were likely to be motivated to do exercise before starting this programme. This may give a slightly skewed view compared to the general population. However, the number of people adhering to the programme is higher than commonly in exercise programmes where the same bias is introduced. To measure adherence, self-reported diaries were used, fully acknowledging that self-reporting comes with some limitations, including under- or over reporting (Bollen, Dean et al. 2014). However, a recent review on self-reported adherence to unsupervised home-based rehabilitation exercise programmes states that at present there is no cheap and

easily available gold standard measurement of unsupervised exercise-based adherence, therefore self-reporting remains a suitable option (Bollen, Dean et al. 2014). A previous study using diaries to record attendance and adherence rate (Uc, Doerschug et al. 2014) found by using just diaries, an attendance rate of 83%, which shows diaries may be an adequate way of self-reporting attendance.

The small amount of supervision during this exercise programme provides a low cost implementable exercise programme for people with Parkinson's disease. In the past, most exercise studies have been executed under strict supervision; hence adherence was often higher than in the current study. A systematic review states that adherence is often not reported, however, when reported adherence was over 70% and often 100% (Allen, Sherrington et al. 2012). However, programmes with high supervision are costly. Whether or not findings from exercise under strict supervision can be generalized to community settings where participants receive only little supervision is unclear (Uc, Doerschug et al. 2014).

Overall we found similar adherence numbers in both groups, showing that we created an effective control group.

There were a low number of adverse events in this study with only two adverse events related to the study. Adverse events are often poorly reported in exercise programmes (Allen, Sherrington et al. 2012). In a systematic review that included adverse events, 72% of the studies did not report adverse events, in the other fifteen trials, eleven adverse events occurred (Allen, Sherrington et al. 2012). Overall, it can be concluded that participants in exercise programmes normally do not suffer from adverse events. Exercise programmes seem to be safe to implement in people with Parkinson's disease.

5.4.3 Predictors of adherence

The findings presented in the results indicate that participants that perform better at baseline on performance tests like the 2MWT, and the aerobic capacity test as indicated by $\dot{V}O_2$, were more likely to attend more sessions prescribed in the exercise programme. Furthermore, participants who rated their physical health high on the SF-36 were more likely to attend more sessions in the gym; the number of sessions attended did not correlate with self-reported mental health of the participants. This is in line with other research into

adherence to medication where adherence to medication has shown that a higher quality of life correlates with a higher adherence (Carballo, Cadarso-Suarez et al. 2004). The results from the current study show that more able participants attend the gym sessions. This is an important result and has to be taken into account when interpreting outcomes of an exercise programme.

The relationship between the numbers of sessions attended and fatigue as indicated by the Fatigue Severity Scale almost reached significance, indicating that people that are more fatigued are less likely to attend many of the prescribed exercise sessions. This result could indicate a vicious circle where the participant might be too fatigued to do the exercises, whilst not doing any exercise may result in more fatigue. It is important to try and break this vicious circle (Falk, Granger et al. 2007).

5.4.4 Sub-analyses of the exercise group

Sub-analyses investigating the relationship between attended gym sessions and the outcomes of the exercise programme found no significant correlations. This indicates that participants who attended more sessions of the exercise programme, did not improve more on any of the outcome measures than participants who attend fewer sessions. This finding likely links in with the predictors of adherence in that participants that were more likely to attend more sessions had a higher performance on tests like the 2MWT, and the aerobic capacity test as indicated by $\dot{V}O_2$. Because of this, it is likely that there was little room for improvement in the group of participants that attended more sessions and therefore no correlations have been found between the number of sessions and the outcomes measured.

Finally, sub analyses in the exercise group show a small effect sizes in the MDS-UPDRS III which indicates that participants who have been randomised to the exercise group show a small improvement in disease severity over time, which is in line with previous studies (Comella, Stebbins et al. 1994, Ridgel, Vitek et al. 2009, Sage and Almeida 2009). As explained before, this is an important finding since it shows that exercise has the possibility of diminishing motor symptoms in people with Parkinson's disease. The sub-analyses in the exercise group showed an effect size approaching 0.2 for the PASE. It seems that people's self-reported activity went up slightly in the exercise group. A possible reason for the discrepancy between the self-reported measure and the activity monitor may be that participants often choose to do the aerobic component of the gym exercises on the

bicycle ergometer. Previous research has shown that cycling activity is underestimated by a wrist worn accelerometer (Parkka, Ermes et al. 2007). Finally, sub analyses in the exercise group showed an effect size approaching 0.2 for the SF-36 physical health, showing that exercise possibly improves self-reported physical health.

Correlations between self-reported fatigue and physical activity, exercise tolerance, and self-reported fatigue during exercise tolerance that were shown to be significant at baseline, were not significant at 6 months. This indicated that with training it may be possible to push people during an exercise tolerance test regardless of their fatigue. Furthermore, physical activity may not be influenced by self-reported fatigue after training.

5.4.5 Limitations

There are some limitations to this study. First of all, participants were purposively recruited to an exercise study, possibly resulting in a skewed sample. This may have resulted in the sample in this study being particularly mobile (as indicated by the 2 minute walk test). Generalisability to people with Parkinson's disease has to be done with caution. Furthermore, only participants that were able to walk were included in the study. In future research it should be explored whether exercise, could be beneficial for people that are less mobile, including people in a wheelchair, including exploring the feasibility of community delivered exercise to less mobile people with Parkinson's disease

5.4.6 Conclusion

It can be concluded that the exercise programme had a small effect on disease severity in favour of the exercise group, however no other benefits were found. A possible explanation for this may be the dosage of the exercise programme: Two hours per week may not have been enough exercise to show any health benefits (Ringbaek, Broendum et al. 2000). Moreover, the fact that the participants overall were highly functioning at the start of the programme so that there was little room for improvement. Finally, this study shows it is safe and feasible to have patients with Parkinson's disease exercise in a community setting. Although previous research has shown that patients with a neurological disorder are less likely to go to the gym due to several barriers, this study showed that with a little extra support initially, patients are doing exercise in community based gyms in a safe matter. The opportunity for patients to exercise in a community based setting rather than either a specialised setting, or for example under constant supervision of a

physiotherapist is of great importance as it can reduce the costs of exercise for patients, and therefore, the quantity of doing exercise can be increased which is thought to have a beneficial impact. Furthermore, doing exercises in a community setting might lower the burden of the family, as transport is less likely to be an issue in a community setting compared to having to travel to an specialised institution.

Chapter 6 Overall Discussion and Conclusion and Future studies

Summary

This chapter gives an overall conclusion of the work done for this thesis, based on the aims set out in Chapter 1. Furthermore, limitations are discussed and finally possibilities for further research are proposed.

6.1 Exploring fatigue

This thesis set out to explore fatigue in people with Parkinson's disease. Fatigue is a difficult concept, not only to describe, but also to measure.

As part of this work, a systematic review and meta-analysis was conducted that provided new insights into treatment methods of fatigue in people with Parkinson's disease. The study included fourteen studies investigating interventions for self-reported fatigue in people with Parkinson's disease and concluded that at this point in time, there is no definite treatment for fatigue. Consensus into determining the best way to measure fatigue in people with Parkinson's disease would further improve research in this area. As long as fatigue is defined and measured in different ways, research is not likely to provide strong robust answers regarding treatment of fatigue in people with Parkinson's disease. Exercise seems to be a treatment method used in other areas such as Multiple Sclerosis, but is hardly explored in people with Parkinson's disease.

6.2 Fatigue in a population of people with Parkinson's disease

In order to establish whether an exercise programme could improve self-reported fatigue in people with Parkinson's disease, correlations between self-reported fatigue and physical measures including disease severity, aerobic capacity and mobility that can be improved using an exercise programme were explored. An association was found between respiratory exchange ratio and self-reported fatigue. The correlations found show that if respiratory exchange ratio can be improved by for example an exercise programme, self-reported fatigue may be improved as well.

6.3 Adherence to a six months twice weekly exercise programme and the effects of the exercise programme

Finally, this knowledge was implemented and a single blind randomised controlled trial was set up to explore whether exercise could be effective as a treatment method for fatigue in people with Parkinson's disease. The study found that out of 54 participants randomised to the exercise group, 37 participants adhered to the programme to some extent, with 24 participants attending at least 75% of all the sessions. Furthermore, there we no adverse events related to the intervention, indicating the intervention is feasible to implement.

The exercise programme had a small effect on disease severity in favour of the exercise group, however no other benefits were found. A possible explanation for this may be the dosage of the exercise programme, two hours per week may not be enough exercise to show any health benefits (Ringbaek, Broendum et al. 2000), and the fact that the participants overall were highly functioning at the start of the programme so that there was little room for improvement.

The randomised controlled trial was conducted in a larger team. The focus of this work has been fatigue, including the systematic review and meta-analysis exploring fatigue in people with Parkinson's; subsequently, the comparisons at baseline between fatigue and measures of physical activity and exercise tolerance; and finally by exploring fatigue in the larger randomised controlled trial.

6.4 Limitations of the work

Although great effort was made to study fatigue in people with Parkinson's disease as specific as possible, there are limitation to this work.

As discussed in Chapter 2, fatigue can be a result of depression. Although it is acknowledged that fatigue in Parkinson's disease is present in the absence of depression (Karlsen, Larsen et al. 1999, Herlofson and Larsen 2002, Alves, Wentzel-Larsen et al. 2004, Okuma, Kamei et al. 2009) results from studies also suggest that depression is significantly higher in fatigued people with Parkinson's disease. A limitation of the current study is that depression was not explored using a separate questionnaire, meaning that it is difficult to draw conclusions about the occurrence of depression in this group of people and the relation of the possible presence of depression and fatigue. However, as drugs were

recorded as part of the study, it can be concluded that the rate of depressed people was not very high, as only 12 participants (11%) were on anti-depressant medication. Going forward, it is important to measure confounders of fatigue like depression and sleepiness to get a full picture of fatigue in people with Parkinson's disease.

Furthermore, fatigue was measured as an average, however, fatigue measured throughout the day could give a completer picture of fatigue and can inform the development of any future exercise programme's by taking into account fatigue levels and fluctuations of fatigue levels of people with Parkinson's disease throughout the day.

6.5 Overall conclusion

This thesis set out to explore fatigue which is a complex phenomenon and not well studied in people with Parkinson's disease. Even though there are studies exploring different treatment methods for fatigue in Parkinson's disease, the systematic review and meta-analysis conducted in Chapter 3 showed that currently there seems to be no effective treatment for fatigue in people with Parkinson's disease. This thesis set out to look into the possibilities of treating fatigue in people with Parkinson's disease by means of an exercise programme using a single blind randomised controlled trial.

Fatigue was diminished in both the exercise group and the control group. Although studies in Multiple Sclerosis and other populations like cancer have shown a reduction in fatigue after exercise, this study failed to show a significant effect of the exercise on fatigue. One explanation for this may be that the exercise programme did not seem to affect any of the measures, showing that the intensity of the programme may not have been enough to improve mobility, aerobic capacity, quality of life or fatigue.

This is the first study to explore the effects of a combined (aerobic and anaerobic) exercise community based longer term (six months) exercise programme on fatigue in people with Parkinson's disease. Results show that both arms of the interventions were adhered to reasonably well and small effects were found showing exercise improved disease severity in people with Parkinson's disease; no effects were found in relation to fatigue.

6.6 Future

This work shows that fatigue in Parkinson's disease is a complex phenomenon that is difficult to address. Further research into understanding fatigue in Parkinson's disease is an important step in order to explore further treatment methods of fatigue. Exploring fatigue in more detail and closely throughout days can give a clearer picture of when people are fatigued and why; this then could contribute to informing any further treatment programmes.

Furthermore, as mentioned, confounding factors around fatigue like depression and sleepiness should be explored in future studies to give a full and clear picture of fatigue.

Following results found in this study a future study should design an exercise programme specifically to treat fatigue in people with Parkinson's disease. Building on from literature in other populations such as Multiple Sclerosis and Cancer an exercise programme should be built to specifically address fatigue. As results in this study around fatigue are inconclusive, an exercise programme that is intensive enough (three times a week rather than two) should be developed. Attendance and progression should be monitored closely by means of for example a diary (as used in this study) in order to make correct conclusions of the effect of the programme.

Finally, as this study showed positive effects of exercise on disease severity, a full randomised controlled trial should be designed and conducted to establish effectiveness of the six months exercise trial in people with Parkinson's disease.

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Appendices

Appendix 1: UK Parkinson's Disease Society Brain Bang Clinical Diagnostic Criteria

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA
(Hughes, Daniel et al. 1992)

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
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine 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

Appendix 2: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Appendix 3: Search Strategy Systematic Review and Meta-analysis

Pubmed search

1. Parkinson disease [MESH]
2. "Parkinson disease"
3. Parkinsonian disorders [MESH]
4. "Parkinson's"
5. Fatigue [MESH]
6. "fatigue"
7. 1 OR 2 OR 3 OR 4
8. 5 OR 6

7 AND 8

Appendix 4: Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a method of evaluating the impact on fatigue on you. The FSS is a short questionnaire that requires you to rate your level of fatigue.

The FSS questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

A low value indicates strong disagreement with the statement, whereas a high value indicates strong agreement.

FSS Questionnaire

During the past week, I found that:	**Disagree <----------> Agree**							
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7	
2. Exercise brings on my fatigue	1	2	3	4	5	6	7	
3. I am easily fatigued	1	2	3	4	5	6	7	
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7	
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7	
6. My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7	
7. Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7	
8. Fatigue is among my three most disabling symptoms	1	2	3	4	5	6	7	
9. Fatigue interferes with my work, family, or social life	1	2	3	4	5	6	7	
					Total Score:			

Appendix 5: MDS-UPDRS

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of Parkinson's Disease. In administering Part III of the MDS-UParkinson's DiseaseRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response. **OFF** is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.1 7), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? No Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON: On is the typical functional state when patients are receiving medication and have a good response.

OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? No Yes
3.C1 If yes, minutes since last levodopa dose: _____

3.1 SPEECH	**SCORE**
Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation ifnecessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	
3.2 FACIAL EXPRESSION	
Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	

3.3 RIGIDITY	SCORE
Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0: Normal: No rigidity. 1: Slight: Rigidity only detected with activation maneuver. 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved	R L
3.4 FINGER TAPPING	
Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions ordecrements.	R L

3.5 HAND MOVEMENTS	**SCORE**
Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/ her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions orhesitations of the movement; b) slight slowing; c) the amplitude decrements nearthe end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; the amplitude decrements midway in the task. 3:Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe:Cannot or can only barely perform the task because of slowing, interruptions or decrements.	R L
3.6 PRONATION-SUPINATION MOVEMENT OF HANDS	
Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movement; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements	R L

3.7 TOE TAPPING	**SCORE**
Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; the amplitude decrements midway in the task. 3:Moderate: Any of the following: a) more than 5 interruptions during the tapping movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	R L
3.8 LEG AGILITY	
Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movement; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements	R L

3.9 ARISING FROM CHAIR	**SCORE**
Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum of two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from arms of chair without difficulty. 3:Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4: Severe: Unable to arise without help.	
3.10 GAIT	
Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviours: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for 'freezing of gait' (next item 3.11) while the patient is walking. Observe posture for item 3.13 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	

3.11 FREEZING OF GAIT	**SCORE**
Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movement especially when turning and reaching the end of the task. To the extent that safety permits, patient may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3:Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	
3.12 POSTURAL STABILITY	
Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the centre of gravity so that the patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitation rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	

3.13 Posture	**SCORE**
Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for an older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3:Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINEASIA)	
Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	
3.15 POSTURAL TREMOR OF HANDS	
Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with the palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude	

3: Moderate: Tremor at least 3 but less than 10 cm in amplitude 4: Severe: Tremor is at least 10 cm in amplitude	

3.16 KINETIC TREMOR OF HANDS	
Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches each target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude 3: Moderate: Tremor at least 3 but less than 10 cm in amplitude 4: Severe: Tremor is at least 10 cm in amplitude	
3.17 REST TREMOR AMPLITUDE	
Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands place on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating Extremity ratings 0: Normal: No tremor 1: Slight: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 3 cm in maximal amplitude. 3: Moderate: 3 – 10 cm in maximal amplitude. 4: Severe: > 10 cm in maximal amplitude Lip/jaw ratings 0: Normal: No tremor 1: Slight: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 2 cm in maximal amplitude. 3: Moderate: 2 – 3 cm in maximal amplitude. 4: Severe: > 3 cm in maximal amplitude	

3.18 CONSTANCY OF REST TREMOR	SCORE
Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating. 0: Normal: No tremor. 1: Slight: Tremor at rest is present < 25% of the entire examination period. 2: Mild: Tremor at rest is present 26-50% of the entire examination period. 3: Moderate: Tremor at rest is present 51-75% of the entire examination period. 4: Severe: Tremor at rest is present >75% of the entire examination period.	
DYSKINESIA IMPART ON PART III RATINGS A. Where dyskinesias (chorea or dystonia) present during examination? No Yes **B.** If yes, did these movement interfere with your rating? No Yes	
HOEHN AND YAHR STAGE	
0: Asymptomatic. 1: Unilateral involvement only. 2: Bilateral involvement without impairment of balance. 3: Mild to moderate involvement: some postural instability but physically independent; needs assistance to recover from pull test. 4: Severe disability: still able to walk or stand unassisted. 5: Wheelchair bound or bedridden unless aided.	

Appendix 6: Short Form 36

General Health Status Questionnaire (SF-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer these questions by "check-marking" your choice. Please select only one choice for each item.

1. In general, would you say your health is:
□ 1. Excellent □ 2. Very good □ 3. Good □ 4. Fair □ 5. Poor

2. Compared to ONE YEAR AGO, how would you rate your health in general NOW?
□ 1. MUCH BETTER than one year ago.
□ 2. Somewhat BETTER now than one year ago.
□ 3. About the SAME as one year ago.
□ 4. Somewhat WORSE now than one year ago.
□ 5. MUCH WORSE now than one year ago.

3. The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	**1. Yes, Limited A Lot**	**2. Yes, Limited A Little**	**3. No, Not Limited At All**
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
b) **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
c) Lifting or carrying groceries?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
d) Climbing **several flights** of stairs?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
e) Climbing **one** flight of stairs?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
f) Bending, kneeing or stooping?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
g) Walking **more than a mile**?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
h) Walking **several** blocks?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all
i) Walking **one** block?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all

j) Bathing or dressing yourself?	□ 1. Yes, limited a lot	□ 2. Yes, limited a little	□ 3. No, not limited at all

4- During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities *as a result of your physical health*?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Were limited in the **kind** of work or other activities?	□ 1. yes	□ 2. No
d) Had **difficulty** performing the work or other activities (for example it took extra effort)?	□ 1. yes	□ 2. No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Didn't do work or other activities as **carefully** as usual?	□ 1. yes	□ 2. No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

□ 1. Not at all
□ 2. Slightly
□ 3. Moderately
□ 4. Quite a bit
□ 5. Extremely

7. How much **bodily pain** have you had during the **past 4 weeks**?

□ 1. None
□ 2. Very mild
□ 3. Mild
□ 4. Moderate
□ 5. Severe
□ 6. Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

□ 1. Not at all
□ 2. A little bit
□ 3. Moderately
□ 4. Quite a bit
□ 5. Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week**s

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
b) Have you been a very nervous person?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
c) Have you felt so down in the dumps that nothing could cheer you up?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
d) Have you felt calm and peaceful?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
e) Did you have a lot of energy?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
f) Have you felt downhearted and blue?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
g) Do you feel worn out?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
h) Have you been a happy person?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time
i) Did you feel tired?	□ 1. All of the time	□ 2. Most of the time	□ 3. A good bit of the time	□ 4. Some of the time	□ 5. A little of the time	□ 6. None of the time

10. During the **past 4 weeks**, how much of the time has your **physical health** or **emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

□ 1. All of the time
□ 2. Most of the time.
□ 3. Some of the time
□ 4. A little of the time.
□ 5. None of the time.

11. How TRUE or FALSE is **each** of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?	□ 1. Definitely true	□ 2. Mostly true	□ 3. Don't know	□ 4. Mostly false	□ 5. Definitely false
b) I am as healthy as anybody I know?	□ 1. Definitely true	□ 2. Mostly true	□ 3. Don't know	□ 4. Mostly false	□ 5. Definitely false
c) I expect my health to get worse?	□ 1. Definitely true	□ 2. Mostly true	□ 3. Don't know	□ 4. Mostly false	□ 5. Definitely false
d) My health is excellent?	□ 1. Definitely true	□ 2. Mostly true	□ 3. Don't know	□ 4. Mostly false	□ 5. Definitely false

Appendix 7: Physical Activity Scale for the Elderly

I am interested in how much time you have spent doing the following activities over the last 7 days.

Leisure time activity
1. Walking outside the home
How much time was spent on the activity over the last 7 days
(tick as appropriate)

Never (0 days)	Seldom (1 to 2 days)	Sometimes (3 to 4 days)	Often (5 to 7 days)

How many hours per day did you spend on this activity?

Less than 1hour	1 to 2 hours	2 to 4 hours	More than 4 hours

2. Light sport/recreation
Name the activity/activities_____
How much time was spent on the activity over the last 7 days
(tick as appropriate)

Never (0 days)	Seldom (1 to 2 days)	Sometimes (3 to 4 days)	Often (5 to 7 days)

How many hours per day did you spend on this activity?

Less than 1hour	1 to 2 hours	2 to 4 hours	More than 4 hours

3. Moderate sport/recreation
Name the activity_____
How much time was spent on the activity over the last 7 days (tick as appropriate)

Never (0 days)	Seldom (1 to 2 days)	Sometimes (3 to 4 days)	Often (5 to 7 days)

How many hours per day did you spend on this activity?

Less than 1hour	1 to 2 hours	2 to 4 hours	More than 4 hours

4. Strenuous sport/recreation
Name the activity_____
How much time was spent on the activity over the last 7 days
(tick as appropriate)

Never (0 days)	Seldom (1 to 2 days)	Sometimes (3 to 4 days)	Often (5 to 7 days)

How many hours per day did you spend on this activity?

Less than 1hour	1 to 2 hours	2 to 4 hours	More than 4 hours

5. Muscle strength/endurance exercises
Name the activity_____
How much time was spent on the activity over the last 7 days
(tick as appropriate)

Never (0 days)	Seldom (1 to 2 days)	Sometimes (3 to 4 days)	Often (5 to 7 days)

How many hours per day did you spend on this activity?

Less than 1hour	1 to 2 hours	2 to 4 hours	More than 4 hours

Household Physical Activities

Have you performed the following activities over the last 7 days
(tick appropriate box)

1. Light housework

No	Yes

2. Heavy housework and chores

No	Yes

3. Home repairs

No	Yes

4. Lawn work

No	Yes

5. Outdoor gardening

No	Yes

6. Caring for another person

No	Yes

Work related physical activity
In the last 7 days how many hours paid work have you done._____

Would you describe your work as mainly: (Please tick appropriate box)

1. Sitting with slight arm movements	
2. Sitting or standing with some walking	
3. Walking with some handling of materials generally weighing less than 50 pounds	
4. Walking and heavy manual work often requiring handling of materials weighing over 50 pounds.	

Appendix 8: Fitness case report form

Fitness test CRF

Weight (kg)	Saddle height	Mask size

Temp (°C)	Pressure (mb)	Humidity (%)

Resting

Heart Rate	BP sys/dia	Lactate	RPE breath	RPE legs
	/			

Exercise assessment

Increment (min)	Power (watts)	Weight (kg)	Heart Rate	RPE breath	RPE legs	Cadence*
0 (0-3)	0	(Unloaded)				
1 (3-5)	50	1				
2 (5-7)	75	1.5				
3 (7-9)	100	2				
4 (9-11)	125	2.5				
5 (11-13)	150	3				
6 (13-15)	175	3.5				
7 (15-17)	200	4				
8 (17-19)	225	4.5				
9 (19-21)	250	5				
10 (21-23)	275	5.5				
11 (23-25)	300	6				
12 (25-27)	325	6.5				
13 (27-29)	350	7				
14 (29-31)	375	7.5				

*If not 50

End test

Heart Rate	BP sys/dia	Lactate	RPE breath	RPE legs
	/			

Physical Activity Readiness-Questionnaire (PAR-Q)

Please read the following carefully and answer as accurately as possible by ticking the appropriate box for each question.

	Yes	**No**
Has a doctor ever said you have heart trouble?	□	□
Do you ever suffer frequently from chest pains?	□	□
Do you often feel faint or have spells of dizziness?	□	□
Has a doctor ever said you have epilepsy?	□	□
Has a doctor ever said you have high blood pressure?	□	□
Has a doctor ever said you have diabetes?	□	□
Has a doctor ever said you have asthma?	□	□
Do you have a bone, joint or muscular problem which may be aggravated by exercise?	□	□
Do you have any form of injury?	□	□
Are you currently taking any prescription medications?	□	□
Have you suffered from a viral illness in the last two weeks?	□	□

	Yes	**No**
Have you eaten anything within the ***last hour***?		
Have you consumed alcohol within the ***last 24 hours***?		
Have you performed exhaustive exercise within the ***last 48 hours***?		

If you have answered **YES** to any of the above questions, or know of any possible reason (physical or psychological) that might affect the safety or accuracy of the tests - please inform a member of staff.

Appendix 9: Borg CR-10 Scale

0	Nothing at all
0.5	Extremely weak
1	Very Weak
2	Weak
3	Moderate
4	
5	Hard
6	
7	Very Hard
8	
9	
10	Extremely Hard

Appendix 10: CONSORT guidelines

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			

Section/Topic	Item No	Checklist item	Reported on page No
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	

Section/Topic	Item No	Checklist item	Reported on page No
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

Appendix 11: TiDier (Template for Intervention Description and Replication) Checklist

Item number	Item	Where located	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.		
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).		
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.		
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.		
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.		

Item number	Item	Where located	
		Primary paper (page or appendix number)	Other † (details)
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.		
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.		
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.		
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.		
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.		

Appendix 12: Exercise Diary

OXFORD BROOKES UNIVERSITY

Blood Pressure				
Heart rate (HR)				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				

Exercise and Physical Activity Diary

24 Week programme

WEEK No 1

Session 1 **Session 2**

4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

Date__
_____
_____
_____

Date__
_____
_____
_____

WEEK No 2

Session 1

Date_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Session 2

Date_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 3

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 4

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 5

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 6

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 7

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 8

Session 1

Date_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Session 2

Date_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 9

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 10

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 11

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 12

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 13

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 14

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 15

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 16

Session 1

Date_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Session 2

Date_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 17

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 18

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 19

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 20

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 21

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 22

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 23

Session 1 **Session 2**

Date_____ **Date**_____

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

WEEK No 24

Session 1 **Session 2**

Date_____ **Date_____**

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	20 20	
Final resting BP				
Final resting Heart Rate				

Blood Pressure				
Heart rate				
30mins Aerobic training	Mins	HR	RPE	Distance
1.Treadmill				
2. Rower				
3. Bike				
4. X Trainer				
Stretching				
	Weight	Sets	Reps	
Leg press		1. 2.	10 10	
Leg extension		1. 2.	10 10	
Sit to stand		1. 2.	10 10	
2 arm Pull-down		1. 2.	10 10	
Rotation Wood chop		1. 2.	10 10	
Arm raises (alternate)		1. 2.	10 10	
Final resting BP				
Final resting Heart Rate				

The printed version incorporates a published journal article at this point, 'Interventions for Fatigue in Parkinson's Disease: A Systematic Review and Meta-analysis', M. Franssen, C. Winward, J. Collett, D. Wade and H. Dawes, Movement Disorders, vol. 29, no. 13 (2014)

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