

PROMOTION OF PHYSICAL ACTIVITY IN PARKINSON'S DISEASE

FEASIBILITY AND EFFECTIVENESS

ARLÈNE D. SPEELMAN

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PROMOTOREN

- Prof. dr. B.R. Bloem
- Prof. dr. F.J.G. Backx (UMC Utrecht)

COPROMOTOREN

- Dr. M. Munneke
- Dr. B.P van de Warrenburg

MANUSCRIPTCOMMISSIE

- Prof. dr. R. Nijhuis-van der Sanden (voorzitter)
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**“Sometimes when I consider
what tremendous consequences
come from little things,
I am tempted to think
there are no little things.”**

Bruce Barton

CONTENTS

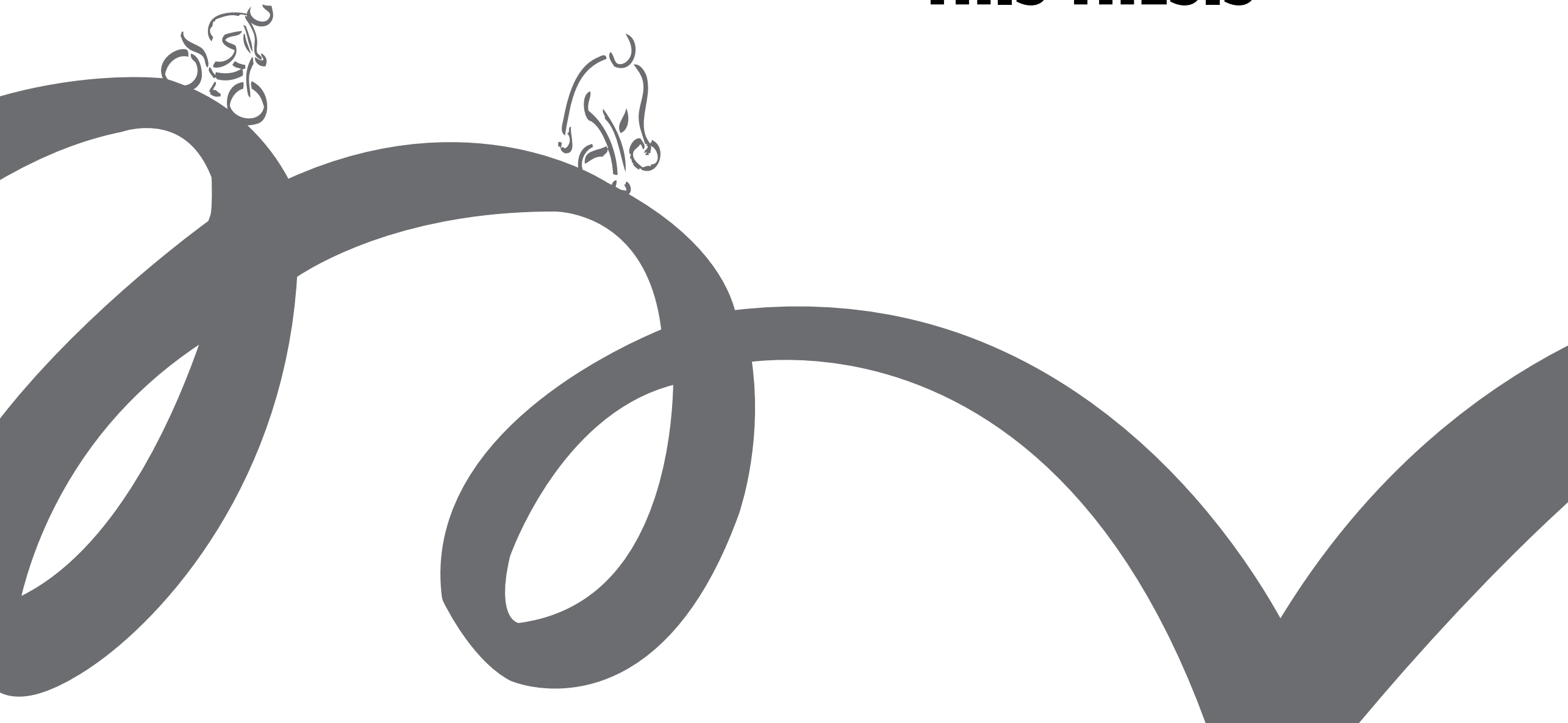
CHAPTER 01	PAGE 09
GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS	
CHAPTER 02	PAGE 15
HOW MIGHT PHYSICAL ACTIVITY BENEFIT PATIENTS WITH PARKINSON'S DISEASE?	
Nature Review Neurology 2011;7(9):528-534	
CHAPTER 03	PAGE 31
BONE MINERAL DENSITY AND VITAMIN D STATUS IN PARKINSON'S DISEASE PATIENTS	
Journal of Neurology 2012; In press	
CHAPTER 04	PAGE 43
PARKINSON'S DISEASE AND OSTEOPOROSIS	
Age and Ageing 2012; In press	
CHAPTER 05	PAGE 55
MONITORING OF WALKING IN PARKINSON'S DISEASE: VALIDATION OF AN AMBULATORY ACTIVITY MONITOR	
Parkinsonism and Related Disorders 2011; 17(5):402-404	
CHAPTER 06	PAGE 61
CARDIOVASCULAR RESPONSES DURING A SUBMAXIMAL EXERCISE TEST IN PATIENTS WITH PARKINSON'S DISEASE	
Journal of Parkinson's Disease 2012; 2:241-247	
CHAPTER 07	PAGE 73
PROMOTION OF PHYSICAL ACTIVITY AND FITNESS IN SEDENTARY PATIENTS WITH PARKINSON'S DISEASE, A RANDOMIZED CONTROLLED TRIAL	
British Medical Journal 2012; In press	

CHAPTER 08	PAGE 89
EVALUATION OF IMPLEMENTATION OF THE PARKFIT PROGRAM: A MULTIFACETED INTERVENTION AIMED TO PROMOTE PHYSICAL ACTIVITY IN PATIENTS WITH PARKINSON'S DISEASE	
Submitted	
CHAPTER 09	PAGE 103
SUMMARY	
CHAPTER 10	PAGE 111
GENERAL DISCUSSION AND FUTURE PERSPECTIVES	
CHAPTER 11	PAGE 121
NEDERLANDSE SAMENVATTING	
CHAPTER 12	PAGE 129
DANKWOORD	
CHAPTER 13	PAGE 135
13.1	REFERENCES PAGE 137
13.2	LIST OF PUBLICATIONS PAGE 161
13.3	CURRICULUM VITAE PAGE 163
13.4	DISSERTATIONS OF THE PARKINSON CENTRE NIJMEGEN (PARC) PAGE 165

CHAPTER

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

01



PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disorder. The prevalence is estimated to be about 1.3% to 1.5% for persons above the age of 60 years in Europe.¹ The number of individuals with PD will have doubled by the year 2030.² PD results from an accelerated loss of dopamine-producing cells in the substantia nigra, a sentinel node in the basal ganglia circuitry. The resultant dopamine depletion leads to a number of typical motor features. During life the diagnosis of PD is clinically based, but the ultimate confirmation of the PD diagnosis requires neuropathological investigations. The presence of typical motor features (asymmetrical resting tremor, bradykinesia, or both), often in combination with rigidity and postural instability, exclusionary symptoms, and response to levodopa is required to meet established clinical criteria.³ Some additional clinical features and auxiliary investigations allow, to a large extent, a differentiation between PD and the closely related forms of atypical parkinsonism.⁴ Besides these motor symptoms, PD is also characterized by a wide variety of non-motor symptoms such as depression, fatigue, autonomic dysfunction, cognitive decline, and sleep disturbances.⁵ Non-motor symptoms generally correlate with advancing age and disease severity, although some of these (most notably constipation, insomnia and REM sleep behavior disorder) can occur early in the course of the disease, or might even become manifest before the motor symptoms.⁶ PD is a complex and thereby incapacitating disease. As a result, many PD patients carry a relatively heavy illness burden in the physical, mental and social dimensions of health-related quality of life compared with many other neurological or chronic conditions.⁷

MANAGEMENT OF PD

Currently, there is no cure for PD. The treatment of PD is therefore symptomatic, and primarily involves dopaminergic medication.⁸ Deep brain surgery is an alternative, but this is only available for a selective group of patients whose symptoms are dopamine responsive but who experience debilitating response fluctuations.⁹ There is also a wide variety of non-pharmacological treatment options, including physical therapy*, occupational therapy, and speech and language therapy. The evidence to support these interventions is gradually growing, and treatment guidelines (partially based on evidence, partially on practical clinical experience) for some of these allied health care interventions have been developed.¹⁰⁻¹² Integrating these various treatment options into a bundled multidisciplinary approach (along with pharmacological and surgical treatment) is widely felt to represent an optimal therapeutic strategy for this complex, multifaceted disease.^{13,14}

* In the Netherlands, the content of the evidence-based guideline for physiotherapy in PD is identical to the guidelines for Cesar exercise therapists and Mensendieck exercise therapists. Therefore, the term 'physiotherapy' also includes Cesar and Mensendieck exercise therapies.

but to date there is surprisingly little evidence to support this assumption. In the Netherlands, there are regional professional networks (the so-called ParkinsonNet networks) which consist of specifically trained health professionals who treat large numbers of PD patients and who collaborate well with other professionals within the network.^{15,16} ParkinsonNet networks have been specifically developed to improve the PD-specific expertise of health professionals, to increase the patient volume per participating therapist, and to enhance communication and collaboration between professionals.¹⁶ A large cluster-controlled trial has shown that the ParkinsonNet concept achieves these goals, and also leads to a substantial cost reduction that may be as high as 1400 Euros per patient per year.¹⁵

PHYSICAL INACTIVITY

Many patients with PD lead a sedentary lifestyle. Overall, PD patients are 29% less physically active in comparison with age-matched controls. This reduced level of physical activity is particularly observed in patients with advanced disease.¹⁷ The motor and non-motor features of PD contribute directly or indirectly to this sedentary lifestyle. Being physically inactive is likely to have deleterious consequences for PD patients, for various reasons. A sedentary lifestyle is one of the leading causes of death among individuals in the general population¹⁸ and is associated with an increase in all-cause mortality.^{18,19} Lower levels of physical activity are a modifiable risk factor for several chronic diseases like type 2 diabetes mellitus, cancer, obesity, hypertension, bone and joint disease (osteoporosis and osteoarthritis), and depression.^{19,20} Furthermore, physical inactivity could increase the risk of cardiovascular disease directly.^{19,20} In one study, three weeks of bed rest caused a greater deterioration in cardiovascular and physical working capacity than did 30 years of aging.²¹ Finally, the sedentary lifestyle of PD patients could lead to a worsening of specific symptoms that are already present because of the disease itself; examples include insomnia, constipation, and depression.

REASONS WHY PARKINSON PATIENTS SHOULD BECOME MORE ACTIVE

Patients with PD have many reasons to become (more) physically active. In general, physical activity reduces the risk of cardiovascular disease, cancer and osteoporosis.¹⁹ Physical activity could also have potential disease-specific effects, for example by improving cognitive dysfunction and mood.²²⁻²⁴ Animal studies indicate that exercise can prevent and decelerate the development of experimental parkinsonism through several mechanisms that involve neural plasticity of the dopaminergic and glutamatergic system.²⁵⁻²⁸ This is further supported by studies that investigated the relationship between physical activity and the risk of developing PD in humans, which have shown that moderate to vigorous exercise may protect against later development

of PD.²⁹⁻³⁰ Increasing physical activity in PD could also have some risks. PD patients have an increased risk of falls and fall-related injuries.³¹ In the general population, more active men and women have a higher incidence rate of leisure time and sport-related injuries than less active adults.³² Furthermore, exercise is associated with an increased risk of cardiovascular complications.³² However, compared to sedentary counterparts and those with low aerobic fitness, physically active or aerobically fit individuals have 25% to 50% lower overall risk of developing cardiovascular disease.³³

THE CHALLENGE OF BEHAVIORAL CHANGE

Although virtually everyone appreciates the potential merits of exercise, simply informing subjects about such health benefits is not enough to change their behavior and to reach a sustained healthy lifestyle.³⁴ Apparently, it is very difficult for people to give up their unhealthy behavior. Even patients who developed lifestyle-related illnesses, such as diabetes, have a hard time to reverse their unhealthy lifestyle. A real and sustained behavioral change is needed to achieve a physically active lifestyle for longer periods of time. In PD patients, several specific barriers exist to become and remain physically active, such as their motor symptoms (gait and balance problems) and non-motor symptoms (like apathy, fatigue, depression, and cognitive dysfunction). To change a sedentary lifestyle into an active lifestyle for longer periods of time, it is necessary to identify and overcome these barriers to physical activity.³⁴ One possible solution is that PD patients might benefit from receiving specific coaching and counseling when attempting to increase their levels of physical activity.

There are several theories about exercise behavior, including the health belief model, the social cognitive theory, and the transtheoretical model.³⁵ Evidence shows that physical activity interventions should be targeted at several principles of behavioral change.³⁴ Major factors to ascertain a sustained behavioral change include: social support from family and friends; self-efficacy; an individually tailored program; activities that reflect the person's preferences and capabilities (as these contribute to greater adherence); goal setting, using for example a health contract; regular performance feedback; and positive reinforcement.³⁴

OUTLINE OF THIS THESIS

This thesis on physical activity and exercise in PD patients aims to develop better insight into the benefits, risks, and measurements of physical activity and exercise in PD, and to develop an approach that stimulates PD patients to lead a sustained, active lifestyle.

Chapter 2 provides an overview of all potential benefits and risks of physical activity in patients with PD. One of the general benefits of physical activity is the prevention or reduction of osteoporosis. In *Chapter 3*, the prevalence of osteoporosis and possible risk factors associated with bone loss in sedentary PD patients are investigated. In *Chapter 4*, we give an overview of the clinical evidence, pathophysiology and treatment of osteoporosis in patients with PD.

The quantitative assessment of physical activity is a complex issue. In *Chapter 5*, the validation of an ambulatory monitor to measure walking distance in PD patients is described. A method to assess physical fitness is described in *Chapter 6*. This chapter reports on the cardiovascular response to a submaximal exercise test in PD patients. Furthermore, physical fitness and test performance of PD patients were compared with healthy controls. The results of a randomized controlled trial that studied the effects of a multifaceted behavioral change program, the ParkFit program, to increase the level of physical activity in PD patients are presented in *Chapter 7*. Finally, the implementation of the ParkFit program is evaluated in *Chapter 8*.

CHAPTER 02

HOW MIGHT PHYSICAL ACTIVITY BENEFIT PATIENTS WITH PARKINSON'S DISEASE?

NATURE REVIEW NEUROLOGY; 2011;7(9):528-534

Arlène D. Speelman, Bart P. van de Warrenburg, Marlies van Nimwegen,
Giselle M. Petzinger, Marten Munneke and Bastiaan R. Bloem



ABSTRACT

PD is a neurodegenerative disorder characterized by progressive motor and nonmotor impairments. These impairments incline many patients towards a sedentary lifestyle, which has many deleterious consequences. Accumulating evidence suggests that patients with PD might benefit from physical activity and exercise in a number of ways, from general improvements in health to disease-specific effects and, potentially, disease-modifying effects (suggested by animal data). Many issues remain to be addressed, including the need to perform clinical trials to demonstrate these presumed benefits of physical activity and exercise in patients with PD. These trials must also address safety issues, such as an increased risk of falls and cardiovascular complications in more-active patients. Identifying ways to induce a sustained behavioral change, using specifically tailored programs that address potential barriers such as depression, apathy and postural instability, may lead to an improved quality of life in individuals with PD.

INTRODUCTION

PD is a neurodegenerative condition characterized by progressive motor symptoms, including gait disturbances and balance instability. Patients with PD can also develop a range of nonmotor complications, such as depression, apathy, sleep disturbances, constipation, and cognitive dysfunction. Together, these motor and nonmotor impairments might encourage the individual to adopt a sedentary lifestyle.^{17–36} This response creates a vicious circle, because physical inactivity can negatively affect several clinical domains of PD (Figure 2.1).

A sedentary lifestyle may represent more than just a consequence of PD; it could reflect a deliberate compensatory strategy to prevent further complications, observed for example in patients with severe postural instability who try to avoid falls by staying indoors. Indeed, fear of falling is common in patients with PD, and might result in a reduction in their outdoor physical activities.³¹ The positive effect of exercise on the healthy human brain has been studied extensively (Box 1) but evidence demonstrating

the benefits of physical activity specifically in patients with PD is limited. Throughout this article, 'exercise' refers to planned physical activity undertaken specifically to maintain or improve physical fitness and functional capacity.^{37–38} Participation in exercise, as well as normal daily physical activities, results in improved physical fitness in healthy individuals as well as those with PD. This state of well-being carries a low risk of premature health problems, and provides the individual with energy to participate in an extended range of physical activities.³⁸

In this Perspectives article, we extrapolate from data on healthy populations, and evidence from clinical trials in patients with PD and other neurological conditions, to present and explore 10 potential reasons why an active lifestyle might benefit patients with PD (Box 2). Possible risks associated with increased physical activity in patients with PD are also discussed, along with the imminent challenges that must be addressed to achieve a sustained, active lifestyle for this group of patients.

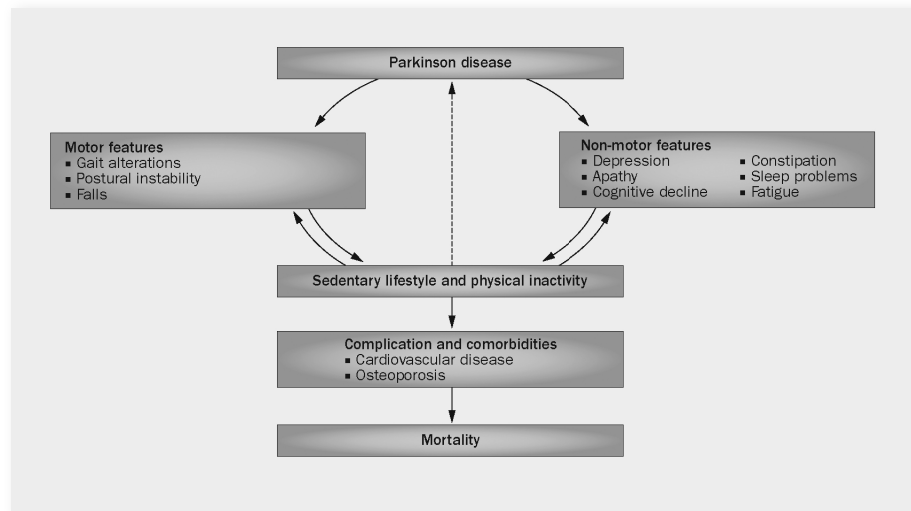
POTENTIAL BENEFITS OF EXERCISE

IMPROVING COGNITIVE FUNCTION

Cognitive impairment is common in individuals in the advanced stages of PD (up to 80% of patients will eventually develop dementia)⁴⁷, and findings from the past 5–6 years suggest that cognitive decline actually begins early in the course of disease.⁴⁸ Only two small studies have investigated the benefits of an aerobic exercise program on cognitive dysfunction in patients with PD.^{49–50} One of these studies investigated the effects of a multimodal physical exercise program in 20 patients with PD. The participants were assigned to either an intervention group (who received general physical training for 6 months) or a control group. The results showed a beneficial effect of training on executive function.⁴⁹ The other study evaluated the benefits of exercise in 28 patients with PD, who were allocated to either an intervention program of twice-weekly exercise for 12 weeks or a control group. The researchers concluded that exercise had

FIGURE 2.1

THE VICIOUS CYCLE OF PHYSICAL INACTIVITY IN PD



Patients with PD tend to lead a sedentary lifestyle, owing to a combination of motor and nonmotor features. A sedentary lifestyle has various adverse effects (solid arrows): secondary worsening of PD-related symptoms and signs (for example, constipation can worsen because of physical inactivity); development or worsening of comorbidities and complications (such as cardiovascular disease); and increased mortality risk. In addition, by extrapolation from studies in rodents with experimentally induced parkinsonism we speculate that a sedentary lifestyle could negatively influence the course of PD itself (dotted arrow). Abbreviation: PD, Parkinson disease.

selective benefits on cognitive functioning by improving frontal-lobe-based executive function.⁵⁰ Additional evidence from studies in elderly individuals and patients with Alzheimer disease suggests that exercise may postpone cognitive deterioration²² and delay the onset of dementia.²³ The aerobic component of exercise, in particular, drives these clinical effects.⁵¹ These promising results should now be explored further in large trials of exercise in patients with PD.

ARREST OF OSTEOPOROSIS

The prevalence of osteoporosis is high in patients with PD: up to 63% of women with PD and 20% of men with PD have this condition.^{52,53} By comparison, in age-matched healthy populations the prevalence of osteoporosis is 29% in women and 12% in men.⁵⁴ Several factors might contribute to accelerated bone loss in patients with PD, such as physical inactivity, vitamin D

BOX 1

THE EFFECTS OF EXERCISE ON THE HUMAN BRAIN

The beneficial effects of physical activity on brain functions in healthy people presumably work via adaptive neuroplasticity—the brain's capacity to adjust through dynamic neuronal reorganization.³⁷ Studies in healthy older rodents have shown that regular aerobic activity triggers plasticity-related changes in the CNS, including synaptogenesis, enhanced glucose utilization, angiogenesis, and neurogenesis.³⁹ In older adults who are free of cognitive impairment, aerobic exercise promotes brain health by reducing inflammation, suppressing oxidative stress, and stabilizing calcium homeostasis.⁴⁰ Furthermore, release of endogenous neurotrophins (such as brain-derived neurotrophin, glia-derived neurotrophin factor, nerve growth factor, and galanin) during regular aerobic exercise is associated with synaptic plasticity and enhanced cognitive performance, learning and memory.^{41,42}

Several imaging studies have underpinned the beneficial cerebral effects of exercise in humans. For example, aerobic fitness increased the volume of gray and white matter in sedentary people.⁴³ Furthermore, increased physical activity (achieved via cognitive behavioral therapy) produced an increase in gray matter volume in patients with chronic fatigue syndrome.⁴⁴ Currently, no data are available as to whether exercise can induce structural or functional brain alterations in patients with PD, and at what level potential neuroplastic changes might occur. Adaptive neuroplasticity can occur spontaneously in patients with PD, at the level of both the basal ganglia and the cortex,⁴⁵ and such compensatory processes may even start in the preclinical phase.⁴⁶ Studies to determine whether exercise can drive or facilitate these processes should be high on the research agenda.

BOX 2

POTENTIAL BENEFITS OF EXERCISE

The 10 possible benefits of exercise in patients with PD are as follows:

- ❶ Prevention of cardiovascular complications
- ❷ Arrest of osteoporosis
- ❸ Improved cognitive function
- ❹ Prevention of depression
- ❺ Improved sleep
- ❻ Decreased constipation
- ❼ Decreased fatigue
- ❽ Improved functional motor performance
- ❾ Improved drug efficacy
- ❿ Optimization of the dopaminergic system

deficiency, muscle weakness, low body weight, and hyperhomocysteinemia. Most of these factors evolve during the course of PD and reinforce each other. Patients with PD also have a high risk of falling³¹ which, in combination with osteoporosis or osteopenia, increases the risk of fall-related fractures.⁵⁵ Prevention or reduction of osteoporosis would, therefore, be of great benefit for individuals with PD.

Conversely, physical activity and exercise are associated with improved bone health.⁵⁶ Although the optimal training method for stimulating bone growth in adults has not yet been defined, evidence points to a combination of high-impact activities such as jumping, and weight-bearing exercises such as sprinting, jogging or stair climbing.⁵⁷ Whether patients with PD can improve their bone health by adapting to a physically active lifestyle, or by following an exercise program, remains to be demonstrated in appropriately designed studies. The high-impact exercises required to examine this effect may not be suitable for all patients, owing to their high risk of falls; less-hazardous weight-bearing exercises such as regular walking, aerobics or dancing may be more appropriate for patients with PD.

PREVENTION CARDIOVASCULAR EVENTS

The precise incidence of cardiovascular events, such as myocardial infarction or cerebrovascular disease, is unclear in patients with PD. In general, cardiovascular risk factors (including diabetes, a history of smoking, hypertension, and high cholesterol levels) are less common in patients with PD than in controls.⁵⁸ A review suggested that patients with PD might have an increased propensity to develop comorbid cerebrovascular complications,⁵⁹ but more work is needed to confirm this association.

A sedentary lifestyle is one of the leading causes of death among individuals in the general population.¹⁸ In addition, the amount of physical activity is inversely related to all-cause mortality.¹⁸ In particular, exercise training positively influences cardiovascular risk factors and reduces the incidence of cardiovascular disease (including cerebrovascular events).⁶⁰ The American College of Sports Medicine and the British Association of Sports and Exercise Sciences recommend, therefore, that all healthy adults aged between 18 and 65 years old should regularly participate in physical activity to promote and maintain health.³²⁻⁶¹ Prospective studies suggest that adherence to this recommendation is associated with reductions of 20–30% in the risk of cardiovascular disease.⁶² The general benefits of physical activity and exercise can also be expected to apply to individuals with PD; however, such effects remain to be demonstrated in this population. In terms of intrinsic capacity to engage in exercise, studies have shown that the maximal oxygen uptake of patients with PD was no different from that of controls, but men with PD reached their maximal oxygen uptake earlier than did controls, suggesting less mechanical efficiency of movement during exercise, perhaps due to their muscle rigidity.⁶³ This earlier saturation of maximal oxygen consumption indicates that patients with PD must stop exercising earlier than controls.

PREVENTING DEPRESSION

The relationship between physical activity and mental health has been widely investigated in populations without PD. A systematic review of 11 randomized controlled trials concluded that exercise is an effective treatment for depression in healthy individuals,²⁴ although the underlying mechanisms remain poorly understood.

Depression is a common neuropsychiatric symptom associated with PD. The prevalence of depression depends on the patient's age and the severity of their motor symptoms, increasing from 15.6% in Hoehn and Yahr stages I–II, to 47.9% in stages IV–V.⁶⁴ Several studies have also examined the effect of a physical activity intervention on depression in patients with PD. One study reported a statistically significant improvement in depression in the group who had received the intervention, as compared to a group with no intervention or a massage group,⁶⁵ whereas other studies reported no clear improvement in depression with exercise.⁴⁹⁻⁶⁶⁻⁶⁸ The reader should note that depression has mostly been included as an exploratory outcome in studies involving patients with PD. Large clinical trials are needed to examine the benefit of physical exercise specifically on depression in this population.

IMPROVED SLEEP

Sleep dysfunction occurs in two-thirds of patients with PD, among whom the most common problem is frequent night-time awakening.⁶⁹ In a small, non-controlled study of 20 patients with PD, some indication of sleep improvement was seen in those who participated in 36 group sessions of aerobic exercises and muscular strengthening.⁷⁰ In the general population, sedentary elderly individuals with moderate to severe sleep dysfunction showed improvements (assessed by the Pittsburgh Sleep Quality Index) in sleep-onset latency and sleep duration after moderate-intensity exercise.⁷¹ To assume that exercise could also improve sleep-related disorders in patients with PD seems reasonable; however, this area clearly needs to be studied in more detail.

DECREASED CONSTIPATION

Constipation is the most common gastrointestinal symptom in individuals with PD, and is reported by 50–80% of patients.⁷² Although the causes of constipation in patients with PD are multifactorial, this symptom is in part attributable to a lack of physical exercise.⁷³ No studies have yet evaluated the influence of exercise or increased physical activity on constipation in patients with PD; however, we might reasonably expect that patients with PD would experience similar benefits to those seen in healthy individuals, in whom cross-sectional studies have shown an inverse relationship between physical activity and the risk of constipation.⁷⁴ The mechanisms underlying the positive effect of exercise on constipation are unclear, but could include increased colonic motility, decreased blood flow to the gut, biomechanical stimulation of the gut during bouncing movements (such as running) or compression of the colon by abdominal musculature, and increased fiber intake as a result of increased energy expenditure.⁷⁴

DECREASED FATIGUE

Fatigue is experienced by 30–50% of patients with PD;⁷⁵ in a community-based population study, 44.2% of 233 patients with PD reported fatigue, compared with 18% of 100 age-matched controls.⁷⁶ Longitudinal studies in the general population showed that the amount of physical activity undertaken was inversely correlated with the presence of fatigue.⁷⁷ This pattern was also apparent in patients with PD.⁷⁷ Results obtained from studies in patients with chronic fatigue syndrome showed that cognitive behavioral training effectively reduced fatigue; however, changes in physical activity did not reduce levels of fatigue.⁷⁸ A review of nine randomized controlled trials found encouraging evidence that patients with chronic fatigue syndrome benefit from exercise therapy, but also concluded that more studies are needed.⁷⁹ If these findings can be extrapolated to patients with PD, exercise training in patients with PD might be useful to avoid or reduce fatigue in this population, although there no data have been obtained from clinical trials to support this hypothesis. The other side of the coin is that exercise may paradoxically increase fatigue, so future trials should tailor the level of exercise to each patient's individual capacity.

IMPROVED MOTOR PERFORMANCE

Individuals with PD invariably experience functional decline in a number of motor domains, including posture, balance, gait, and transfers (such as moving between a bed and chair). Several studies, including systematic reviews and a meta-analysis, have evaluated the effects of exercise on these functional deficits (Table 2.1). The overall conclusions of these studies were that exercise can improve physical functioning, health-related quality of life, leg strength, balance, posture, gait, and physical condition. The data showing that exercise improves functional motor performance in patients with PD seem robust; however, the question remains as to which exercise protocol is best suited for individual patients.

IMPROVED LEVODOPA EFFICACY

Several studies⁸⁰⁻⁸³ have investigated the association between exercise and the pharmacokinetics of levodopa, one of the drugs most commonly used to treat the symptoms of PD. Levodopa is transported to the brain and converted to dopamine, which ameliorates the dopamine deficit that occurs in patients with PD. Although most studies have found no effect of exercise on the efficacy of levodopa,⁸¹⁻⁸² one report revealed a trend towards improved absorption of this drug during physical activity.⁸³ In theory, exercise might stimulate levodopa absorption because of accelerated gastric passage or increased mesenteric blood flow.⁸³ Alternatively, levodopa might cross the blood–brain barrier more efficiently, due to higher blood pressure and heart rate during exercise.⁸⁴ However, these prior studies only evaluated a single, brief bout of exercise (maximum 2 h). Clearly, further studies are needed, particularly of prolonged exercise interventions, to assess the effect of exercise on the response to levodopa therapy in individuals with PD.

OPTIMIZED DOPAMINERGIC SIGNALING

Exercise could potentially influence endogenous production and release of dopamine in patients with PD, leading to enhanced dopaminergic neurotransmission.⁸⁵ This postulated mechanism is in line with behavioral studies that reported a positive effect of endurance exercise on both simple and more-complex movements in patients with PD, both of which were executed faster after exercise.⁸⁶ Although no concurrent neuroimaging studies were performed, the authors speculated that this improved performance could be attributed to an augmented synthesis and release of dopamine and other catecholamines in the prefrontal cortex, nucleus accumbens and basal ganglia.⁸⁶ However, some researchers have expressed concern that, when exercising, the motor response of PD patients may be pushed towards more normal values and the motor system might use up the available levodopa faster, leading to a greater (or earlier) dopamine shortage in the hours following exercise. This hypothesis needs to be studied in detail.

PREVENTION OF PD

The preceding section dealt with how exercise might improve motor and nonmotor dysfunction in patients who have clinically overt PD. However, the fascinating possibility exists that physical activity or exercise could also postpone the onset of parkinsonism, or perhaps even prevent disease manifestations altogether, in asymptomatic individuals who are predisposed to develop

BOX 3

THE PARKFIT STUDY

Our research group designed the ParkFit program—a multifaceted intervention to promote physical activity in sedentary patients with PD. This intervention is being studied in the ParkFit trial, which will investigate whether this program affords increased levels of physical activity that persist for 2 years.⁸⁷ The trial will also evaluate the possible health benefits and risks of increased physical activity.⁸⁷

The ParkFit trial is a multicenter, randomized controlled trial that will compare two different exercise interventions: physical therapy with a specific emphasis on promoting a physically active lifestyle (the ParkFit program); and matched physical therapy with a specific emphasis on the safety and quality of performing daily activities (the ParkSafe program). The ParkFit program emphasizes behavioral change, using a combination of accepted motivational techniques and strategies, and personal health coaches to induce a lasting increase in exercise behavior for patients with PD. The ParkFit program incorporates several specific elements: an educational workbook (including a health contract and logbook) designed to educate the patient about the benefits of physical activity, provide advice about suitable activities, help to identify and overcome perceived barriers to engagement in physical activity, and provide information on recruiting social support; a personal activity coach; goal setting; ambulatory monitoring with visual feedback; and physical therapy. The first results of the trial are expected by the end of 2011.

the disease. This issue is all the more pertinent because we are starting to identify people who are at an increased risk of developing PD: individuals with rapid eye movement sleep behavior disorder; family members (of individuals with PD) who have a reduced sense of smell; people with chronic constipation; or those who carry a mutation in a PD susceptibility gene.⁹²

The holy grail in the field of PD is to reliably identify these individuals as early as possible and to expose them to treatments that might slow down, or even arrest, the underlying disease process that will ultimately result in parkinsonism. Although such pre-emptive treatments are not yet available, we may logically assume that exercise could prove to be an intervention. This idea is further supported by epidemiological studies that investigated the relationship between physical activity and the risk of subsequently developing PD, and by studies in mouse models of PD that have highlighted the neuroprotective and neurorestorative effects of exercise.²⁹ However, whether the association between exercise and risk of PD can be explained by a truly preventive effect of exercise on the development of PD, or by a decrease in baseline recreational activity as a result of preclinical PD, is not yet clear.³⁰

RISKS OF EXERCISE IN PD

Individuals with PD have an increased risk of falls and fall-related injuries, such as fractures.³¹ The rates for falls and injuries might increase still further if these patients are stimulated to become more active, as even in the general population physically active adults have a higher incidence of leisure-time and sport-related injuries than their less active counterparts.³² In patients with PD, fall rates seem to taper off in the end stages of the disease, as the patients become progressively less mobile.³¹

Paradoxically, although exercise may increase the likelihood of falls in individuals with PD, it could also reduce the overall risk associated with falls and the associated fractures; for example, by improving strength, fitness, bone density or overall balance.⁹³ One study investigated the effects of a home-based exercise program in patients with PD. The results suggested that this intervention tended to reduce the incidence of fall events and injurious falls.⁹⁴ Additional evidence came from the RESCUE study—a large, multicenter study of rhythmic somatosensory cueing, in which a vibrating cylinder attached to the wrist was used to improve gait in patients with PD.⁹⁵ The researchers reported that the intervention led to improved mobility without an increased risk of falls.⁹⁵ The case as to whether exercise increases the patient's risk of falling is, therefore, far from closed; moreover, this issue should be considered in future trials.

Exercise is also associated with an increased risk of cardiovascular complications. Although the risk of sudden cardiac arrest or myocardial infarction is very low in generally healthy adults during activities of moderate intensity, the risk of these events increases during vigorous

physical activity, especially in sedentary individuals or those with pre-existing coronary artery disease.³² Nonetheless, physically active or aerobically fit individuals enjoy a 25–50% reduction in their lifetime overall risk of developing cardiovascular disease.³² Comparable data are not available for patients with PD, but they are unlikely to be an exception to this general rule. However, the risk of comorbid cerebrovascular disease seems to be higher in patients with PD than in the general population.⁵⁹ This increased risk is likely ameliorated by exercise, because regular moderate exercise has been shown to be a protective factor for development of cerebrovascular disease.⁵⁹ Other potential adverse effects of exercise include increased fatigue and levodopa requirements, as discussed earlier.

BOX 4

EVIDENCE FROM ANIMAL STUDIES

In rodent models of PD, which rely on administration of neurotoxins (6-OHDA or MPTP) to induce parkinsonian symptoms, exercise attenuates the degree of injury to midbrain dopaminergic neuron, and restores basal ganglia function through adaptive mechanisms of dopamine and glutamate neurotransmission.^{26-28 101}

In rats, voluntary or forced exercise (on a running wheel or treadmill) initiated before or during the administration of 6-OHDA and continued for an additional 1–5 weeks afterwards leads to the preservation of neurons in the substantia nigra pars compacta and to the attenuation of terminal loss in striatal and nigrostriatal dopaminergic neurons.^{28 101} Similarly, intensive treadmill exercise facilitates brain recovery in MPTP-treated mice, even when exercise commenced after neurotoxin-induced cell death was complete. These animals also demonstrated compensatory changes in the remaining dopaminergic neurons, such as altered dopamine handling (increased release and decreased uptake) and neurotransmission (increased dopamine numbers of D2 receptors expression) in surviving dopaminergic neurons and their targets.¹⁰²

Exercise may also reverse the increased glutamatergic drive characteristic of the parkinsonian state at the level of striatal medium spiny neurons, by modulating the subunit composition of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (a glutamate receptors subtype), and by diminishing the amplitude of the spontaneous excitatory post-synaptic potential at glutamatergic corticostriatal terminals. Several potential exercise-induced mechanisms of neuroprotection and neurorestoration exist at the cellular level: elevation of transcription factors; activation of signal transduction pathways; and the induction of neurotrophic factors, such as brain-derived neurotrophin and glia-derived neurotrophin.^{103 104}

Abbreviations: 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

TABLE 2.1

SUMMARY OF PUBLISHED REVIEWS ON THE EFFECT OF EXERCISE ON MOTOR DISABILITY IN PD

Review	Topic	Numbers of:		Criteria for inclusion	Conclusions
		Studies	Patients		
Goodwin et al. (2008) ^{68*}	Exercise or physical activity	14 RCTs	495 patients with PD	An exercise or physical activity intervention compared with any comparator Outcomes included physical performance or functioning, falls or HRQOL	Exercise is effective at improving physical functioning, HRQOL, leg strength, balance and walking Insufficient evidence that exercise improves falls and depression
Crizzle et al. (2006) ⁸⁸	Physical or therapeutic exercise	7 studies (including 3 RCTs)	438 patients with PD	Interventions comprising physical or therapeutic exercise Effects of physical exercise were evaluated Published in a peer reviewed journal	Patients improve physical performance and activities of daily living through exercise
Keus et al. (2007) ⁸⁹	Physical therapy	29 studies (including 23 RCTs)	Not applicable	Physical therapy Only trials with sufficient data Core areas of physical therapy Published in English, Dutch or German	Four specific recommendations: cueing strategies to improve gait; cognitive movement strategies to improve transfer; exercises to improve balance; training of joint mobility and muscle power to improve physical capacity
Kwakkel et al. (2007) ⁹⁰	Physical therapy	23 RCTs	1,063 patients with PD	Core areas of physical therapy Published in English, German or Dutch	Evidence in favor of specific task-oriented exercise training to improve posture, balance control, gait and gait-related activities, and physical condition
Mehrholz et al. (2010) ^{91*}	Exercise	8 RCTs	203 patients with PD†	Treadmill training versus no treadmill training	Patients who receive treadmill training are more likely than those who do not to improve their impaired gait hypokinesia

* Meta-analysis. †UK Brain bank criteria. Abbreviations: HRQOL, health-related quality of life; PD, Parkinson disease; RCT, randomized controlled trial.

CHANGING SEDENTARY LIFESTYLES

Regular physical activity is commonly accepted to be an important component of a healthy lifestyle. However, simply informing people about the health benefits of physical activity is not enough to attain a sustained behavioral change, which might explain why so many citizens (not just patients with PD) lead a sedentary life. Inducing a lasting change in exercise behaviors offers a particularly great challenge for patients with neurological disorders. In patients with PD, several specific barriers to such changes exist—not only the motor disabilities (gait and balance problems), but also the diverse nonmotor problems (cognitive decline, apathy, and depression). The progressive nature of these symptoms provides reasons to doubt whether patients with PD can be motivated to remain active in the long term.

If a true behavioral change can be attained in patients with PD, they might need specific coaching and counseling (rather than the general advice given to healthy adults). Evidence shows that effective physical activity interventions in this group should incorporate behavioral change principles.³⁴ Social cognitive theories propose that the control of behavior is based on two types of expectations: self-efficacy (individuals' belief in their ability to perform actions to attain a desired outcome) and outcome expectations (the belief that a certain consequence will be produced by personal action).⁹⁶ To change lifestyle and attain an enduring behavioral shift might, therefore, call for specific strategies tailored to the individual's preferences and needs. These behavioral programs should focus on appropriate supervision and social support from spouses and caregivers.⁹⁷⁻⁹⁸ Our research group has begun to address these issues in the ParkFit study (Box 3). Further research is needed to develop combined counseling and exercise programs for patients with PD, which focus on a behavioral change and have long-term follow-up. So far, the available studies have had no postintervention exercise-free period, and only short follow-up.⁹⁹⁻¹⁰⁰ Extended follow-up is important to evaluate whether the beneficial effects of exercise persist, and whether a reduced-intensity maintenance exercise program is needed to uphold the effects. Other studies should try to separate symptomatic effects from potential disease-modifying effects.

CONCLUSIONS

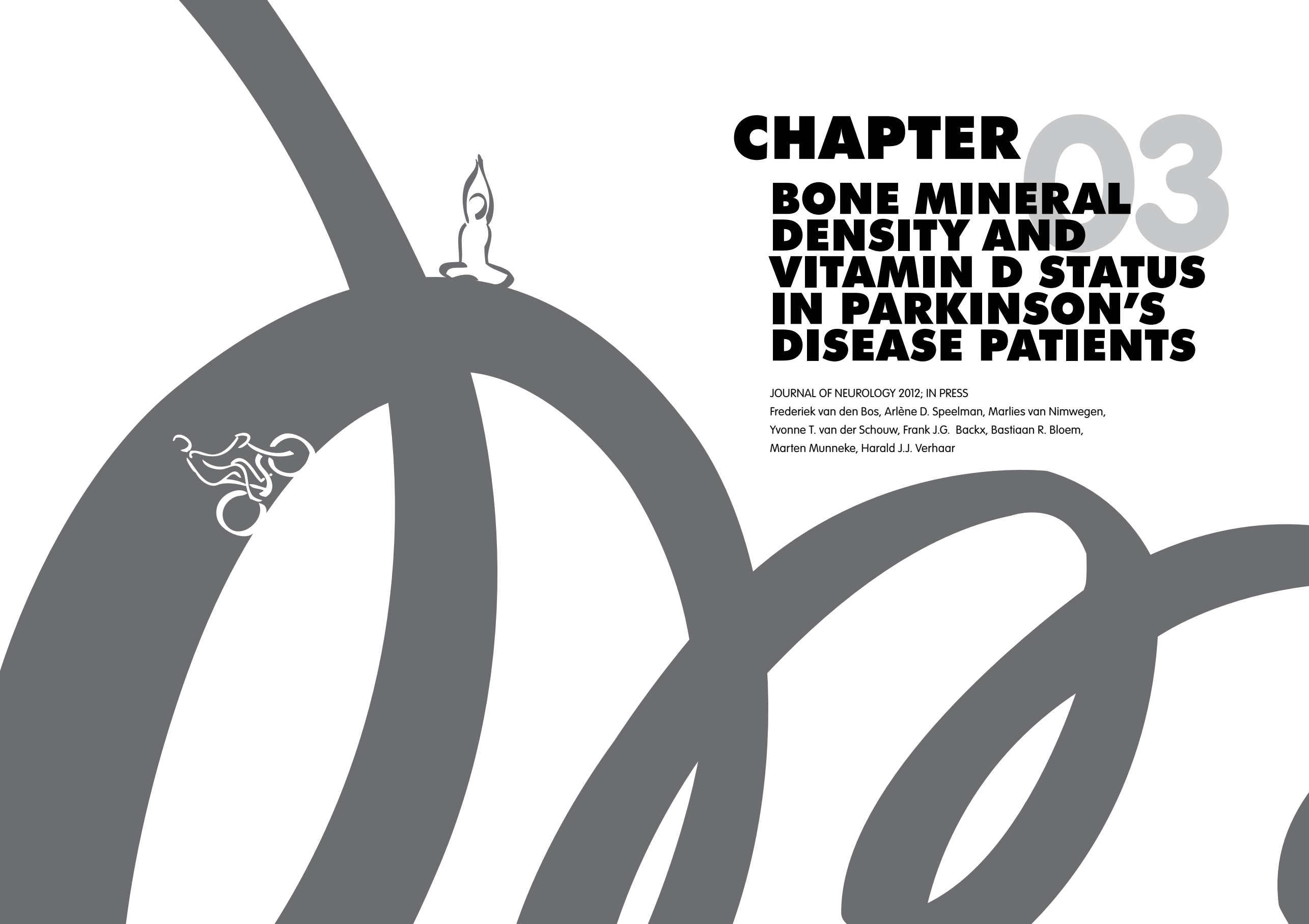
Compelling theoretical reasons support the avoidance of a sedentary lifestyle and the promotion of physical activity (including muscle strengthening, aerobic exercise and weight-bearing exercise) for people with, or at risk of developing, PD. Currently, however, we lack adequate knowledge about the merits of exercise specifically in patients with PD. The best available evidence stems from studies in healthy individuals or patients with other neurodegenerative diseases, which suggest a beneficial effect of exercise on cardiovascular mortality or morbidity¹⁸ and on cognitive dysfunction²²⁻²³ or mood.²⁴ Animal studies have raised the fascinating possibility that exercise might exert a neuroprotective effect in experimentally induced parkinsonism (Box

4) but these findings have yet to be translated to the human disease.

Development of a reliable strategy to stimulate an active lifestyle in patients with PD will be essential, and these efforts must pay careful attention to safety issues and each patient's individual capacities. Such exercise programs must also consider various barriers that could impede an active lifestyle specifically in patients with PD, such as apathy, fatigue, depression and cognitive dysfunction. The primary aim of these approaches is to induce a sustained behavioral change, with the hope of providing symptomatic relief of both motor and nonmotor disability, and perhaps to slow down progression in patients with overt PD. If exercise is proven to have disease-modifying effects, the ultimate goal will be to deliver strategies to postpone, or possibly prevent, the first disease manifestations in asymptomatic populations at risk of developing PD.

ACKNOWLEDGMENTS

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CHAPTER 03

BONE MINERAL DENSITY AND VITAMIN D STATUS IN PARKINSON'S DISEASE PATIENTS

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Frederiek van den Bos, Arlène D. Speelman, Marlies van Nimwegen,
Yvonne T. van der Schouw, Frank J.G. Backx, Bastiaan R. Bloem,
Marten Munneke, Harald J.J. Verhaar

ABSTRACT

BACKGROUND

Bone loss is more common in PD than in the general population. Several factors may be involved in the development of bone loss, including malnutrition, immobilization, low body mass index, decreased muscle strength, vitamin D deficiency and medication use. This study investigates the prevalence of osteoporosis and possible risk factors associated with bone loss in early stage PD.

METHODS

In 186 PD patients (Hoehn and Yahr stage 1 - 2.5, mean age 64.1 years, 71% men) bone mineral density (BMD) measurements were performed with DEXA. T- and Z-scores were calculated. Univariate linear regression analysis was performed to identify variables that contributed to BMD. 25-OH-vitamin D status of PD patients was compared with 802 controls (mean age 63.3 years, 50% men) using linear regression analysis.

RESULTS

Osteoporosis (11.8%) and osteopenia (41.4%) were common in PD patients. Mean Z-score for the hip was 0.24 (SD 0.93), and for the lumbar spine 0.72 (SD 1.91). Female gender, low weight, and low 25-OH-vitamin D were significantly correlated with BMD of the hip and lumbar spine. PD patients had lower 25(OH)D serum levels than controls ($B=-10$, $p=0.000$).

CONCLUSION

More than half of the patients with early stage PD had an abnormal BMD. Female gender, low weight, and low vitamin D concentration were associated with bone loss. Furthermore, vitamin D concentrations were reduced in PD patients. These results underscore the importance of proactive screening for bone loss and vitamin D deficiency, even in early stages of PD.

INTRODUCTION

PD is a common and incapacitating disorder affecting a sizeable proportion of the ageing community. Patients with PD have an increased risk of sustaining fractures.¹⁷⁻¹⁰⁵ The main causes for fractures in PD are falls, due to underlying gait and balance disorders, and a decreased bone mineral density (BMD).¹⁰⁶⁻¹⁰⁷ Bone loss appears to be more common in PD compared to the general population. Several factors may be involved in the development of bone loss, including malnutrition, physical inactivity, low body mass index, decreased muscle strength, vitamin D deficiency and certain medications.⁵³ Furthermore, osteoporosis is an important risk factor for fragility fractures, which are associated with increased morbidity and mortality. Therefore, screening for osteoporosis might need special attention in PD patients. Although several studies of bone loss in PD have been conducted, most studies included also patients with advanced disease (Hoehn and Yahr 3 or more).¹⁰⁸⁻¹¹¹ Moreover, etiological factors have been reported entirely consistently. This study evaluated the prevalence of osteopenia and osteoporosis in patients with early PD, and also studied possible risk factors associated with bone loss.

METHODS

SUBJECTS

PD patients

The study population consisted of subjects from the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral change program to increase physical activity in sedentary PD patients. The rationale and study design have been described previously.⁸⁷ Patients participating in the ParkFit study were invited to also participate in the present study. Data collection took place between September 2008 and January 2010. Eligibility criteria were: (a) PD, according to the UK Brain Bank Criteria³; (b) age between 40 and 75 years; (c) sedentary lifestyle defined as: <3 times a week vigorous-intensity physical activity for <60 minutes; or <3 times a week moderate-intensity physical activity for <150 minutes; (d) Hoehn and Yahr ≤ 2.5 . Exclusion criteria were: (a) unclear diagnosis (no gratifying and sustained response to dopaminergic therapy); (b) MMSE <24; (c) unable to complete Dutch questionnaires; (d) severe co-morbidity interfering with daily functioning; (e) daily institutionalized care; and (f) deep brain surgery. Informed consent was obtained before the first assessment. All subjects gave written informed consent prior to the study, as approved by the local Medical Ethical Committee.

MEASUREMENTS PD PATIENTS

Dual-Energy X-ray absorptiometry

Between 0-6 months after inclusion of the ParkFit study patients received a dual-energy X-ray absorptiometry (DEXA). BMD measurements were performed with DEXA using a Hologic

QDR1000. Scanning was performed according to the instructions of the manufacturer. Quality assurance, including calibration was performed routinely every morning for DEXA, using the standard provided by the manufacturer. BMD was measured at the femoral neck, trochanteric and intertrochanteric regions and in the first four lumbar vertebrae. The difference between an individual's BMD and the mean for a reference population is expressed in standard deviation (SD) units. T- and Z-scores were calculated where the T-score is the SD of the individual BMD compared with the mean BMD score in a young healthy population and the Z-score is the SD of the individual BMD compared to the mean BMD score of a similar sex-, age-, weight- and height-matched population. We used the WHO classification range to categorize subjects as normal ($T > -1$), osteopenic ($-2.5 < T \leq -1$), or osteoporotic ($T \leq -2.5$).

Physical activity

The level of physical activity was measured with a 7-day recall, based on a interview-based physical activity questionnaire, the LASA Physical Activity Questionnaire (LAPAQ).¹¹² Patients were asked to list their daily amount of activity (frequency and duration), so total time spent on physical activity (in hours per week) could be calculated.

Isometric grip strength

Isometric grip strength was measured using an adjustable hand held dynamometer (JAMAR dynamometer) at the non-dominant hand. The subjects were seated with their shoulder adducted and neutrally rotated. The dynamometer was held freely, without support. The elbow was flexed at 90° and care was taken that it did not touch the trunk. The forearm was in a neutral position, and the wrist was held between $0-30^\circ$ dorsiflexion and between $0-15^\circ$ ulnar deviation. The subjects were told to put maximal force on the dynamometer. The maximal value of two trials was noted in kilograms.

Body composition

Height and weight were measured in standing position without shoes. Body mass index (BMI) was calculated as the weight in kilograms divides by the square of heights in meters.

Other variables

A wide range of other variables was assessed: disease severity (Hoehn and Yahr staging¹¹³; motor section of the Unified Parkinson's Disease Rating Scale (UPDRS))¹¹⁴, disease duration (date of diagnosis), mobility (Timed Up and Go test (TUG)) and gait speed (participants were timed while walking four meters at their normal pace).

Participants were asked about current and past medication use. All participants were interviewed about their smoking and alcohol habits. The participants were asked to complete questionnaires about diet and sunlight exposure. The mean weekly dietary calcium and vitamin D intake was calculated for each participant. Furthermore, serum samples of both calcium and vitamin

D were measured. Since low levels of testosterone have been shown to have a detrimental effect on bone density in men we analyzed if testosterone levels were related to bone density. All patients were measured on dopaminergic medication.

25-OH-vitamin D

25-OH vitamin D (25(OH)D) levels were measured on the E170 modular (Roche Diagnostics, Mannheim, Germany) and compared with a reference group. The reference group consisted of 402 independently living women¹¹⁵ and 400 independently living men.¹¹⁶ Their mean age was 63.3 years (range 40-80). Vitamin D deficiency was defined as a 25(OH)D level of less than 50 nmol/l.

X-rays

X-ray radiographics of the spine and thoracal vertebrae were performed to assess vertebral compression fractures.

STATISTICAL ANALYSIS

Bivariate associations were determined using the chi-square test for categorical variables and the unpaired t-test for continuous variables. Univariate linear regression analysis was performed to study the association between the several factors mentioned above and BMD. Age, gender, height and weight were included in the analysis, as these factors may influence BMD. Linear regression analysis was used to investigate the 25(OH)D concentration between patients and controls after controlling for covariates age, gender, weight, height, smoking and alcohol consumption. A significant level of 0.05 was set for all statistical tests.

RESULTS

Of the 586 PD patients included in the ParkFit study, 186 PD patients participated in the present study (Table 3.1). Characteristics of the PD patients in the ParkFit study and PD patients of the present study are presented in Table 3.2.

BONE MINERAL DENSITY IN PD

The summed prevalence of osteoporosis and osteopenia was 53.2% (41.4% for osteopenia, 11.8% for osteoporosis) in PD patients (Table 3.3). The mean Z-score for the hip was 0.24, and for the lumbar spine 0.72.

DETERMINANTS OF BMD

Univariate regression analyses showed that female gender, low weight and low 25-OH-vitamine D were significantly correlated with BMD of the hip and lumbar spine (table 3.4). Physical activity and isometric grip strength were also correlated with the BMD of the hip. No relationships between other factors and BMD were present. Multivariate regression analysis showed that the BMD of the hip and lumbar spine were related to female gender, low weight and low 25-OH-vitamine D (table 3.5).

25 (OH) D CONCENTRATION PD VERSUS CONTROLS

In PD patients 56.2% had a vitamin D deficiency (mean vitamin D concentration 48.3 nmol/l) compared to 43.2% in the control groups (mean 56.7 nmol/l) (table 3.1). 25(OH)D vitamin D serum levels were significantly lower in PD compared to controls (difference = -10.2 nmol/l, $p < 0.000$). A higher portion of the samples were drawn in the winter to spring (when vitamin D levels are lower). The portion of samples drawn in the winter to spring were significantly lower than the portion drawn in the summer to fall (43.4 nmol/l vs. 58.8 nmol/l, $p < 0.00$), but these seasonal differences had no influence on the regression analyses we performed.

TESTOSTERONE LEVELS

Regression analysis showed that testosterone levels have no significant relationship with BMD of the hip and lumbar spine (Hip: $B = 0.000$, $p = 0.820$; Lumbar spine: $B = 0.001$, $p = 0.781$)

TABLE 3.1

CHARACTERISTICS OF PATIENTS AND CONTROLS

Variable	PD patients (n=186)	Control group (n=802)
Demographics		
Age	64.1 (7.7)	63.3 (8.9)
Men (%)	71%	50%
Weight (kg)	80 (13.1)	76.8 (13.9)
Height (cm)	173.8 (8.6)	170.9 (9.7)
BMI	27.2 (4)	26.2 (3.9)
Vitamin D		
25-OH-vitamine D nmol/l	48.3 (20.2)	56.7 (22.9)
25-OH-vitamine D % insufficiency	56.2%	43.2%
PD characteristics		
Disease duration (years)	4.9 (4.2)	-
UPDRS III	31 (9.0)	-
HY 1	2.1%	-
HY 1.5	2.1%	-
HY 2	83.2%	-
HY 2.5	9.9%	-
Physical activity		
Level of physical activity (hours/week)	12.2 (8 to 20.2)	-
Sunlight exposure		
Regular (> 3 time a week going outside)	97%	-

Data reflect mean (SD), percentage or median (IQ-range). PD=Parkinson's disease, BMI = Body Mass Index, UPDRS III= unified Parkinson's disease rating scale part III, HY= Hoehn and Yahr stage.

TABLE 3.2

CHARACTERISTICS OF PATIENTS OF THE PARKFIT STUDY AND SUBGROUP

Variable	Participants without DEXA (n=400)	Participants with DEXA (n=186)
Age	65.8 (7.7)	64.8 (7.5)
Gender (%men)	62.5% (n=250)	71% (n=132)
Weight (kg)	81.1 (15.4)	82.0 (13.0)
Height (cm)	171.0 (10.3)	173.8 (8.9)
BMI	27.7 (4.3)	27.2 (4.0)
Disease duration (years)	5.4 (4.7)	4.9 (4.2)
UPDRS III	33.5 (11.0)	31.0 (9.0)
HY 1	1.8%	2.2%
HY 1.5	3.3%	2.2%
HY 2	71.3%	85.5%
HY 2.5	16.3%	10.2%

Data reflect mean (SD), percentage or median (IQ-range). PD=Parkinson's disease, BMI = Body Mass Index, UPDRS III= unified Parkinson's disease rating scale part III, HY= Hoehn and Yahr stage.

TABLE 3.3

BONE MINERAL DENSITY IN PARKINSON'S DISEASE

BMD	PD patients
Osteoporosis/osteopenia (%)	98 (53.2%)
Normal bone mineral density	88 (46.8%)
BMD total hip g/cm ²	0.94 (0.1)
BMD lumbar spine g/cm ²	1.06 (0.2)
Z-score hip right	0.25 (0.9)
Z-score hip left	0.22 (0.9)
Z-score lumbar spine	0.72 (1.9)

Data reflect mean (sd) or number (percentage %) BMD= Bone Mineral Density, PD=Parkinson's Disease.

TABLE 3.4

UNIVARIATE REGRESSION ANALYSIS BMD LUMBAR SPINE AND HIP TOTAL

Variable	BMD Lumbar Spine B (SE)	BMD Hip total B (SE)
Age	0.001 (0.002); p=0.551	-0.001 (0.001); p=0.471
Weight	0.006 (0.001); p=0.000	0.004 (0.001); p=0.000
Gender	-0.087 (0.033); p=0.009	-0.107 (0.020); p=0.000
25-OH-Vitamin-D	0.002 (0.001); p=0.013	0.001 (0.00); p=0.025
Physical activity	-0.013 (0.019); p=0.501	-0.031 (0.012); p=0.010
HY	-0.069 (0.056); p=0.216	-0.045 (0.035); p=0.202
TUG	0.004 (0.005); p=0.389	-0.005 (0.003); p=0.139
Isometric grip strength	0.001 (0.001); p=0.152	0.001 (0.000); p=0.001
Levodopa use	-0.075 (0.035); p=0.032	-0.014 (0.023); p=0.541
Homocystein	-0.001 (0.003); p=0.797	-0.002 (0.002); p=0.265
Testosterone	0.001 (0.003); p=0.781	0.000 (0.002); p=0.820

TABLE 3.5

MULTIVARIATE REGRESSION ANALYSIS BONE MINERAL DENSITY IN PARKINSON'S DISEASE

Variable	Regression coefficients (standard error); p-value	
	Multivariate analysis BMD Lumbar Spine	Multivariate analysis BMD Hip total
Gender	- 0.09 (0.03); p<0.01*	-0.1 (0.02); p<0.00*
Weight	0.01 (0.00); p<0.00**	0.00 (0.00); p<0.00**
25-OH-vitamine D	0.002 (0.001); p=0.01***	0.001 (0.00); p=0.02***
Physical activity	-	-0.021 (0.011); p=0.063**
Isometric grip strength	-	0.00 (0.001); p=0.604**

DISCUSSION

This study showed that over 50% of sedentary patients with early PD had an abnormal BMD. Specifically, 41.4% had osteopenia and 11.8% had osteoporosis. These findings are largely consistent with previous studies,^{106 107 110 111 117 118} although the prevalence observed here was lower compared to other studies, which may be explained by the lower H&Y stages in our cohort. Indeed, others have found a greater decrease in BMD in the subgroup of patients with more advanced disease.¹⁰⁹ A higher prevalence of bone loss in more advanced PD can be explained by further diminished activities in daily life,¹⁷ greater motor impairment, less sunlight exposure due to greater immobility, and continuing weight loss,¹¹⁹ which all result in a further lowering of vitamin D levels.

We should point out that the median Z-scores for bone loss were very close to zero. Therefore, the prevalence of osteoporosis in PD may not be more common than in the general population.¹²⁰ However, the absolute prevalence of osteopenia and osteoporosis is very high in this sample. Considering the morbidity and mortality related to hip fractures, especially in PD¹²¹, it is important to be aware of this high prevalence of bone loss even in early stages of the disease. Together with the high risk of falls (even in HY stage 2-2.5),³¹ bone loss is an important risk factor for fractures in PD patients. In our study, female gender, weight loss and low 25-OH-vitamin D levels were identified as significant risk factors associated with a lower BMD. Female gender and weight loss are well recognized risk factors for bone loss in the general population and in patients with PD.^{53 118} Weight loss is reported frequently in PD, also during early stages of the disease, and women with PD are at higher risk.^{122 123}

To help to prevent such fractures, preventive strategies are needed, including supplementation of the vitamin D deficiency observed here and by others,^{110 124 125} or by promoting physical activities.^{50 87 126} Preventing or reverting weight loss might also help, as reduced body weight was an additional risk factor for bone loss. In addition, gait and balance training (and in particular treatment strategies aimed at reducing freezing of gait) may help to reduce falls.^{94 127 128} The high incidence of vitamin D deficiency observed in the present study is remarkable. It has been suggested that vitamin D deficiency is caused by sunlight deprivation, and low vitamin D levels induce compensatory hyperparathyroidism, with further contributes to low BMD in patients with PD.¹²⁹ However, in our study patients experienced sufficient sunlight exposure. Furthermore, our results demonstrated that PD patients had significant lower levels of 25-OH-vitamin D compared with controls. Several studies have confirmed these findings.^{124 130 131} One study additionally showed that vitamin D deficiency was more common in PD compared to patients with Alzheimer disease.¹²⁴ Larger studies remain necessary to further investigate the association between vitamin D and bone loss. Pending further evidence, it is important to be alert of vitamin D deficiency in PD and its possible effect on BMD and muscle strength. We therefore recommend to consider routine measurement of vitamin D in older patients with PD, even in early stages of their disease.

The present study is the largest series of PD patients who received bone densitometry measurement. The results of previous studies on the prevalence of osteoporosis are inconsistent and not all studies used the same methods of assessment of BMD or the WHO definitions. A major advantage of our study is that many risk factors associated with bone loss were taken into account. Our study also had several limitations. First, due to its cross-sectional nature, the associations observed here cannot be taken as definitive evidence of a causal relationship. Second, the lack of a control group for the BMD is a limitation. However, bone mineral density inherently has its own controls owing to the method of the statistical measurement of T and Z-scores. As such, a mean Z score of 0 would equate to an equivalent age-matched population. Finally, the present study was performed in a subgroup of patients selected from the ParkFit trial, an RCT that specifically selected sedentary PD patients, aiming to promote their levels of physical activity. The present findings can therefore not be extrapolated to all PD patients, but may apply only to this selected subpopulation.

We conclude that BMD is often affected, even in early PD. The lower BMD is mainly associated with vitamin D deficiency, lower body weight and female gender. These could be clinically important because of the concomitant risk of fractures in combination with an increased fall risk. We recommend that older patients with PD are evaluated for the risk of osteoporosis. Besides classical risk factors, vitamin D deficiency and weight loss should be addressed. In the case of osteoporosis, treatment with bisphosphonates could be considered, in combination with calcium and vitamin D supplementation.

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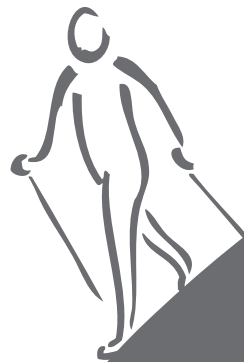
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CHAPTER 04

PARKINSON'S DISEASE AND OSTEOPOROSIS

AGE AND AGEING 2012; IN PRESS

Frederiek van den Bos, Arlène D. Speelman, Monique Samson,
Marten Munneke, Bastiaan R. Bloem, Harald J.J. Verhaar



INTRODUCTION

PD is a common neurodegenerative disease characterized by both motor and non-motor symptoms. As a result, many PD patients are limited in their daily activities.¹⁷ Compared to age-matched controls, PD patients have a significantly increased risk of fractures, mainly of the hip.^{55 107 132-135} The consequences of such hip fractures in PD can be devastating, including decreased functionality, length of hospital stay, risk of nursing home admission and high mortality rates.^{121 136-138} One explanation for the increased fracture risk in people with PD are falls, due to postural instability and gait disturbances. However, not all fractures in PD – and especially vertebral fractures – are related to falls.^{55 107 137} The bone mineral density (BMD) of patients with PD is lower compared to healthy controls, thus worsening the fracture risk.^{55 107 134 139} However, it is unclear how many patients with PD experience bone loss. Published estimates of prevalence of osteoporosis in PD vary considerably, and the causes of bone loss, in particular, are not well described in the literature. The aim of this study is to systematically review studies reporting bone loss in PD. In this review, we focus specifically on the pathophysiological mechanisms of bone loss, and treatment in patients with PD.

LITERATURE SEARCH

A Medline search was performed for articles published between January 1975 and January 2011, using the keywords 'bone mineral density', 'bone loss', 'BMD', 'bone metabolism', 'fractures', 'Parkinson's disease', and 'parkinsonism'. Moreover, reference lists from the included studies were checked and author's names were searched for additional studies. All the articles were screened on the basis of their title and abstract. Studies were included if participants had PD and the study evaluated risk factors for, or interventions to prevent, bone loss. Only studies in which dual energy X-ray absorptiometry of the hip and/or spine was used to measure BMD were included. Articles written in languages other than English, expert opinions, case reports, and articles of which the full text was not available were excluded.

SEARCH RESULTS

This search yielded 403 studies. Twelve papers were considered eligible, using the above mentioned criteria (Figure 4.1). Three of those studies were prospective cohort studies, with a follow-up ranging from 1 to 6 years. The others were observational (mostly case control studies). Men and women were equally distributed and mean age varied from 60 to 78 years. Not all studies reported disease severity and duration, but when reported UPDRS varied from 25 to 33. Almost all patients had a Hoehn & Yahr stage greater than 2, and mean disease duration varied from 2 to 6.5 years. Most studies did not take all relevant confounders (e.g. vitamin D concentration) into account. The characteristics of these studies are summarized in Table 4.1.

CLINICAL EVIDENCE

Data from observational and case-control studies suggested an independent association between PD and lower BMD.^{52 106 108-111 117 118 140 141} These data were confirmed by three longitudinal studies.^{52 107 132} We will discuss these three latter studies in more detail next. Two studies investigated annual loss of BMD in PD patients. Lörefalt et al. found significant reductions of total body, total hip and femoral neck BMD (3.9% vs 1.2%) in 26 PD patients compared with 26 controls. Low body weight and low physical activity were risk factors for low BMD, whereas rigidity seemed to be protective, possibly by increasing the mechanical load on bones. BMD however did not correlate with the severity of PD. An important limitation of this study is the small number of patients en controls.⁵²

In the Osteoporotic Fractures in Men Study Fink et al found a significantly ($p < 0.001$) greater total hip bone loss of 1.1% compared to only 0.4% in community-dwelling male patients (19 patients, 4357 controls). However, this study had several limitations: the number of men with PD was limited; PD was self-reported; and the number of patients with follow-up date was low.¹³² Schneider et al. investigated a cohort of community-dwelling women with and without PD for 6 years (73 patients, 8032 controls). The authors found no significant difference in baseline BMD and in bone loss between the two groups after correcting for confounders. Body weight accounted for 60% of the difference in BMD. Because of the small number of patients at follow-up the authors were unable to assess the association of PD with rate of change in hip BMD. Besides the small proportion of patients, this study was also limited by the self-reporting of PD, so the duration and severity of the disease could not be taken into account.¹⁰⁷

PATHOPHYSIOLOGY

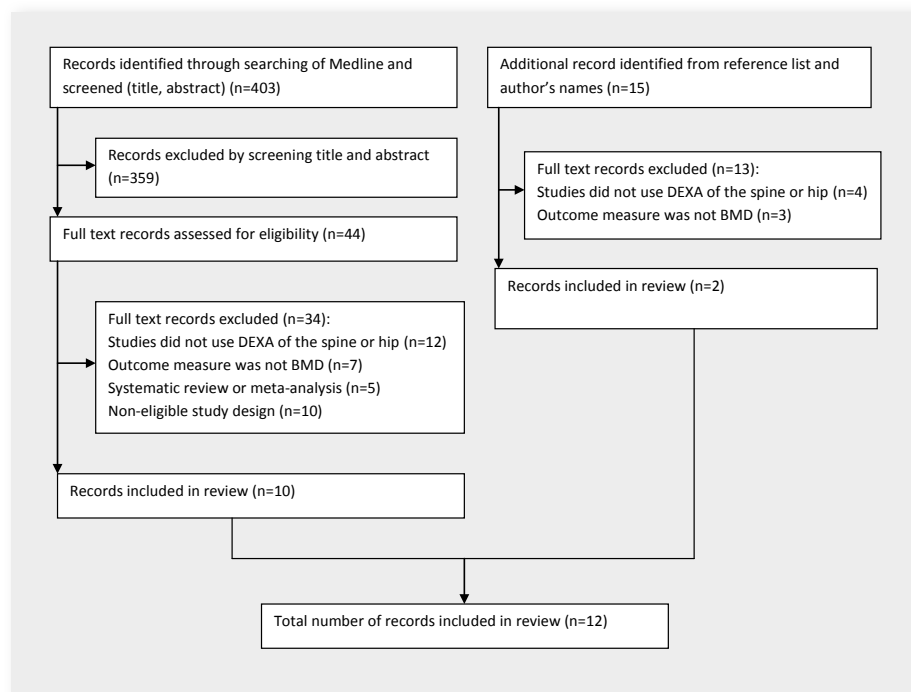
Several factors may contribute to bone loss in PD (Figure 4.2). Most of these develop in the course of PD and affect or reinforce each other.

PHYSICAL ACTIVITY AND EXERCISE

PD patients are less active compared to healthy controls.⁸⁷ Bone tissue is sensitive to its mechanical environment and is continuously stimulated by muscle contraction and weight-bearing movements, and is responding to mechanical stress. Osteocytes and their dendritic connections are able to sense fluid flow driven by stresses placed upon bone. In response to these stresses, osteocytes produce signaling molecules that stimulate bone remodeling by osteoclasts and osteoblasts.^{142 143} Subnormal mechanical stress as a result of immobilization leads to bone loss, with the rate of bone loss being influenced by the duration, intensity, and acuteness of immobilization.¹⁴⁴ There are indications that immobility is associated with bone loss in PD, but research into this is limited. Only three studies investigated the association between physical

FIGURE 4.1

FLOW DIAGRAM OF STUDY SELECTION PROCESS



performance/exercise and BMD in PD. The authors Lam and Fink found no association, Lorefält, on the other hand, found that the amount of BMD in PD patients was directly correlated to physical activity.^{52 106 108} Data on the association between BMD and the severity of PD are also conflicting. Only one prospective study mentioned severity. They found no correlation between BMD and severity of PD symptoms. However, besides the small number of patients, none of the patients was severely disabled.⁵² In contrast, results of most observational studies have suggested a significant association between disease severity and BMD. These studies also consisted of small number of patients. Most studies did not account for all potential confounders.^{109-111 140 141} Although the evidence is scarce, it seems plausible that physical inactivity, which worsens as the disease progress, contributes to bone loss in PD.

TABLE 4.1

LITERATURE ABOUT BMD AND PD

First Author (reference nr)	Year of publication	Number of patients/ controls		Outcome measure (DEXA)	Results
Lam ¹⁰⁸	2010	108	215	Hip (four subregions), lumbar spine and body BMD	Female, but not male patients with PD have lower hip BMD ($p=0.005$). After multivariate adjustment, the result did not reach statistical significance.
Abou-Raya ¹⁹²	2009	82	68	Lumbar spine and femoral neck BMD.	PD patients have significantly lower BMD at lumbar spine and femoral neck (respectively $p=0.005$ and $p=0.001$).
Song ¹⁰⁹	2009	107	100	Lumbar spine and femoral neck BMD.	Femoral neck and lumbar spine BMD were significantly lower in PD ($p<0.00$).
Bezza ¹¹¹	2008	52	52	Lumbar spine and dual femur BMD	BMD at lumbar spine and hip was lower in PD (respectively $p<0.001$ and $p=0.02$).
Fink ¹³²	2008	46	5891	Hip BMD	Total hip bone loss was greater in men with PD ($p<0.001$).
Schneider ¹⁰⁷	2008	73	8032	Total hip and femoral neck BMD	Total hip BMD was lower in women with PD ($p<0.01$). After multivariate adjustment, the result did not reach statistical significance.
Kamanli ¹⁴¹	2008	28	31	Lumbar spine, proximal femur and hand BMD.	In female, but not male, patients hand and femoral neck BMD were significantly lower ($p<0.05$).
Lörefält ⁵²	2007	26	26	Hip and total body BMD	The BMD was lower at all sites in PD at year 1 and 2 compared with controls ($p<0.05$) and decreased during the investigated year.
Di Monaco ¹⁴⁰	2006	28	28	Hip (five subregions) BMD	BMD did not differ significantly between PD patients and controls with hip fracture
Wood ¹¹⁸	2005	105	-	Hip (three subregions) and lumbar spine BMD	41.9% of the PD patients had osteoporosis and 34.5% osteopenia.
Fink ¹⁰⁶	2005	52	5943	Hip (three subregions) and lumbar spine BMD	PD was associated with lower BMD at the spine ($p=0.04$) and total hip ($p=0.07$)
Taggart ¹¹⁷	1995	51	51	Hip and lumbar spine BMD	Total hip ($p=0.014$) and femoral neck ($p<0.004$) BMD were decreased in PD patients. No significant difference was found for the lumbar spine.

VITAMIN D DEFICIENCY

Vitamin D has a crucial role in bone metabolism, and a shortage of vitamin D is correlated with an increased risk of falls and fractures.¹⁴⁵ Vitamin D deficiency results in hypocalcemia and compensatory hyperparathyroidism, and an excess of parathyroid hormone causes bone resorption by stimulating osteoclast activity.¹⁴⁴⁻¹⁴⁶ Vitamin D deficiency is common in PD and may be related to malnutrition, immobility and sunlight deprivation. The prevalence of vitamin D insufficiency is significantly higher in patients with PD compared to healthy controls or patients with Alzheimer disease, which suggests that there is a specific association between PD and vitamin D deficiency.^{124 147 148}

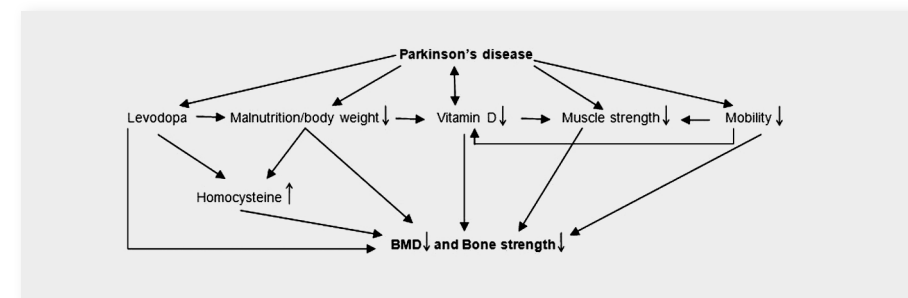
Vitamin D has an important role in the human brain. 1,25(OH)₂D is synthesized in neurons and microglia by 1 α -hydroxylase. Active vitamin D binds to vitamin D receptors (VDR) and regulates several genes involved in cell differentiation, proliferation, and apoptosis. VDR are expressed throughout the brain, with the strongest expression of both 1 α -hydroxylase and VDR being found in the (presumably dopaminergic) neurons of the substantia nigra.¹⁴⁹ Matkovits et al showed that dopamine can induce VDR-mediated signaling in the absence of active vitamin D.¹⁵⁰ This supports the hypothesis that vitamin D has autocrine and paracrine functions in the nervous system. Vitamin D also seems to have neuroprotective actions, by inhibiting the synthesis of nitric oxide, by exerting direct antioxidant-like effects and anti-ischemic actions, and by modulating cytokine release.^{151 152} Vitamin D and PD are also linked at a gene level. Kim et al found an association between PD and VDR gene polymorphisms, using genomic DNA extracted from peripheral blood from patients with PD and controls.¹⁵³ Newmark and Newmark even hypothesized that a chronically inadequate vitamin D intake may contribute to the pathogenesis of PD. They suggested that a continuous inadequate intake of vitamin D leads to a chronic loss of dopaminergic neurons in the brain.¹⁵⁴ A recent longitudinal study supported this hypothesis. Knekt et al. investigated a cohort of 3173 men and women free of PD in Finland with a follow up of 29 years and concluded that low vitamin D status predicted the development of PD (50 cases, 3123 non-cases). However, this study had some weaknesses, such as a small number of cases, the single measurement of vitamin D, and the possibility of residual confounders due to the fact that risk factors for PD are not well known.¹⁵⁵

MUSCLE STRENGTH

Both vitamin D deficiency and decreased mobility reduce muscle strength (figure 4.2). Muscle strength has been negatively associated with BMD in various populations, and bone formation and remodeling may be affected by local mechanical signals generated by muscle contraction.¹⁵⁶⁻¹⁵⁸ Environmental influences (exercise, nutrition, vitamin D) as well as genetic factors influence this bone-muscle relationship.^{130 159} The isokinetic muscle strength of patients with PD is reduced compared with age-matched controls, even in early disease stages, and declines further with disease progression. The specific cause of this weakness is not known.¹⁶⁰ One study reported lower extremity muscle strength (isometric hip flexion and knee extension) to be associated with hip BMD in women with PD (34 patients, 30 controls), after correcting for several confounders.¹³⁰ Another study

FIGURE 4.2

FACTORS INFLUENCING BMD AND BONE STRENGTH IN PD



investigated the association between lumbar spine BMD and trunk muscle strength and found trunk muscle strength to be independently associated with lumbar spine BMD (43 patients, 29 controls).¹³¹ Both studies were limited by small sample sizes and possible selection bias.

LOW BODY WEIGHT

Several studies have suggested that low body weight is a risk factor for low BMD in PD.^{52 111 117} Schneider et al found that weight accounted for 60% of the age-adjusted difference in hip BMD in 73 women with PD compared with 8032 controls.¹⁰⁷ One explanation is the decreased mechanical load. In addition, a lower body fat content is associated with lower estradiol production in postmenopausal women, leading to a reduced BMD.^{161 162} Patients with PD are at high risk of poor nutrition for several reasons, such as impaired hand-mouth coordination, dysphagia, intestinal hypomotility, depression, cognitive deficits, and side effects of medication. At the same time, there is an increased energy requirement due to muscular rigidity and involuntary movements. In addition, malnutrition can lead to low levels of vitamin D, folic acid, and vitamin B12, with negative consequences on bone formation and strength.^{123 163}

HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia is an independent risk factor for osteoporotic fractures.¹⁶⁴⁻¹⁶⁶ The catabolism of homocysteine depends on folic acid, vitamin B12, and vitamin B6, and thus folic acid and vitamin B12 deficiency can cause hyperhomocysteinemia. Homocysteine has a direct effect on bone by binding to extracellular collagen, which interferes with the formation of collagen cross-linking.^{167 168} In addition, in vitro studies have shown that homocysteine stimulates the differentiation of osteoclasts and induces apoptosis of osteoblasts.¹⁶⁹⁻¹⁷¹ The first mechanism results in poor bone quality and the second reduces BMD, both contributing to an increased fracture risk.

Hyperhomocysteinemia is common in PD and is associated with fracture risk and a low BMD.¹⁷²⁻¹⁷⁶ In addition to vitamin B12 and folic acid deficiency, levodopa use may cause hyperhomocysteinemia. Levodopa and dopamine are methylated by catechol O-methyltransferase (COMT), with S-adenosylhomocysteine as methyl donor, to form S-adenohomocysteine. Since S-adenohomocysteine is rapidly converted to homocysteine, levodopa therapy can lead to hyperhomocysteinemia. Theoretically, inhibition of COMT should reduce levodopa-induced hyperhomocysteinemia, but the literature on this is contradictory. These discrepancies in the literature might be related to the different levels of vitamin B12 and folic acid in the included patients.¹⁷⁷⁻¹⁸² Two studies have shown that supplementation of vitamin B12 and folic acid decreases homocysteine levels in levodopa-treated patients.¹⁸³⁻¹⁸⁴ Moreover, Lee et al. concluded that homocysteine-lowering therapy with folic acid and vitamin B12 prevents bone loss in levodopa-treated patients.¹⁸⁵ Another recent study found that not levodopa use, but decreased levels of vitamin B12 and folic acid, cause hyperhomocysteinemia in PD.¹⁷⁶

MANAGEMENT AND TREATMENT

The paragraphs above indicate that a complex interaction between various factors can contribute to bone loss in patients with PD. Optimal management calls for careful assessment of all these factors, followed by tailored treatment where possible. Because scientific evidence concerning the treatment of osteoporosis in PD is scarce, we would like to recommend clinicians to treat PD patients according to the same principles that apply to non-parkinsonian patients. Specific recommendations for treatment include: (a) lifestyle factors & exercise; (b) dietary supplementation; and (c) anti-osteoporotic medication.

The WHO developed the calculation tool FRAX to evaluate fracture risk of patients based on individual patient models that integrate clinical risk factors as well as BMD at the femoral neck. The risk factors of having 'PD' or 'falls related to PD' have however, not been quantified (sufficiently) in FRAX to give an accurate 10-year probability of fracture in these patient categories. The FRAX calculation tool can therefore not be recommended in calculating fracture risk in PD patients.¹⁸⁶

LIFESTYLE FACTORS / EXERCISE

Smoking and alcohol are well known risk factors for osteoporosis, so patients should be advised to stop smoking and reduce alcohol consumption. Exercise is recognized as key modifiable lifestyle factor that is essential to the prevention and management of osteoporosis. Physical activity programs for maintaining BMD are based on a site-specific modifying effect, in addition to strengthening muscles and improving balance, thus reducing the overall risk of falls and fractures. The influence of exercise on BMD in PD is not well studied. The ParkFit study is currently being conducted. It researches whether a physical activity promotion program can increase physical activity levels in sedentary patients with PD.⁸⁷

DIETARY SUPPLEMENTATION

Sato et al. performed a randomized, double-blind, placebo-controlled trial of 1 α -hydroxyvitamin D3 supplementation (1 μ g/day) for 18 months in patients with PD (43 patients in both groups). After 18 months the treatment group showed a smaller decrease in BMD (1.2% vs 6.7%; $p < 0.00$) and a lower risk of non-vertebral fractures (18.6% vs 2.3%; OR 9.8, $p = 0.003$).¹⁸⁷

Lee et al. studied the effect of homocysteine-lowering therapy on preventing bone loss in patients with PD taking levodopa. Patients were randomly assigned to treatment ($n = 14$) (folate 5 mg daily, mecobalamin 500 μ g three times daily) or no treatment ($n = 13$). Both groups took daily oral supplements of calcium (500 mg) and cholecalciferol (1000 IU). Follow-up was 12 months. The authors found that homocysteine-lowering therapy resulted in significantly greater improvements in BMD at the lumbar spine (4.4%), total femur (2.8%), and femur shaft (2.8%). Although this was a small trial and fracture reduction was not taken into account, it is an easy therapy with minor side effects.¹⁸⁵

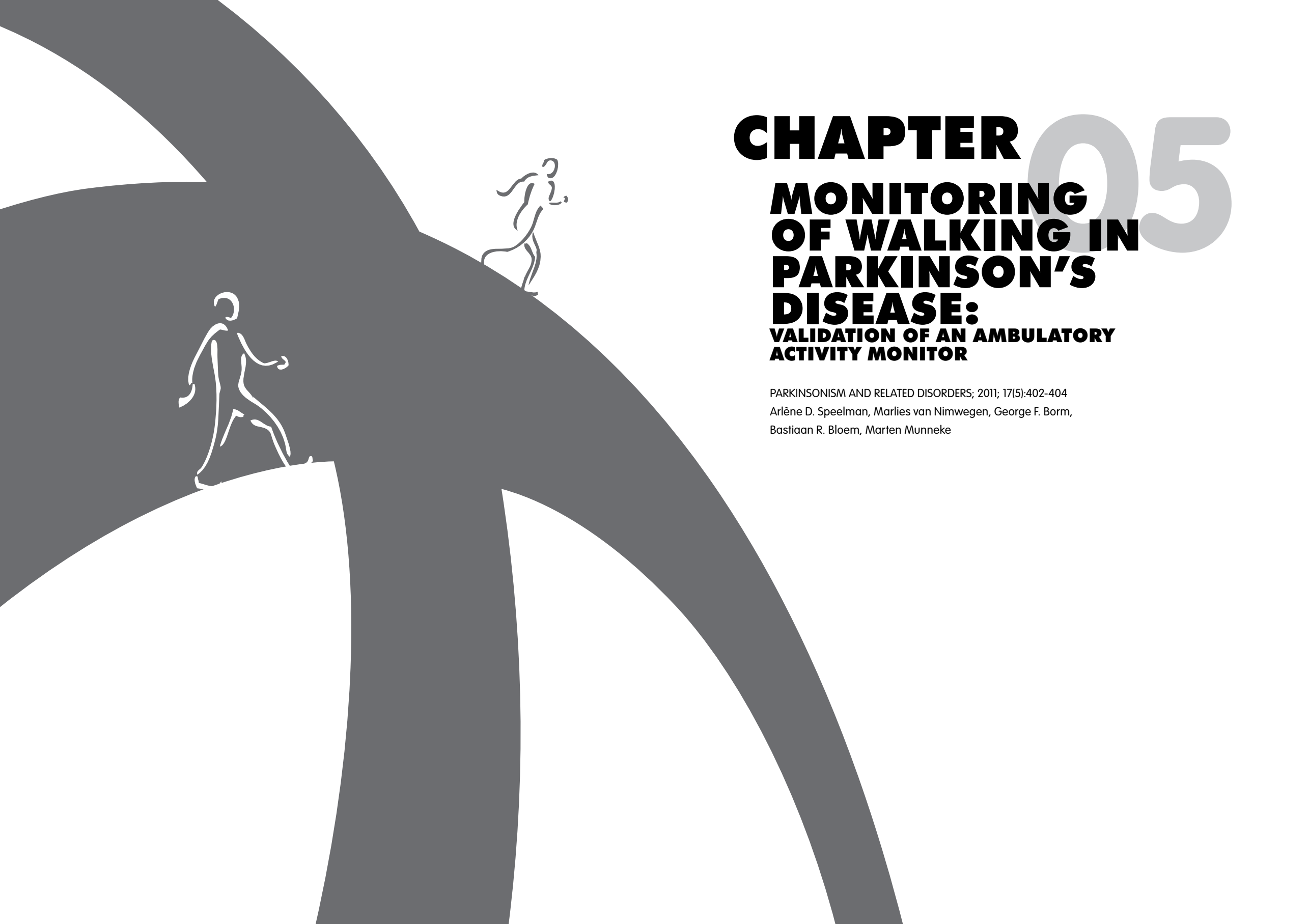
ANTI-OSTEOPOROTIC MEDICATION

Only three studies focused on pharmacological treatment of osteoporosis in PD, all considering bisphosphonates. The role for selective estrogen receptor modulators and strontium ranelate has not been evaluated in patients with PD.

The first study, a 2-year, randomized, double-blind, placebo-controlled trial, studied the effect of risedronate in men with PD (121 patients in both groups). Risedronate (2.5 mg) and ergocalciferol (1000 IU) daily were compared with ergocalciferol (1000 IU) and placebo. BMD increased 2.2% in the risedronate group and decreased 2.9% in the placebo group, while nine patients in the placebo group and three patients in the risedronate group sustained hip fractures. So, risedronate reduced the relative risk of hip fracture by 0.33 (95% CI, 0.09 to 1.20).¹⁸⁸ The same authors reported similar benefits in a study of elderly women with PD allocated to once weekly 17.5mg risedronate and ergocalciferol compared to ergocalciferol and placebo (136 patients in both groups).¹⁸⁹ The third study investigated the effect of alendronate in a 2-year randomized, double-blind, placebo-controlled trial of elderly women with PD (144 patients in both groups). Patients were treated daily with alendronate (5 mg) or placebo, and both groups received ergocalciferol (1000 IU). BMD increased 1.3% in the intervention group and decreased 2.8% in the control group. Alendronate reduces the relative risk of hip fractures (14 vs 4 fractures) by 0.29 (95% CI, 0.10-0.85).¹⁹⁰ A shortcoming of these studies was that BMD measurements were performed at the second metacarpal using computer X-ray densitometry and not DEXA at the hip. Nevertheless, they found a decrease in the number of fractures. Altogether, bisphosphonates seems to be effective for osteoporosis in PD. No drug interaction occur with levodopa or other medications used to treat PD and when a patient experience dysphagia bisphosphonates can be administrated intravenously.

CONCLUSION

Patients with PD have a lower BMD than age-matched controls. This reduced bone mass, in combination with frequent falls, explains the increased fracture risk. The BMD reduction in PD is multifactorial in origin, involving reduced mobility, vitamin D deficiency, hyperhomocysteinemia (caused by levodopa use, or vitamin B12 or folic acid deficiency), malnutrition/low body weight, and decreased muscle strength. All these factors are common in PD and act synergistically (figure 4.2). It is essential to monitor these factors in order to assess the risk of osteoporosis and, consequently, reduce fracture risk. Patients with PD are currently not routinely screened for osteoporosis¹⁹¹, yet the high incidence of fractures in these patients, resulting in an increased morbidity and mortality, makes careful management necessary. An extensive risk assessment should be performed, including medication use, level of immobilization, muscle strength, and nutritional status. If a patient has several risk factors, then BMD should be measured with DEXA. If osteoporosis is present, treatment should be started with bisphosphonates and vitamin D supplementation, and an adequate intake of calcium. Osteoporosis in PD has not been extensively studied and further research is needed. Larger and more powerful studies should investigate the pathophysiology of osteoporosis in PD and ways to prevent bone loss and reduce the incidence of fractures.

A large, stylized illustration in the background shows two white human figures walking on a dark grey, curved path that resembles a road or a track. The path curves from the bottom left towards the top right. The figures are simple line drawings. The overall design is minimalist and modern.

CHAPTER

05

MONITORING OF WALKING IN PARKINSON'S DISEASE:

VALIDATION OF AN AMBULATORY ACTIVITY MONITOR

PARKINSONISM AND RELATED DISORDERS; 2011; 17(5):402-404

Arlène D. Speelman, Marlies van Nimwegen, George F. Borm,
Bastiaan R. Bloem, Marten Munneke

INTRODUCTION

Nearly all patients with PD experience gait problems, often already in early disease stages, with clear worsening as the disease progresses. It would be helpful to have a simple and objective tool to quantify gait, both in the laboratory setting and in the patient's own home environment. This could facilitate clinical decision making, or can be used as outcome measure in clinical trials. It is currently possible to provide very detailed assessments in the gait laboratory, for example using motion analysis systems. While accurate, such evaluations are also expensive, and not necessarily reflective of real-life performance. Moreover, the gait laboratory only documents walking impairments, but does not investigate the subject's actual walking behavior.

To address these limitations, ambulatory gait monitors have been introduced to quantify movements of the limbs or trunk during a prolonged time in daily life. In healthy subjects, ambulatory monitors can record spatiotemporal gait parameters such as stride cycles, numbers of left and right steps, step length and walking speed over ground walking.¹⁹³ Later work also concentrated on applying activity monitors in patients with PD.¹⁹⁴⁻¹⁹⁶ However, none of these studies evaluated the ability of activity monitors to estimate walking distances in patients with PD. We therefore evaluated the ability of a simple activity monitor (based on tri-axial accelerometers) to estimate walking distance in PD.

METHODS

We conducted two separate experiments. In Experiment A we evaluated the ability of the activity monitor to estimate short (maximum distance 27 meters) and simple (straight) walking trajectories. In Experiment B we evaluated the ability to quantify a much longer (maximum distance 1097 meters) and more complex 'real life' walking trajectory (walking in the hospital corridors, with curves and path deviations).

SUBJECTS

In Experiment A, we included 28 PD patients (Table 5.1). In Experiment B we included a separate new cohort of 23 PD patients (Table 5.1). All patients were randomly recruited from the Parkinson Centre Nijmegen. Inclusion criteria was idiopathic PD. In experiment A, patients had to be able to walk a distance of 30 meters. In experiment B, patients had to be able to walk a distance of 2000 meters. Exclusion criterion was a relevant gait impairment other than PD. All patients were measured in the 'ON' state. Before the experiment the Unified Parkinson's Disease Rating scale (UPDRS) motor score and Hoehn and Yahr stage were obtained by a neurologist. Height, body weight and leg length were also measured. All subjects gave written informed consent prior to the study, as approved by the local Medical Ethical Committee.

MATERIALS

The activity monitor that was used in this study (DynaPort AM, Mc Roberts BV, The Hague, The Netherlands) is a small (64x62x13) and lightweight (55 g) instrument that measures accelerations of the lower trunk using tri-axial accelerometers. The sample rate is 100 Hz. Data is stored on a SD card. The device is placed in a belt, positioned on the lower back between the posterior superior iliac spines. To study walking distances, the activity monitor was first calibrated by walking two trajectories of 10 meter and two of 20 meter before starting the experiment.

EXPERIMENT A: SHORT AND LINEAR WALKING TRAJECTORY

For this purpose, patients walked at their preferred speed along a marked linear distance in a hallway (ranging between 21 and 27 meters).

EXPERIMENT B: LONG AND MORE COMPLEX 'REAL LIFE' WALKING DISTANCE

For this purpose, we created a walking trajectory through a public building, composed of five segments (figure 5.1A). The length of each segment was measured three times with a measuring wheel. The average served as the reference distance. The total trajectory amounted 1097 meters. Halfway the walk patients were asked if they were able to walk the whole trajectory. If this was not possible, because of exhaustion for instance, the trajectory was shortened to 913 meters. 74% of the patients walked the whole trajectory.

DATA-ANALYSIS

The DynaPort Gait Monitor software (McRoberts, The Hague, The Netherlands) was used for data analysis. Walking distance and step length were estimated based on the amplitude of vertical pelvic displacement and leg length, using a simple inverted pendulum model of walking.¹⁹⁷

STATISTICS

The actually measured walking distance was taken as the gold standard. All analyses were done on the log-transformed data, because the logarithmic transformation removed the skewness. We then used the normal distribution (on the logarithmic transformed data) to calculate the limits of agreement, i.e. the 5th and 95th percentiles of the differences between the methods.

RESULTS

Mean (sd) distance measured with the activity monitor in the subgroups of patients (shortened trajectory and whole trajectory) in experiment B were 1037.6m (sd: 189.3) and 1059.04m (sd: 195.9) (Figure 5.1B). The measured distance of the activity monitor was not significantly different between the subgroups ($p = 0.819$). Analysis of the short and long walking distance did not suggest any relevant systematic errors. We therefore calculated the unadjusted limits of agreement. In case of short walking distances the difference between the results and the gold standard was smaller than 16%. In case of a longer walking distance the limits of agreements were -43 and +41%. The difference between the results and the golden standard did exceed more than 40%. The subjects did not experience interference or inconvenience of the body-fixed instrumentation.

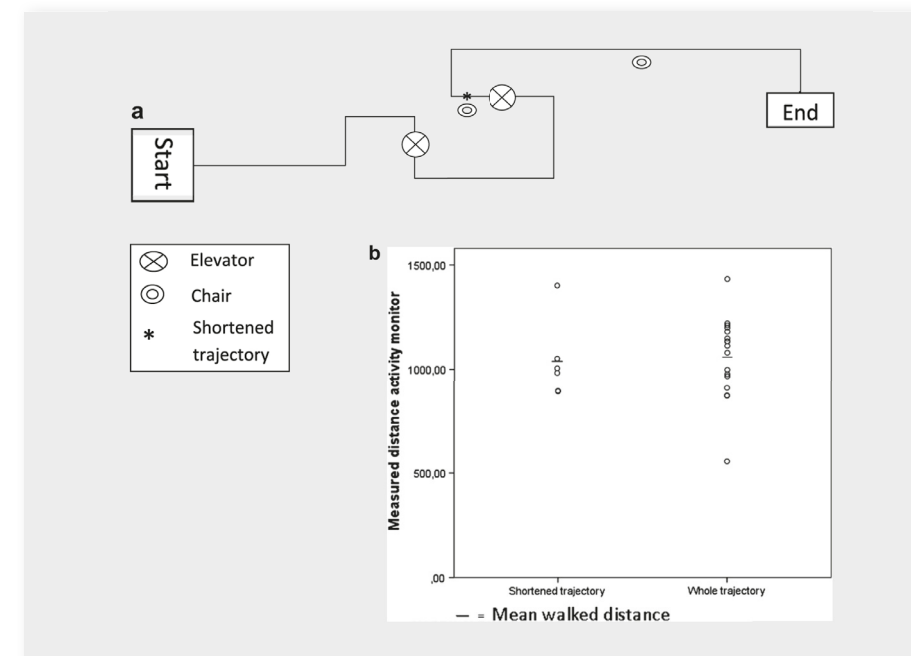
TABLE 5.1
PATIENT CHARACTERISTICS

	Experiment A	Experiment B
N	28	23
Age mean (sd)	65.6 (6.6)	63.8 (9.4)
Gender (male/female)	19/9	17/6
Height (cm)	173 (10.7)	175.1 (9.7)
Body mass (kg)	77 (14.7)	75.8 (12.6)
FOGQ	5.8 (5.7)	6.3 (5.8)
% Freezers	39.3%	34.8%
UPDRS	29.4 (12.5)	27.9 (8.8)
HY 1,5	1	-
HY 2	11	7
HY 2,5	5	4
HY 3	8	6
HY 4	2	-

DISCUSSION

The aim of this study was to evaluate the ability of the Dynaport activity monitor to estimate walking distances in PD. Precision of this activity monitor to estimate short walking distances was good, as demonstrated by adequate limits of agreement. However, the precision to estimate long walking distances was less appropriate, with wide limits of agreement. This means that the device can measure a changed walking distance in evaluative research, but only large changes can be detected or large patient groups are needed. This moderate precision limits the use of this activity monitor for clinical purposes. This activity monitor might be used as a screening tool, to estimate walking distances, but the actual walking distance might be the measured distance plus or minus 40%.

FIGURE 5.1
WALKING TRAJECTORY AND WALKED DISTANCE



Activity monitors are most often used to assess physical activity levels or energy expenditure in elderly subjects. For this purpose activity monitors are reliable and valid.¹⁹³ The use of activity monitors for long-term monitoring of walking distance is still limited. Besides accelerometry, Global Positioning Systems (GPS) seem to be a promising approach. However, there are limitations to the use of GPS, because this requires signals from satellites to estimate position. Interference of the signals, caused by blockages due to buildings, travel public transport, tunnels or local topography, will affect the accuracy of the GPS. Furthermore, there is a limited storage capacity and GPS combined with accelerometry is less feasible because subjects have to wear two systems

ACKNOWLEDGEMENTS

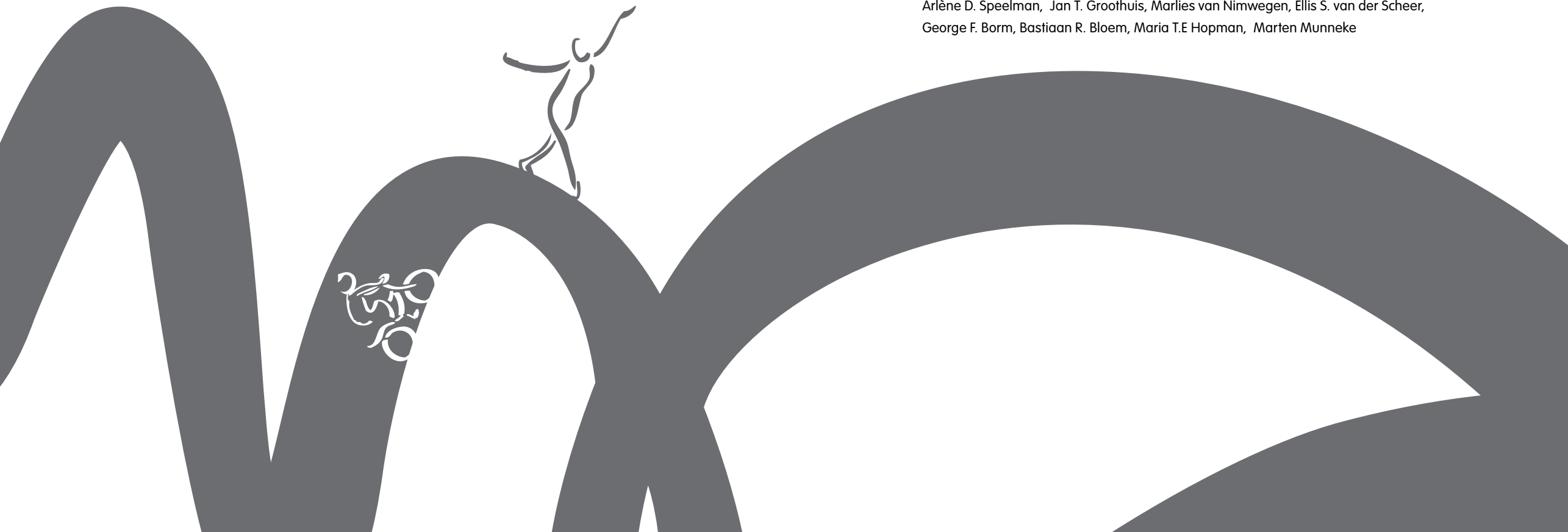
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CHAPTER 06

CARDIOVASCULAR RESPONSES DURING A SUBMAXIMAL EXERCISE TEST IN PATIENTS WITH PARKINSON'S DISEASE

JOURNAL OF PARKINSON'S DISEASE; 2012; 2:241-247

Arlène D. Speelman, Jan T. Groothuis, Marlies van Nimwegen, Ellis S. van der Scheer,
George F. Borm, Bastiaan R. Bloem, Maria T.E Hopman, Marten Munneke



ABSTRACT

BACKGROUND

Patients with PD are physically less active than controls, and autonomic dysfunction may contribute to this sedentary lifestyle. Specifically, an altered cardiovascular response to physical effort may restrict physical activities. Here, the cardiovascular responses to a submaximal exercise test were assessed in PD patients and controls

METHODS

546 sedentary PD patients and 29 sedentary healthy controls performed the Åstrand-Rhyming submaximal cycle exercise test. The average heart rate was used to estimate maximal oxygen consumption ($\text{VO}_{2\text{max}}$). Variables that may affect submaximal activity in PD patients, including disease severity, fatigue, and level of physical activity in daily life, were recorded.

RESULTS

Fewer PD patients (46%) completed the submaximal exercise test successfully than the controls (86%). The estimated $\text{VO}_{2\text{max}}$ of patients with a successful test was 34% lower than the controls ($p < 0.001$). Multivariate regression analyses revealed that higher body weight, lower systolic blood pressure, lower resting heart rate, and lower maximal workload were associated with an increased risk of an inadequate heart rate increase during submaximal exercise ($R^2 = 27\%$). PD patients with a successful submaximal exercise test had lower estimated $\text{VO}_{2\text{max}}$ values than controls.

CONCLUSION

Importantly, half of the PD patients had an inadequate heart rate increase during submaximal exercise, which was likely caused by cardiac sympathetic denervation leading to autonomic dysfunction. PD patients should therefore be screened to identify their limitations in exercise performance. Caution should be applied when prescribing beta blockers, as they might limit physical activities further.

INTRODUCTION

Patients with PD are physically less active than controls.¹⁷ Several possible factors may account for this physically inactive lifestyle. Patients with PD develop a range of motor symptoms, including gait disturbances and balance instability. Furthermore, patients with PD develop several non-motor symptoms such as depression, apathy, and cognitive dysfunction. Taken together, these motor and non-motor symptoms can discourage PD patients from becoming physically active.

Here, we tested the hypothesis that autonomic dysfunction is be an additional contributing

factor of physical inactivity in PD. Autonomic dysfunction occurs in more than 50% of PD patients¹⁹⁸ and can affect cardiovascular responses to physical activity, thereby restricting exercise performance.^{199 200} However, the influence of autonomic dysfunction on exercise in PD has not been investigated extensively. To examine whether PD patients have an altered cardiovascular response to submaximal activity, we studied changes in heart rate and maximal oxygen consumption in sedentary PD patients while performing a standardized submaximal exercise test.

METHODS

PARTICIPANTS

The study population consisted of 586 PD patients participating in the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in PD patients⁸⁷, and 29 age- and gender-matched controls (Table 6.1). Patients were recruited from September 2008 through January 2010, and controls were recruited from January 2011 through June 2011. Eligibility criteria for all participants were as follows: (a) age between 40 and 75 years; and (b) a sedentary lifestyle that was defined as <3 times a week of vigorous intensity physical activity for <60 minutes or <3 times a week of moderate intensity physical activity for <150 minutes.²⁰¹ All PD patients were diagnosed in accordance with the UK Brain Bank Criteria.³ Exclusion criteria for all participants were as follows: (a) inability to complete Dutch questionnaires; (b) severe co-morbidity interfering with daily functions; (c) daily institutionalized care; (d) pulmonary disease; and (e) high risk of cardiovascular complications. For the PD patients, the following additional exclusion criteria were applied: (a) unclear diagnosis (i.e. no gratifying and sustained response to dopaminergic therapy); (b) Mini-Mental State Examination score <24; and (c) deep-brain surgery.

Each subject provided written informed consent prior to the study, which was approved by the local Medical Ethics Committee (CMO Regio Arnhem-Nijmegen).

EXPERIMENTAL PROCEDURES

Physical fitness was assessed using the Åstrand-Rhyming submaximal exercise test on a stationary bicycle.²⁰² The subjects were seated on a model 939E bicycle ergometer (Monark, Vansbro, Sweden). The exercise protocol started after a one-minute warm-up stage at 50-watt resistance. After warming up, the workload was increased during the first three minutes of the test. During the last three minutes, the workload was kept constant in order to achieve a steady-state heart rate. The subjects were asked to maintain a cycling rate of 70 rpm, and the total duration of the test was six minutes. If the heart rate in the fifth and sixth minutes of the test differed by more than five beats per minute, the test was prolonged by one minute in order to achieve a steady-state heart rate. This submaximal exercise test was followed by a cooling-down period of at least three minutes. All patients were asked to take their dopaminergic medication two hours before assessment.

ASSESSMENTS

The level of physical activity was measured using a validated interview-based 7-day recall in the form of the LAPAQ questionnaire.¹¹² Fatigue was measured using the Fatigue Severity scale (FSS).²⁰³ In the PD patients, disease stage was scored according to the modified Hoehn and Ya hr scale (H&Y)¹¹³, and motor function was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS III, motor examination).²⁰⁴ In addition, clinical characteristics such as disease time since diagnosis and daily levodopa equivalent dose were assessed. Blood pressure at rest was measured in the right upper arm using an automatic blood pressure device (Microlife, model BP3AC1-1). During the submaximal exercise test, heart rate was continuously recorded using a Polar Pacer Tester (Polar, Favor, Kempele, Finland). Perceived exertion was recorded at the end of the test using the Borg's 6–20 rating of perceived exertion (RPE) scale in which a score of 6 indicates 'light exertion', and a score of 20 indicates 'extreme exertion'.^{205 206}

DATA ANALYSIS

The submaximal exercise test was considered to be successful if it fulfilled the following criteria: 1) a steady-state heart rate (i.e. no more than a 5-bpm change in heart rate in the last two minutes of the test) and 2) a heart rate >120 bpm in the last two minutes of the test (70–75% of the estimated maximal heart rate²⁰⁷). When the submaximal exercise test met these criteria, physical fitness was then estimated using maximal oxygen consumption ($\text{VO}_{2\text{max}}$), which was estimated from the Åstrand-nomogram using mean steady-state heart rate with corrections for age and gender.²⁰²

STATISTICAL ANALYSIS

Differences in $\text{VO}_{2\text{max}}$ between the PD patients and controls were evaluated using a t-test and Chi-squared test. Univariate logistic regression analysis was used to determine the variables that were significantly associated with achieving a heart rate >120 bpm in the PD patients during the

test and included age, gender, resting heart rate, blood pressure, level of daily physical activity, fatigue, maximal workload, perceived exertion, UPDRS III motor examination, disease duration, and PD-related medication. Logistic multiple stepwise regression analysis was used to determine whether the different variables jointly affected the exercise test in PD patients.

RESULTS

Five hundred and forty-five of the original 586 PD patients and 29 controls performed the submaximal exercise test; 41 PD patients did not perform the submaximal exercise test due to technical problems. Ninety-two (17%) of the patients were excluded from the analyses due to the use of beta blockers (Figure 6.1); none of the controls used beta blockers. The characteristics of the remaining 453 patients and 29 controls are presented in Table 6.1.

Two hundred and forty-one (53%) of the PD patients and four (14%) of the controls had an unsuccessful submaximal exercise test. Of these 241 patients and four controls, 53 (22%) patients and three controls terminated the submaximal exercise test prematurely due to exhaustion, 57 patients (24%) did not reach a steady-state heart rate at the end of the test (i.e. had a >5-beat per minute variance), and 131 (54%) patients and one control reached a steady-state heart rate during the submaximal exercise test but had an inadequate heart rate increase (<120 bpm). This left 212 (46%) patients and 25 (86%) controls with a steady-state heart rate and an adequate heart rate increase during submaximal exercise for inclusion in the analysis (Figure 6.1).

The estimated $\text{VO}_{2\text{max}}$ of the PD patients with a successful test was significantly lower than controls ($p < 0.001$) (Table 6.2). Similar results were obtained when the level of daily physical activity was included in the analysis as a covariate.

Next, the 131 PD patients with an unsuccessful submaximal exercise test due to an inadequate increase in heart rate were compared with the 212 patients with a successful submaximal exercise test (Table 6.3). With the exceptions of H&Y stage and PD medication, all factors were significantly associated with the ability to increase heart rate sufficiently during submaximal exercise. Multiple stepwise regression yielded a model in which higher body weight, lower systolic blood pressure, lower resting heart rate, and lower maximal workload were associated with an increased risk of an inadequate heart rate increase during submaximal exercise. This model explained 27% of the variance. No relationship between the factors disease duration, H&Y stage, UPDRS III motor examination, and PD medication and the ability to increase heart rate during submaximal exercise was found.

TABLE 6.1

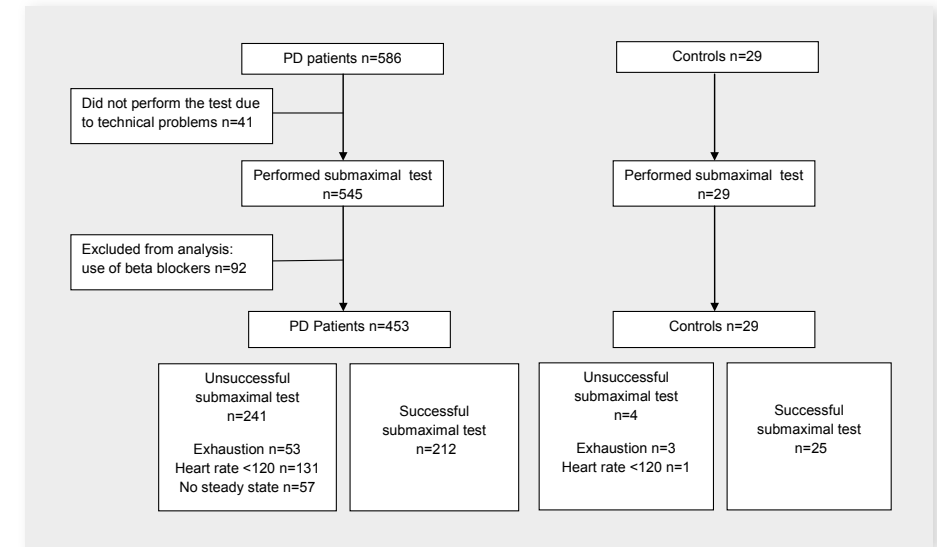
CHARACTERISTICS OF PD PATIENTS AND CONTROLS

Variable	PD patients (N= 453)	Controls (N=29)
Age, years (SD)	64 (7.7)	61.5 (10.8)
Men	66%	69%
Weight, kg (SD)	81 (13.9)	80.1 (10)
Height, cm (SD)	172 (10.1)	171 (8.6)
BMI, kg/m ² (SD)	27.3 (4.1)	27.3 (3.1)
H&Y stage, number of patients (%)		
1	7 (1.5%)	-
1.5	16 (3.5%)	-
2	339 (74.8%)	-
2.5	68 (15%)	-
3	23 (5.1%)	-
UPDRS III (SD)	32.7 (10.2)	-
Disease duration, years (SD)	5.2 (4.5)	-
Level of physical activity (hours/week)		
LAPAQ total (inter-quartile range)	13.2 (8.6 – 20.9)	10.2 (5.2 – 12.9)

Data reflect mean (SD), median (IQ-range) or number (%). PD = Parkinson's disease, BMI = body mass index, UPDRS III = unified Parkinson's disease rating scale part III. LAPAQ = LASA Physical Activity Questionnaire

FIGURE 6.1

OVERVIEW OF THE PARTICIPANTS IN THE PRESENT STUDY

**TABLE 6.2**

PERFORMANCE DURING THE ÅSTRAND-RHYMING SUBMAXIMAL EXERCISE TEST

Variable	PD patients (N=212)	Controls (N=25)	95% CI
Mean heart rate end of test, bpm (SD)	135.8 (12.2)	138.6 (11.8)	-7.8 to 2.3
Maximal workload, W (SD)	88.0 (27.9)	95.6 (29.9)	-19 to 4.5
Perceived exertion (SD)	15.4 (2)	14.1 (1.8)	0.4 to 2.1
VO ₂ max, ml/min/kg (SD)			
Both genders	21.9 (5.4)	33.0(8.5)	-13.5 to -8.7
Men	23.1 (5.1)	35.7 (8.7)	-15.5 to -9.7
Women	20.1 (5.3)	27.5 (4.3)	-11.3 to -3.6

Data reflect mean (SD). 95% CI = Confidence interval, PD = Parkinson's disease, W = Watts, VO₂max = maximal oxygen consumption, BPM = beats per minute

TABLE 6.3

THE GROUPS OF PD PATIENTS WHO DID OR DID NOT REACH A HEART RATE >120 BPM

Variable	PD Patients HR <120 (N= 131)	PD patients HR >120 (N=212)	95% CI
Demographics and disease severity			
Age, years (SD)	66.1 (6.8)	61.8 (7.7)	2.7 to 5.9
Men	73.3%	62.7%	0.044
BMI, kg/m ² (SD)	28.1 (3.9)	26.9 (4.1)	0.3 to 2.0
Height, cm (SD)	173.3 (9.7)	172.6 (10.1)	-1.5 to 2.9
Weight, kg (SD)	84.5 (15.2)	80.1 (12.9)	1.4 to 7.5
UPDRS III (SD)	33.8 (9.5)	31 (10.3)	0.6 to 5.0
Disease duration, years (SD)	5.7 (4.8)	4.7 (4.2)	0.1 to 2.1
Total LED doses (SD)	523.3 (428.5)	436.5 (363.4)	1.3 to 172
Level of physical activity, hours/ week (inter-quartile range)	12.5 (7.9 – 18.5)	14 (9.3 – 21)	-3.7 to 0.7
Fatigue Severity Scale (SD)	44 (1.5)	3.8 (1.6)	0.2 to 0.9
Test variables			
Mean heart rate end of test, bpm (SD)	106.3 (10.1)	135.8 (12.2)	-32 to -27
Maximal workload, W (SD)	78 (24.6)	88 (27.9)	-16.2 to -4.5
Perceived exertion (SD)	15.7 (2.2)	15.4 (2)	-0.2 to 0.8
Resting heart rate, bpm (SD)	70.7 (11.2)	80.8 (13.2)	-12.9 to -7.4
Blood pressure systolic, mmHg	138	143	-8.6 to -0.3
Blood pressure diastolic, mmHg	81	85	-6.6 to -2.0

Data reflect mean (SD), median (IQR-range) or percentage (%). CI = Confidence interval, PD = Parkinson's disease, BMI = Body Mass Index, UPDRS III = Unified Parkinson's Disease Rating Scale part III, bpm = beats per minute, W = watts, HR = heart rate.

DISCUSSION

We found that only 46% of sedentary PD patients adequately increase their heart rate during a submaximal exercise test, whereas nearly all sedentary controls (86%) achieved an adequate increase in heart rate during the same test. Moreover, the PD patients who were unable to successfully complete the test (i.e. reached a steady-state heart rate but had an inadequate heart rate increase) had a lower resting heart rate and lower systolic blood pressure. Finally, we found that PD patients who successfully completed the submaximal exercise test had a lower estimated $\text{VO}_{2\text{max}}$ than the controls.

This is the first study to demonstrate altered cardiovascular responses during submaximal exercise in sedentary PD patients with respect to healthy controls. An abnormal cardiovascular response to maximal exercise has been demonstrated previously^{63 199 208-211}; however, these studies focused on heart rate during maximal effort and did not find an altered cardiovascular response during submaximal exercise. For example, Werner et al.¹⁹⁹ reported that during higher exercise intensities, half of the PD patients failed to reach 85% of the age predicted target heart rate, but they found no differences between PD patients and controls during submaximal exercise. In addition, Reuter et al.²¹⁰ measured cardiovascular function using a cycle exercise test with a ramp protocol and found a less-responsive systolic blood pressure during the exercise test and a slightly elevated heart rate in the PD patients during low-intensity exercise.²¹⁰ Katzel et al. studied 63 PD patients and found that only 11% of patients achieved a true $\text{VO}_{2\text{max}}$ on a maximal-effort treadmill test.²¹¹ Most studies included only a relatively small number of PD patients, thereby limiting the robustness (i.e. statistical power) of their results. Because we included a much larger number of PD patients (n=586), we were able to detect a significant difference in cardiovascular responses compared to healthy controls.

The inadequate increase in heart rate during exercise that was observed in this study may have been caused by dopaminergic therapy. Dopaminergic therapy can aggravate the impairment of the automatic control of the blood pressure and heart rate in PD patients.²¹² Another explanation of the inadequate increase in heart rate may be cardiac sympathetic denervation that led to autonomic dysfunction.²¹³⁻²¹⁵ This hypothesis is supported by the lower resting heart rate that was associated with an unsuccessful submaximal exercise test. Goldstein et al. reported that many PD patients have cardiac sympathetic denervation²¹⁵, which can be present in the presymptomatic phase of PD^{214 216} and does not seem to either be restricted to severe cases or occur as a late consequence of the disease.²¹⁵ An early onset of cardiac sympathetic denervation might explain why the cardiovascular response to the submaximal exercise test was not related to disease severity in our study. The lower heart rate and blood pressure at rest that were observed in our study may be an additional indication of symptomatic denervation of the heart.

Cardiac sympathetic denervation causes decreased heart rate and cardiac contractility,²¹³ which cause decreased cardiac output during exercise and are associated with shortness of breath²¹⁷ and fatigue.²¹⁸ This can restrict PD patients during the daily activities and might force them to lead a more sedentary lifestyle.¹⁷ Therefore, in an early disease stage, PD patients should be screened for the exercise behavior, and they should be tested to determine whether any limitations in their exercise performance are secondary to cardiac sympathetic denervation and/or autonomic dysfunction, which could have therapeutic consequences, as PD patients with autonomic dysfunction can still exercise but need to be cognizant of their cardiovascular limitations. Importantly, beta blockers should be prescribed with caution in these patients, as beta blockers can aggravate the inadequate cardiac response to exercise.

Even the PD patients with a successful submaximal exercise test had some autonomic abnormalities, as we found a 31% lower estimated $\text{VO}_{2\text{max}}$ in these patients than in the controls. The estimated $\text{VO}_{2\text{max}}$ values that were observed in our study are similar to the values obtained in previous studies of PD patients. However, in these previous studies, no significant difference was found between PD patients and controls.^{63,209} Our study of a much larger cohort of PD patients and controls compared to previous studies likely underlies these differences.

Changes in the body composition of PD patients may explain the low cardiovascular fitness of PD patients. A stooped posture or stiff chest wall muscles can potentially influence aerobic capacity. This was found in a study of patients with ankylosing spondylitis that showed an association between musculoskeletal limitations and restrictive respiratory impairment and significantly impaired pulmonary function compared to controls.²¹⁹

The estimated $\text{VO}_{2\text{max}}$ in our PD patients (22 ml/kg/min) indicates poor cardiovascular fitness, which may have a considerable influence on daily functions. Using an exercise program, it should be possible for PD patients to improve their $\text{VO}_{2\text{max}}$. Indeed, several studies have shown that an exercise program can both improve physical fitness and ameliorate disease-related symptoms such as sleep disturbances, cognitive dysfunction, and functional motor performance.²²⁰

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CHAPTER 07

PROMOTION OF PHYSICAL ACTIVITY AND FITNESS IN SEDENTARY PATIENTS WITH PARKINSON'S DISEASE, A RANDOMIZED CONTROLLED TRIAL

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Arlène D. Speelman[§], Marlies van Nimwegen[§], Sebastiaan Overeem, Bart P. van de Warrenburg, Katrijn Smulders, Manon L. Dontje, George F. Borm, Frank J.G. Backx, Bastiaan R. Bloem, and Marten Munneke

on behalf of the ParkFit Study Group

[§] These authors contributed equally to this work



ABSTRACT

BACKGROUND

The sedentary lifestyle of patients with PD adversely affects their health. Reversing this lifestyle is difficult because of combined physical and cognitive handicaps that are intrinsic to PD. Here, we evaluate whether a multifaceted behavioral change program increases physical activities in PD.

METHODS

We performed a multicenter, randomised controlled trial to increase physical activity levels in sedentary PD patients. Patients were randomly assigned to the ParkFit program or a matched general physiotherapy intervention. ParkFit is a multifaceted behavioral change program, designed specifically to achieve an enduring increase in the level of physical activity program (coaches using motivational strategies; ambulatory feedback). Primary endpoint was the level of physical activity, measured every six months using a standardized 7-day recall the LAPAQ questionnaire. Secondary endpoints included two other measures of physical activity (activity diary; and ambulatory activity monitor), quality of life (PDQ-39), and fitness (6-minute walk test).

RESULTS

586 sedentary patients with idiopathic PD between 40 and 75 years with mild to moderate disease severity (Hoehn and Yahr stage ≤ 3) were randomized; 540 patients (92.3%) completed the primary outcome. During follow-up, overall time spent on physical activities was comparable between both groups (adjusted group difference 7%; 95% CI -3 to 17%; $p=0.19$). Analyses of three secondary outcomes indicated increased physical activity in ParkFit patients, as suggested by the activity diary (difference 30%; $p<0.001$), the activity monitor (difference 12%; $p<0.001$), and 6-minute walk test (difference 4.8 meters; $p=0.05$). PDQ-39 did not differ between ParkFit and controls (difference -0.9 points; $p=0.14$). The number of fallers was comparable between ParkFit (62%) and controls (67%).

CONCLUSION

The ParkFit behavioral change program did not increase overall physical activity, as measured with the LAPAQ. The analysis of the secondary endpoints justifies further work into the possible merits of behavioral change programs to increase physical activities in daily life.

INTRODUCTION

PD is a common neurodegenerative disease, characterized by motor symptoms²²¹ and a wide variety of non-motor symptoms like depression or apathy.²²² Despite optimal medical treatment, PD remains a progressive disease that negatively affects quality of life. Therefore, allied health interventions are increasingly deployed to treat both the motor and non-motor symptoms of PD. The evidence to support the merits of these interventions is growing, and treatment guidelines (based partially on evidence, and partially on practical clinical experience) for several allied health-care interventions have been developed.^{10 11 89} In recent years, a number of physiotherapy programs have been tested in patients with PD.^{99 100 223-225} Reviews and meta-analyses generally found evidence to support 'exercise' as being beneficial with regard to physical functioning, strength, balance and gait speed.^{25 68 226-228} However, the physiotherapy programs as

tested in these studies were apparently insufficient to achieve an active lifestyle. Indeed, because of their combined physical limitations and mental changes, many PD patients lead a sedentary lifestyle.²²⁹ Reversing this lifestyle could have generic health benefits, including increased survival.^{19 230 231} Promoting physical activity may also improve specific symptoms of PD, such as insomnia, depression or constipation.²³² Furthermore, rodent work suggests that physical activity might counter neurodegeneration in experimental parkinsonism.^{101 102} An individually tailored, disease-specific training program is needed to improve physical activity in PD.²³³ We developed such an intervention (the ParkFit program⁸⁷) based on models of behavioural change^{98 234} and containing established behavioural change techniques.²³⁵⁻²³⁷ To evaluate this program, we designed a randomized controlled trial (RCT) comparing ParkFit with a matched control intervention.⁸⁷

METHODS

The ParkFit trial is a multicenter RCT to increase physical activity levels over the course of two years in sedentary PD patients. The study design has been detailed elsewhere.⁸⁷

STUDY PARTICIPANTS

Recruitment ran from September 2008 to January 2010. Patients treated in 32 community hospitals were invited to participate. Eligibility criteria were: (a) PD according to UK Brain Bank Criteria²²¹; (b) age 40–75 years; (c) sedentary lifestyle, defined as: participation in vigorous-intensity physical activity <3 times a week, and for <60 minutes in total per week; or participation in moderate-intensity physical activity <3 times a week, and for <150 minutes in total per week²³³; and (d) Hoehn and Yahr stage ≤ 3 . Exclusion criteria were: (a) MMSE <24 ; (b) unable to complete Dutch questionnaires; (c) co-morbidity that interfered with daily functioning; (d) daily institutionalized care; and (e) previous deep brain surgery. The protocol was approved by the local ethics committee. Informed consent was obtained before the first assessment.

STUDY OUTCOMES

Baseline characteristics

Disease stage was scored according to the modified Hoehn and Yahr scale. Motor function was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS part III, motor examination).

Primary endpoint

Several amendments were made in the initial phase of the study, at a time when recruitment was underway for only two months. We here report our final selection of endpoints, as specified on ClinicalTrials.gov, in the adapted final research protocol that was accepted by the Ethical Committee (CMO) Arnhem Nijmegen and in a recent design article.⁸⁷

Primary endpoint was the LAPAQ Questionnaire, a validated interview-based 7-day recall of physical activities. The LAPAQ was highly correlated with a 7-day diary ($r = 0.68$, $P < .001$), and moderately with a pedometer ($r = 0.56$, $P < .001$).²³⁸ LAPAQ asks patients about their daily amount of specific activities, allowing for calculation of total time spent on physical activities (expressed in hours per week). LAPAQ covers the frequency and duration of the net sum of the following activities: walking outdoors, cycling, gardening, light and heavy household activities and sport activities.²³⁸ Consequently, higher scores on the LAPAQ (in hours per week) indicated more time spent on physical activity. LAPAQ was measured at baseline, and after 6, 12, 18 and 24 months. At baseline, and after 12 and 24 months, LAPAQ was completed during face-to-face interviews; after six and 18 months, LAPAQ was completed by telephone. We assumed that patients would increase their level of physical activity during the first months of the intervention, and would then maintain this level. Therefore, the main endpoint was the average of the level of physical activity during the entire follow-up period (i.e. average of 6, 12, 18 and 24 months). This approach has several advantages. First, it provides a global assessment of the results of the intervention. Second, it provides maximal power. As the number of assessments that is taken into account increases, so does the power. We did not compare all individual time points (at 6, 12, 18 and 24 months) separately, because this leads to multiplicity.

Secondary endpoints

We defined four secondary endpoints:⁸⁷ (1) physical fitness, as measured with the 6-minute walk test²³⁹ at 12 and 24 months (i.e. average of all measurements); (2) quality of life, as measured with the PDQ-39²⁴⁰ at 6, 12, 18 and 24 months (i.e. average of all measurements); (3) physical activity, measured subjectively every six months with a 7-day activity diary (i.e. average of all measurements);²⁴¹ and (4) physical activity, measured objectively every six months with an ambulatory activity monitor (i.e. average of all measurements).²⁴²

The diary detailed the frequency and total duration (hours/week) spent on five specific activities: walking outdoors for >10 contiguous minutes; moderate-intensity cycling for >10 contiguous

minutes; high-intensity cycling for >10 contiguous minutes; sport activities; and other strenuous activities (e.g. cutting wood). The activity monitor (triaxial accelerometer)²⁴² was worn as a necklace, on the belt or in the pocket. Data were collected during waking hours for 14 days and were stored minute by minute for each axis; output was expressed in kilocalories/minute. Only completely observed days were included in the analysis.²⁴³ The monitor was additionally used as feedback-tool by patients allocated to the ParkFit program, using light-emitting diodes that reflected the amount of actually delivered daily physical activity. Control patients received no feedback of their activity monitor.

Safety and falls

Safety was assessed by spontaneous reports of adverse events. Serious adverse events were classified as events that caused death, were life-threatening, or necessitated hospital admission. Falls were monitored monthly with an automated telephone system.²⁴⁴ Information about adverse events was additionally collected at each physical assessment.

INTERVENTION

After baseline assessment, patients were randomly assigned to either the ParkFit program or a matched physiotherapy intervention aimed at safety of movements. The investigators logged in on a protected website and entered region, Hoehn & Yahr stage, age, gender and current physical activity level of the patients. Based on a minimization algorithm with these factors, the treatment was allocated and registered. Before inclusion, patients were informed that the trial compared two potentially beneficial interventions. We used 'active' names for both interventions ('ParkFit' and 'ParkSafe' program). To ensure blinding, patients were examined by trained assessors who were unaware of group allocation. Patients were instructed not to discuss the nature of their physiotherapy with the assessors.

Both interventions were delivered solely by experienced physiotherapists in the Dutch ParkinsonNet.²⁴⁵ In total, 154 physiotherapists were trained to deliver both interventions. This ascertained that differences in personality or style of the physiotherapists could not bias the results. All patients were offered an equal maximum number of treatment sessions (35/year). The full study protocol has been detailed elsewhere.⁸⁷

ParkFit program

The ParkFit program was designed specifically to achieve a sustained increase in physical activity levels, based on theories and models of behavioural change^{98 234} and on effective behavioural change techniques.²³⁵⁻²³⁷ Important elements were: (a) activity coaches who guided each patient towards a more active lifestyle during monthly personal coaching sessions; (b) educational brochure about the benefits of physical activity and suitable activities for PD patients; (c)

identifying and overcoming any perceived barriers to engage in physical activity; (d) systematic goal setting, using a health contract and logbook; (e) stimulation to participate in group exercises; and (f) ambulatory monitor with automated feedback reflecting actually delivered physical activities.²⁴² Ambulatory monitor data were uploaded to a personalized website, where both the patient and coach could monitor progress.

The ParkFit program also included regular physiotherapy sessions. Based on individual disabilities, the therapist and patient jointly formulated individually tailored treatment aims, according to the evidence-based guideline of physiotherapy for PD.⁸⁹

Control intervention

The control intervention consisted of a general physiotherapy program aimed at safety of movements, according to the evidence-based guideline.⁸⁹ Patients received an identical brochure as ParkFit patients, but now with information about the benefits of physiotherapy and safety of movements. Patients were offered a maximum number of treatment sessions, similar to the ParkFit program. An active lifestyle was not explicitly stimulated. Treatment aims were jointly formulated by therapist and patient, based on perceived individual disabilities.

STATISTICAL ANALYSIS

Main endpoint was the physical activity level during the entire follow-up (6, 12, 18 and 24 months). Because the physical activity level was skewed, medians and interquartile ranges were presented, and analyses were performed after logarithmic transformation. Differences between both interventions were evaluated using a linear mixed model with random nested factors 'patient' and 'exercise group'. Region, Hoehn & Yahr stage, age, gender and current physical activity level of the patients were included as covariables. Results were analyzed according to a modified intention-to-treat principle, whereby only patients that had no follow-up measurements at all were excluded.

Sample size calculation

Based on the following power considerations, we aimed to include a total of 700 patients. In a small observational study on physical activity in PD, patients scored 45% less on the LAPAQ compared to controls (unpublished data). The coefficient of variation was 110%. Based on a difference of 20% in hours per week (with coefficient of variation of 110%) between both treatment arms, the mixed model analysis will have at least 80% power (when the correlation between baseline and follow-up measurements is at least 0.50, and when the correlation between the various follow-up measurements is at most 0.75). The decision to define a 20% increase based on the LAPAQ activity as a clinically relevant difference was a pragmatic choice, because there were no earlier intervention studies that aimed to change activity behavior in PD patients. Moreover, prior behavioural change studies in other diseases (e.g. heart failure, diabetes and

COPD) did not include the LAPAQ as an endpoint. In an earlier study by our group²²⁹, we found that PD patients were 29% less active compared to controls (as measured with the LAPAQ): patients spent 12.9 hours per week on physical activity, while controls spent more than 17.5 hours. We deemed an increase in physical activity among PD patients of more than four hours unrealistic, and reasoned that an increase of two hours per week (i.e. an increase of about 20%) would be feasible. We also considered a 2-hour increase in physical activity to be clinically relevant, for the following reasons. A dose-response relation exists between physical activity and cardiovascular disease or premature mortality.²⁴⁶ Significant risk reductions have been observed with 45-150 minutes/week of brisk walking.²⁴⁷ Additionally, women who walked or exercised vigorously for at least 2.5 hours/week had a 30% lower risk of coronary heart disease.²⁴⁷ Conversely, the risk of cardiovascular disease was higher among women who spent >12 hours/day lying down or sleeping.²⁴⁷ This suggests that a 2-hour increase in physical activities might help to prevent cardiovascular disease. The power is based on two sided 95% confidence intervals. We assumed that the clustering due to the fact that the intervention was carried out in training groups of approximately eight patients leads to an ICC of 0.1. Based on a previous trial of physical therapy in PD,²⁴⁵ we expected a drop-out rate of 10%.

RESULTS

BASELINE CHARACTERISTICS

586 patients were included (Figure 7.1). 299 patients were randomly assigned to the ParkFit program, and 287 to the control intervention. Both groups had comparable demographic and disease characteristics, although ParkFit patients tended to be less active in daily life (i.e. less time spent on physical activity in hours per week, based on LAPAQ) than controls (Table 7.1).

LOST TO FOLLOW-UP

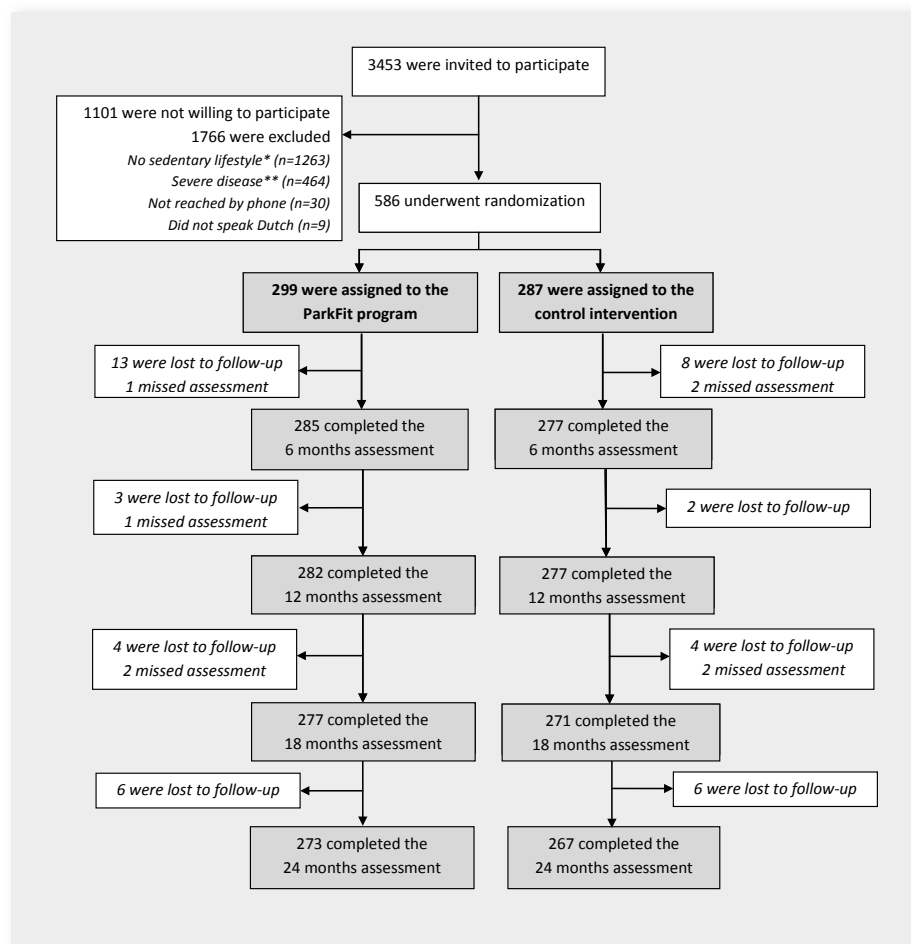
540 of the 586 participants (92.3%) completed the LAPAQ after 24 months. The proportion of patients lost to follow-up was comparable for ParkFit (8.7%) and controls (6.7%). Patients lost to follow-up were similar to those who completed the assessments, except for a higher age.

COMPLIANCE

75 of the 586 participants (12.7%) did not complete the two-year intervention (ParkFit n=44, controls n=31). Main reasons were refusal to change from a regular physiotherapist to a ParkinsonNet physiotherapist, too much burden, or dissatisfaction with the intervention. Reasons for drop-out were similar between both groups. The mean number of annual individual visits to the physiotherapist did not differ between ParkFit (13.6) and controls (13.0). Patients in both groups were satisfied with the intervention and would recommend the intervention to others (73% versus 71%).

FIGURE 7.1

SCREENING, RANDOMIZATION, AND COMPLETION OF THE PRIMARY OUTCOME MEASURE



* No sedentary lifestyle = >3 times a week vigorous-intensity physical activity > 60 minutes; or >3 times a week moderate-intensity physical activity > 150 minutes; ** Severe disease = H&Y > III; MMSE < 24; severe co-morbidity interfering with daily functioning; use of daily care in an institution; or deep brain stimulation

TABLE 7.1

BASELINE CHARACTERISTICS

	ParkFit (n = 299)	Controls (n = 287)
Demographics & Clinical Characteristics		
Age	65.1 (7.9)	65.9 (7.2)
Men	194 (65%)	188 (65%)
BMI	27.4 (4.5)	27.6 (4.0)
Disease duration (years)	5.0 (4.5)	5.5 (4.6)
MMSE	28.1 (1.7)	28.1 (1.7)
Modified Hoehn and Yahr		
1	7 (2.3%)	4 (1.4%)
1.5	7 (2.3%)	10 (3.5%)
2	221 (73.9%)	223 (77.7%)
2.5	48 (16.1%)	36 (12.5%)
3	16 (5.4%)	14 (4.9%)
UPDRS III	33.1 (11.3)	32.3 (9.5)
Daily levodopa equivalent dose (mg)	458 (362)	499 (414)
Level of physical activity		
LAPAQ (hours per week)	12.8 (8.3 - 20.3)	13.8 (8.3 - 23.9)

Data reflect mean (SD), median (IQ-range) or number (%). BMI = Body Mass Index (kg/m²). MMSE = mini-mental state examination. UPDRS III = unified Parkinson's disease rating scale part III. LAPAQ = LASA Physical Activity Questionnaire.

TABLE 7.2

EFFECT OF THE INTERVENTION (IN HOURS PER WEEK) ON THE LEVEL OF PHYSICAL ACTIVITY MEASURED WITH THE LASA PHYSICAL ACTIVITY QUESTIONNAIRE (LAPAQ).

LAPAQ total (primary analysis)	N	ParkFit	N	Controls	Estimated difference (CI)*	p
Baseline	299	12.8 (8.3-20.3)	287	13.8 (8.3-23.9)		
6 months	285	13.2 (9.2-20.5)	277	14.2 (8.5-22.0)		
12 months	281	12.5 (7.2-21.1)	277	12.4 (7.3-17.9)		
18 months	277	12.3 (7.0-19.0)	271	12.3 (6.8-19.1)		
24 months	273	12.5 (6.3-18.4)	267	12.0 (7.0-18.3)		
Estimated difference (CI)*					7% (-3% to 17%)	0.19

Data reflect median (IQR-range); * estimated relative difference, based on mixed model analysis.

ENDPOINTS

Primary endpoint

Compared to baseline, overall time spent in physical activities was comparable between both groups (adjusted group difference 7%; 95% confidence interval (CI) -3 to 17%; $p=0.19$) (Table 7.2).

Secondary endpoints

Both the activity diary and the activity monitor data suggested increased levels of physical activity in ParkFit patients (Table 7.3). Additionally, ParkFit patients increased their physical fitness compared to controls (4.8 meters; 95% CI 0.1 to 9.6; $p=0.05$) (Table 7.3). Quality of life did not differ between the groups (-0.9 points; 95% CI -2.1 to 0.3; $p=0.14$).

Safety and falls

Eight patients died during follow-up because of cardiovascular problems, cancer or medical complications (ParkFit $n=5$, controls $n=3$). These deaths were unrelated to exercise sessions. Controls reported eight hip fractures, ParkFit patients two. Frequency and severity of all other adverse events were similar in both groups: ParkFit $n=221$, controls $n=242$. The number of patients with one or more falls was comparable in both groups: 184 (62%) in ParkFit and 191 (67%) in controls.

TABLE 7.3

EFFECT OF THE INTERVENTION ON THE SECONDARY OUTCOME MEASURE

	N	ParkFit	N	Controls	Estimated difference (CI)*	p
Activity Diary						
Baseline (hrs per week)	297	5.5 (3.1-10.3)	282	6.3 (3.3-10.5)		
Median 6 to 24 months	276	7.6 (4.7-12.4)	276	6.9 (4.2-10.8)		
Mean change	275	1.3	273	0.5	30% (17% to 45%)	<0.001
Activity Monitor						
Baseline (kcal per day)	273	453 (368-618)	269	462 (346-604)		
Median 6 to 24 months	269	504 (390-667)	269	440 (355-582)		
Mean change	254	38.7	258	-14.2	12% (7% to 16%)	<0.001
Quality of Life (PDQ-39)						
Baseline	297	26.0 (13.7)	286	26.2 (13.1)		
Mean 6 to 24 months	278	26.4 (13.7)	277	27.7 (12.7)		
Mean change	278	0.1	276	1.7	-0.9 (-2.1 to 0.3)	0.14
Physical fitness (6MWT)						
Baseline (distance in m)	298	391.6 (87.5)	283	392.9 (84.5)		
Mean 12 and 24 months	256	404 (95.1)	256	394.4 (86.5)		
Mean change	255	8.4	253	-1.6	4.8 (0.1 to 9.6)	0.05

Data reflect mean (SD) or median (IQR-range); * estimated (relative) difference, based on analysis of covariance; PDQ-39 = Parkinson's Disease Questionnaire. 6MWT = 6-minute walk test.

DISCUSSION

This RCT shows that a multifaceted behavioural change program does not promote overall physical activities in sedentary PD patients, as measured with the primary outcome (LAPAQ). Two of our secondary outcomes focused on other measures of physical activity, and did suggest improvements for patients allocated to the ParkFit program. This was demonstrated both subjectively (with activity diaries) and objectively (with an ambulatory activity monitor). Moreover, physical fitness (an indirect reflection of greater physical activity) increased in ParkFit patients. Quality of life did not differ between both study arms. The ParkFit group did not experience more falls.

The ParkFit study is therefore a negative trial, showing no difference for the primary outcome (LAPAQ questionnaire) between both study arms. We selected the LAPAQ as primary outcome because it closely reflected the goals of the ParkFit intervention, namely promotion of physical activities. We regarded an actual increase in physical activity levels as a necessary intermediate and prerequisite to eventually obtain health benefits, including improvements in quality of life. The LAPAQ questionnaire is a validated instrument to measure habitual physical activity in large populations.^{238 248} LAPAQ covers a wide range of daily life activities, and we previously demonstrated that PD patients are 29% less active compared to controls, as measured with the LAPAQ.²²⁹ Our study was powered to detect a 20% increase based on the LAPAQ, which would equate to an increase in physical activities of two hours per week. The ParkFit program did not achieve this, suggesting that more robust interventions are needed to promote physical activities in daily life.

Our choice for the control intervention might have obscured greater differences on the LAPAQ between ParkFit patients and controls. We chose to refer patients in the control arm to a physiotherapist who aimed to improve the safety of movements, but without emphasizing the volume of physical activities. This approach helped to maintain blinding of patients with respect to treatment allocation. An additional reason for having a physiotherapy program as control intervention was that abstaining control patients from physiotherapy for two years was considered unethical, in light of growing evidence for the effectiveness of specific physiotherapy interventions.^{68 226-228} Furthermore, the ParkFit study took place in the 'real world', and physiotherapy in PD is 'usual care', not only in the Netherlands (where at least 60% of PD patients receives physiotherapy annually)¹¹ but also in the United Kingdom.²⁴⁹

Although no effect was found on the primary outcome, two of our secondary outcomes did pick up an increase in physical activities, as measured both subjectively (activity diary) and objectively (activity monitors). Based on the diary, ParkFit patients spent almost 1.5 hour per week extra on physical activity, compared to baseline. This differed significantly from controls, who increased their level of physical activity by 30 minutes compared to baseline. This amount of increase in physical activity, as observed with the diary, is comparable with findings in elderly populations and patients with other chronic conditions.¹⁵⁸⁻¹⁶¹ For example, behavioral counseling for elderly in primary care yielded a one-hour increase in moderate-intensity physical activity.¹⁵⁸ In addition, pedometer-based counseling programs increased total physical activity of cardiac patients by almost 1.5 hour/week.^{159 160} Both the LAPAQ and the diary are subjective instruments, but only the diary showed increased activity levels. One possible explanation for this discrepancy is the fact that the diary merely includes strenuous activities, while the LAPAQ questionnaire reflects the net sum of all physical activities (including household activities). Therefore, we cannot exclude that a possible increase in (strenuous) outdoor and sport activities for ParkFit patients was offset by a concurrent decrease in household activities. The LAPAQ cannot capture such differential effects

on specific physical activities as it merely measures the net sum of all physical activities. We therefore regard our decision to select overall physical activity as primary outcome as a shortcoming in the study design, and this aspect should be addressed in future research in this area.

Objective assessment of physical activity using a tri-axial accelerometer showed an increase in physical activities for ParkFit patients, with a 12% increase in time spent to physical activity after 24 months. Generally, accelerometers underestimate total energy expenditure, because some activities are difficult to detect. This includes upper body movements, specific activities such as cycling, and relatively static movements such as gardening or strength training.⁶⁸ On the other hand, accelerometers as used in our study can reliably measure activities such as indoor and outdoor walking.^{88 128} The accelerometers thus measured a different aspect of physical activity as compared to the LAPAQ, and this could explain the difference in outcome with the LAPAQ. Compliance with use of the accelerometers was good, suggesting it is a feasible surrogate outcome in future studies. The two remaining secondary outcomes aimed at finding possible health benefits. Physical fitness showed a small but significant difference in favor of ParkFit, but quality of life did not differ between the ParkFit and control intervention. The ParkFit intervention had no major adverse effects. We were concerned about possibly increased fall rates, because the amount of physical activity is associated with a greater risk of falling.¹⁶² However, the ParkFit program was not associated with more falls or injuries. In fact, controls reported eight hip fractures, while ParkFit patients reported only two. However, these numbers are very small, and this finding is coincidental as we did not include hip fractures as primary or secondary outcome. Therefore, further research should investigate whether this difference in hip fractures is related to the intervention. Another concern included cardiovascular complications, due to more strenuous activities. All participants received a sports health assessment prior to participation. We observed two cardiovascular deaths in the ParkFit group, but these were unrelated to exercise. Other adverse effects were comparable between both groups. Taken together, this suggest that ParkFit was a safe intervention, but that the program needs to be adjusted to achieve more substantial increases in physical activity that translate into tangible health improvements.

Our experience with this ParkFit study was a lesson in trial design in this newly emerging field. Although the primary outcome was negative, we have shown the possibility of an exercise based trial in disabled people. Several features set the ParkFit study apart compared to previous exercise studies: the prolonged follow-up, showing that patients in both arms were able to comply with the intervention for two years; the careful matching of treatment intensity between both study arms; the large sample size, making the ParkFit trial by far the largest study on physical activity in PD and other chronic diseases;^{68 232 251 252} and the excellent follow-up rate. The feasibility of the study was supported by the ParkinsonNet infrastructure, a nationwide network of allied health professionals who are specialized in PD.²⁵⁶ A generic challenge for trials aiming to

evaluate the merits of allied health treatment is the lack of expertise among therapists who deliver the trial intervention, creating undesirable variability and insufficient contrast with the control arm. Having expert therapists within ParkinsonNet greatly facilitates the delivery of a relatively uniform intervention according to treatment guidelines.^{245 257} As discussed above, our study also highlights the challenges of selecting the appropriate outcomes for a complex intervention such as a behavioural change program. Physical activity is a complex behavior: it includes sports as well as non-sports activities, and it can be characterized by purpose (occupational or leisure), type (cycling, fitness or soccer), intensity (light, moderate or vigorous) and duration. Further research should focus on comprehensive, valid and reliable instruments to accurately measure all these aspects of physical activity behavior. This is a specific challenge in patients with chronic diseases as they perform more light and moderate activities that are easily overestimated when using questionnaires, and which are difficult to detect with activity monitors. Furthermore, our trial revealed new insights in the risk of selection bias. Our participants were on average less sedentary compared with patients who declined to participate.⁸⁷ Hence, those who needed to promote their physical activities most refused participation. It therefore remains unclear whether the effects found here can be generalized to more sedentary PD patients. We can neither extend our findings to patients with severe apathy, severe cognitive impairment or depression, because these were excluded. Finally, the ParkFit program was a multifaceted intervention, with coaches using behavioural change techniques, ambulatory feedback devices, and peer pressure from group exercises. Future work should decide which of these components is most effective, and if any component is also effective when used alone.

We conclude that ParkFit, a multifaceted behavioural change program, does not change the overall volume of physical activities in older, sedentary PD patients. However, analysis of the secondary outcomes did suggest greater participation in specific elements of physical activity, and demonstrated an improved fitness among ParkFit patients. These results for the secondary outcomes suggest that it may be worthwhile to replicate a similar behavioural change study, for example with the secondary outcomes as primary parameters. Such a trial may also put more focus on quality of life and cost aspects.

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Members of the ParkFit Study Group:

A. Winogrodzka (Academisch Ziekenhuis Maastricht); J.C.M. Zijlmans (Amphia Ziekenhuis); G.J. Tissingh (Atrium Medisch Centrum); K. Keizer (Catharina-ziekenhuis); H.J.M.M. Lohmann (Deventer Ziekenhuis); R. van Koningsveld (Elkerliek Ziekenhuis); A.J.W. Boon (Erasmus Medisch Centrum); E. van Wensen and F.E. Strijks (Gelre Ziekenhuizen); G.A. van Meer (Groene Hart Ziekenhuis); A. Mosch (HagaZiekenhuis); J.P. ter Bruggen (Jeroen Bosch Ziekenhuis); M.F. Roesdi (Kennemer Gasthuis); E. Berger ('t Lange Land Ziekenhuis and Medisch Centrum Haaglanden); A.G.G.C. Korten (Laurentius Ziekenhuis); M. Westerink (Maasstad Ziekenhuis); M. Aramideh (Medisch Centrum Alkmaar); R. Rundervoort (Medisch Centrum Haaglanden); F.A. Rooyer (Orbis Medisch Centrum); D.J. Kamphuis (Reinier de Graaf Groep); G.J. de Jong (Sint Franciscus Gasthuis); L. van Hooff (Franciscus Ziekenhuis); K. Lemmen (Slingeland Ziekenhuis); Th.J.M. Breuer (St. Anna Ziekenhuis); J.M.J. Krul and P.M. Laboyrie (Tergooiziekenhuizen); F.J.W. Opstelten (VieCuri Medisch Centrum); A.M.G. Sas (Vlietland Ziekenhuis); P.J. Nederveen (Westfriesgasthuis), J. Lion (Ziekenhuis Bernhoven); and C. Jansen (Ziekenhuis Gelderse Vallei).

CHAPTER 08

EVALUATION OF IMPLEMENTATION OF THE PARKFIT PROGRAM:

**A MULTIFACETED INTERVENTION AIMED TO
PROMOTE PHYSICAL ACTIVITY IN PATIENTS
WITH PARKINSON'S DISEASE**

SUBMITTED

Arlène D. Speelman, Marlies van Nimwegen,
Bastiaan R. Bloem, and Marten Munneke



ABSTRACT

BACKGROUND

We recently completed the ParkFit study, a two-year randomized controlled trial including 586 sedentary PD patients, that evaluated a multifaceted intervention (ParkFit program) to promote physical activity. Analysis of the secondary outcomes suggested greater participation in specific elements of physical activity, and demonstrated an improved fitness among ParkFit patients. Therefore, further implementation of the program could now be considered. To facilitate this process, we here evaluate the implementation of the ParkFit program.

METHODS

The ParkFit program was evaluated in three ways: (a) experiences of patients and physiotherapists, as investigated using interviews and questionnaires; (b) factors associated with changed activity levels; and (c) subgroup analyses to identify differential effects in subgroups of patients based on baseline physical activity level, age, gender, disease severity, disease duration, and mobility.

RESULTS

The ParkFit program was well received: 73% of patients indicated they would recommend the program to other patients, and 90% of physiotherapists indicated they wanted to use the ParkFit program in other patients. The program was effective in almost all subgroups. In women, most sedentary patients and patients with lower disease severity, the estimated effect size was largest.

CONCLUSION

We conclude that the ParkFit program was effective in almost all specific subgroups. Therapists and patients experienced no major hurdles. This knowledge can be used for further implementation into everyday clinical practice to revert the sedentary behavior of patients with PD, and perhaps other chronic conditions as well.

INTRODUCTION

Patients with PD are less active compared with controls, and this physical activity worsens with disease progression.¹⁷ Reversing sedentary lifestyles could have various generic benefits, including increased survival^{230 231} and lower risks of chronic diseases as cardiovascular disease, diabetes, and cancer.¹⁹ Promoting physical activity may also improve specific symptoms of PD, such as insomnia, depression, and constipation.²²⁰ Moreover, rodent work suggests that physical activity may counter neurodegeneration in experimental parkinsonism.¹⁰¹ ¹⁰² This observation has fueled speculation that physical activity might be used to alter the course of PD in humans.

Many patients are well aware of these potential benefits, but changing a sedentary lifestyle is difficult. Simply knowing about the importance of physical activity is not enough to initiate and maintain an adequate physical activity level on a regular basis, and it proves tremendously difficult to give up unhealthy behavior.³⁴ Changing one's lifestyle when old or suffering from a chronic disease such as PD is even harder due to physical limitations (e.g. gait and balance impairment) and mental changes (e.g. depression, apathy and cognitive impairment).

Considerable research has aimed to develop tools for clinicians to enable such high-risk groups to successfully change their lifestyle. Several physical activity promotion programs have shown to be effective; these programs were based on healthy behavior theories, used behavioral change strategies and were indi-

vidually tailored.^{34 258} Such a specific intervention program that considered the complexity of PD and that addressed all possible barriers was not available until recently. Therefore, we developed the ParkFit program, an individually tailored and disease-specific program for patients with PD. In a multicentre, randomized controlled trial including 586 sedentary PD patients, the ParkFit program was compared with a matched physiotherapy intervention according to the evidence based guideline.⁸⁹ The ParkFit program was solely delivered by experienced physiotherapists who participate in the Dutch ParkinsonNet.¹⁵ In total, 116 physiotherapists offered the ParkFit program to 299 patients.

Although the primary analysis of the ParkFit trial showed no differences in levels of activity, our secondary outcomes showed increased physical activity and improved fitness, without causing more falls (van Nimwegen M and Speelman AD et al., BMJ 2012, in press) Stimulated by these findings, further implementation of the ParkFit program into clinical practice could now be considered. To facilitate this potential implementation process, we here evaluate the implementation of the ParkFit program. Specifically, our analyses focused on: (a) experiences of therapists and patients with the ParkFit program; (b) factors associated with changed activity levels; and (c) subgroup analyses, to identify whether specific subgroups of patients might benefit less or more from the ParkFit program.

METHODS

THE PARKFIT STUDY

This study was part of the ParkFit study, a randomized controlled multi-centre trial aiming to increase physical activity levels over a course of two years in sedentary PD patients (van Nimwegen M and Speelman AD et al., BMJ 2012, in press). Patient characteristics were presented in Table 8.1. Ethical approval has been granted for the study and all patients signed informed consent. The full study protocol has been described elsewhere.⁸⁷

PARKFIT PROGRAM

The ParkFit program was specifically designed to achieve a sustained increase in the level of physical activity and was based both on theories and models of behavioral change^{98 234} and on behavioral change techniques with proven effectiveness.^{235 237 259}

Activity Coach

Physiotherapists served as personal activity coaches who guided patients towards a more active lifestyle during monthly personal coaching sessions. Physiotherapists educated patients about the beneficial effects of physical activity and about suitable activities. Additionally, patients were stimulated to participate in group exercise to experience beneficial effects of physical activity and to receive social support from fellow patients.

Education & Health contract

Patients received an educational workbook covering specific elements to promote a behavioral change. This brochure gave information about the benefits of physical activity and the risks of a sedentary lifestyle. Furthermore, suitable activities for PD patients, strategies to identify and overcome barriers to engage in physical activity, setting goals and recruiting social support were covered. The workbook included a health contract, a written agreement between patient and physiotherapist to support patients in initiating and maintaining physical activities by formulating long term activity goals.²³⁷ Additionally, a logbook was included to monitor short term goals. Patients received a bi-annual newsletter accentuating the benefits of physical activity.

Goal setting

During the coaching sessions patients and physiotherapists formulated activity goals. These goals were created in order to obtain the long term goals as formulated in the health contract. During the coaching sessions patient and therapists evaluated these goals as well as the experienced barriers. The formulated activity goals had to be realistic, concrete and individualized and had to be formulated in a systematic way.

Activity Monitor

All patients received a personal ambulatory monitor.²⁶⁰ This triaxial accelerometer was able to show the amount of actually delivered daily physical activity using light-emitting diodes. At a personalized website, patient and coach could formulate a personal goal based on kilocalories; feedback of the monitor was directly related to this personal goal. Since data of the monitor were uploaded to this website, patient and coach could monitor the individual progress.²⁶¹

Physiotherapy

The ParkFit program also included regular physiotherapy sessions. Based on individual disabilities, the therapist and patient jointly formulated individually tailored treatment aims, according to the evidence-based guideline of physiotherapy for PD.⁸⁹

IMPLEMENTATION OF THE PARKFIT PROGRAM

We took several steps to enable a successful implementation of the ParkFit program. We first developed a specific handbook for physiotherapists, including: (a) information about the benefits and risks of physical activity; (b) information about the process of behavioral change; (c) specific user-information for the tools included in the ParkFit program (health contract, activity monitor); and (d) a scheme including each coaching session, to help therapists through the coaching sessions.

Second, we developed the educational workbook for patients which included all elements of the ParkFit program. This workbook was not only intended to inform patients, but also to guide therapists in dealing with all specific elements important for behavioral change.

Third, physiotherapists were trained to treat patients in the ParkFit program during three educational sessions. These sessions covered the following items: (a) models and theories of behavioral change; (b) general strategies to coach people and to help them to overcome barriers; (c) techniques to formulate realistic, concrete and individualized goals; and (d) how to cope with differences in character between patient and therapist, because this greatly influences behavior. The specific elements included in the ParkFit program were also explained, such as use of the Activity Monitor, the educational workbook, the logbook and the health contract.

During the two-year intervention period, therapists could consult the research team at any time for advice. Moreover, the research team contacted therapists every three months by telephone to investigate whether they experienced barriers in delivering the ParkFit program.

Finally, after one year, an evaluation meeting with therapists was scheduled. These meetings aimed to refresh the knowledge of the various ParkFit elements and to discuss therapists' experiences.

EVALUATION OF THE PARKFIT PROGRAM

Experiences

Therapists were interviewed by four independent researchers three to six months after the start of the intervention. This telephone interview included various aspects related to the ParkFit program. Immediately after ending their participation in the trial, therapists and patients were asked to complete a self-administered questionnaire with questions regarding patients' and therapists' opinions about the program.

Factors associated with changed activity levels

In the ParkFit study, the level of physical activity was primary measured with the LAPAQ questionnaire.¹¹² The LAPAQ questionnaire reflects the net sum of 'outdoor and sport activities' plus 'household activities'. Post hoc analyses of the ParkFit trial showed that a significant and possibly relevant increase (24%) in outdoor and sport activities for ParkFit patients was offset by a concurrent decrease in household activities. Here, we identified variables that could be associated with this change in 'outdoor physical activity' as measured with the LAPAQ.

The following variables were evaluated: disease severity (Unified Parkinson's Disease Rating Scale motor part (UPDRS III), Hoehn and Yahr stage (HY))¹¹⁴, disease duration (years), quality of life (Parkinson's Disease Questionnaire (PDQ-39))²⁴⁰, mobility (Timed Up and Go test (TUG)),²⁶² bradykinesia (Nine hole pegboard test, (NHPT)), fatigue (Fatigue Severity Scale (FSS)),²⁰³ anxiety and depression (Hospitality Anxiety and Depression Scale (HADS))²⁶³, physical fitness (6-minute walk test (6MWT))²³⁹, and levodopa equivalent dose (mg). Moreover, general characteristics as body mass index (BMI), gender, age, and marital status were assessed.

Subgroup analyses

In an exploratory setting, the effectiveness of the ParkFit program was evaluated in specific subgroups. Subgroups were defined based on baseline physical activity level, age, gender, disease severity (UPDRS III), disease duration, and mobility (TUG). For each variable we classified two subgroups based on the median of the whole group.

STATISTICAL ANALYSES

Descriptive statistics were used to present quantitative data (i.e. means and percentages). Univariate linear regression analyses were performed to study associations between the change in level of physical activity during the entire follow-up period (i.e. mean of 6, 12, 18 and 24 months) and the possible variables (assessed at baseline). Variables that contributed significantly were included in a forward multivariate linear regression analysis. Because the physical activity level was skewed, medians and interquartile ranges were presented, and analyses were performed after logarithmic transformation. Furthermore, linear regression analyses were performed to determine differences in subgroups for changes in level of physical activity, changes in quality

of life (i.e. mean of 6, 12, 18 and 24 months) and changes in physical fitness (i.e. mean of 12 and 24 months) between both interventions. Fixed factors were treatment arm, score at baseline (level of physical activity, quality of life or physical fitness), H&Y stage, age and gender.

RESULTS

EXPERIENCES

Physiotherapists

Out of 116 therapists, 113 (97%) were interviewed. The mean number of patients treated by each therapist was 2.4 (range 1 – 13). Therapists identified patients' physical limitations (63%), uncertainty about their abilities and fear of falling (41%), and declined cognition (41%) as the most important explanations for their lifestyle.

Nearly all therapists (96%) felt competent to offer the specific ParkFit intervention. Only 1% of therapists believed that their knowledge of behavioral change was not sufficient. Seventy-eight percent was able to deliver the program always or very often. Main reasons for not succeeding were: patients' co-morbidity, cognitive disturbances, patients' lack of motivation, and increased disease severity. Formulating concrete and smart activity goals was difficult according to the therapists; patients' physical limitations and cognitive decline were the main reasons for difficulties in goal setting. Almost all therapists (96%) considered that their patients were motivated to participate in the ParkFit program.

Ninety-three percent completed the questionnaire at the end of the study. Therapists reported education (94%) and the coaching sessions (93%) as the main tools of the ParkFit program (Table 8.2). Most therapists (91%) said they would apply the ParkFit program in other patients with a sedentary lifestyle; 89% would offer the program to other PD patients. Twenty-one therapists (15%) mentioned suggestions to improve the program.

Patients

Out of 299 patients, 255 (85%) completed the questionnaire. Almost all patients (90%) reported they perceived benefits due to the intervention. Seventy-three percent would certainly recommend the program to other patients with PD, and 21% would consider recommending the program. The most popular tool for patients was the Activity Monitor; 83% of patients identified this device as a (very) useful instrument (Table 8.2).

FACTORS ASSOCIATED WITH CHANGED ACTIVITY LEVELS

Lower age, longer disease duration, better mobility, and lower baseline levels of physical activity were associated with larger changes in physical activity (Table 8.3). Multiple forward regression analysis resulted in a model with two variables: less baseline physical activity, and better mobility were associated with larger changes in levels of physical activity ($R^2=38\%$) (Table 8.3).

TABLE 8.1
BASELINE CHARACTERISTICS

	ParkFit (n = 299)	Controls (n = 287)
Demographics & Clinical Characteristics		
Age	65.1 (7.9)	65.9 (7.2)
Men	194 (65%)	188 (65%)
BMI	27.4 (4.5)	27.6 (4.0)
Disease duration (years)	5.0 (4.5)	5.5 (4.6)
MMSE	28.1 (1.7)	28.1 (1.7)
Modified Hoehn and Yahr		
1	7 (2.3%)	4 (1.4%)
1.5	7 (2.3%)	10 (3.5%)
2	221 (73.9%)	223 (77.7%)
2.5	48 (16.1%)	36 (12.5%)
3	16 (5.4%)	14 (4.9%)
UPDRS III	33.1 (11.3)	32.3 (9.5)
Daily levodopa equivalent dose (mg)	458 (362)	499 (414)
Level of physical activity (hours per week)		
LAPAQ total	12.8 (8.3 - 20.3)	13.8 (8.3 - 23.9)
LAPAQ outdoor and sport activities	5.7 (3.0 - 10.3)	6.0 (3.5 - 10.3)
LAPAQ household activities	5.0 (2.0-10.7)	5.3 (2.0-13.0)

Data reflect mean (SD), median (IQR-range) or number (%). BMI = Body Mass Index (kg/m²). MMSE = mini-mental state examination. UPDRS III = Unified Parkinson's disease Rating Scale, part III. LAPAQ = LASA Physical Activity Questionnaire

TABLE 8.2
PERCENTAGES OF BOTH PATIENTS AND THERAPISTS WHO CLASSIFIED THE ELEMENTS OF THE PARKFIT PROGRAM AS USEFUL

	Patients (n=250)	Physiotherapists (n=108)
Education	77%	94%
Goal setting (short term)	60%	88%
Goal setting (long term)	59%	83%
Coaching sessions	71%	93%
Activity Monitor	83%	75%
Sport sessions	58%	74%

TABLE 8.3
REGRESSION COEFFICIENTS (%) AND 95% CONFIDENCE INTERVALS FOR UNIVARIATE AND MULTIVARIATE ANALYSES BETWEEN THE CHANGE IN PHYSICAL ACTIVITY (LAPAQ OUTDOOR AND SPORT ACTIVITIES) AND THE EXPLORATORY FACTORS MEASURED AT BASELINE

	Univariate regression (95% CIs)	Multivariate regression (95% CIs)
Level of physical activity		
LAPAQ outdoor and sport activities	-43.8 (-47.3, -40.1)*	-44.8 (-48.3, -41.3)
Demographic characteristics		
Age	-1.6 (-2.7, -0.5)*	
Gender (men = 0)	-12.7 (-26.7, 3.8)	
Partner (no partner = 0)	5.1 (-16.2, 31.9)	
BMI	0.0 (-2, 1.9)	
Disease characteristics		
Modified Hoehn and Yahr	-12.5 (-32.4, 13.3)	
UPDRS III	-0.6 (-1.4, 0.2)	
Disease duration (y)	2.0 (0.2, 3.9)*	
Daily levodopa equivalent dose (mg)	0.0 (0, 0)	
Additional clinical characteristics		
6MWT	0.1 (0, 0.2)	
TUG	-2.5 (-4.9, -0.1)*	-4.7 (-6.5, -2.8)
PDQ-39	0.1 (-0.5, 0.7)	
NHPT	0.3 (-0.5, 1.1)	
FSS	-1.1 (-6.3, 4.3)	
HADS	0.2 (-1.1, 1.5)	
SCOPA night	0.8 (-1.6, 3.3)	
SCOPA day	0.4 (-2.1, 2.8)	

LAPAQ = LASA Physical Activity Questionnaire. BMI = Body Mass Index (kg/m²). UPDRS III = unified Parkinson's disease rating scale part III. 6MWT = 6-minute walk test. TUG = Timed up and Go test. PDQ-39 = Parkinson's Disease Questionnaire. NHPT = nine hole peg board test. FSS = Fatigue Severity Scale. HADS = Hospital Anxiety and Depression Scale.

TABLE 8.4

EFFECT SIZES OF THE PRIMARY AND SECONDARY OUTCOME MEASURES IN ALL PATIENTS AND FOR SUBGROUPS OF PATIENTS BETWEEN PARKFIT AND CONTROLS

	Change in Physical activity	Change in Quality of Life	Change in Physical Fitness
All patients	24% (10% to 40%)*	-0.9 (-2.1 to 0.3)	4.8 (0.1 to 9.6)*
Subgroups of patients			
Age [#]			
< 67	17% (-1% to 38%)	-1.0 (-2.6 to 0.6)	6.1 (-7.3 to 19.5)
> 67	38% (13% to 68%)*	-0.8 (-2.6 to 1.0)	17.0 (2.6 to 31.4)*
Gender ^{##}			
Men	19% (3% to 37%)*	-0.8 (-2.2 to 0.6)	9.1 (-2.8 to 20.9)
Women	40% (10% to 80%)*	-0.6 (-2.7 to 1.6)	12.0 (-4.4 to 28.4)
Disease duration (years)			
< 3.75	27% (5% to 54%)*	-1.4 (-3.0 to 0.3)	15.9 (2.7 to 29.0)*
> 3.75	23% (3% to 47%)*	0.13 (-1.6 to 1.9)	4.6 (-9.5 to 18.7)
Disease severity (UPDRS III)			
< 32	24% (3% to 51%)*	-1.7 (-3.4 to -0.05)*	15.0 (1.7 to 28.4)*
> 32	30% (9% to 55%)*	-0.2 (-1.9 to 1.6)	7.4 (-6.5 to 21.3)
Mobility (TUG, seconds)			
< 9.25	28% (7% to 52%)*	-1.2 (-2.8 to 0.4)	10.5 (-0.8 to 21.9)
> 9.25	21% (-0.1% to 46%)	-0.3 (-2.2 to 1.5)	9.3 (-6.0 to 24.6)
Baseline physical activity (hours)			
< 6	34% (10% to 64%)*	-0.2 (-2 to 1.6)	1.0 (-13.5 to 15.5)
> 6	17% (-0.1% to 38%)	-1.3 (-2.9 to 0.3)	18.3 (5.5 to 31.0)*

Data reflect estimated differences and 95% confidence intervals; analyses were corrected for age, gender, H&Y, and baseline level; [#]without correction for age; ^{##}without correction for gender; *p < 0.05. Physical activity was measured with the LASA Physical Activity Questionnaire (LAPAQ); quality of life was measured with the Parkinson's Disease Questionnaire (PDQ-39); physical fitness was measured with the 6-minute walk test (6MWT). UPDRS III = motor part of the Unified Parkinson's Disease Rating Scale; TUG = Timed up and Go test.

SUBGROUP ANALYSES

The ParkFit program was effective in changing the level of physical activity in almost all subgroups, except for patients younger than 67, patients with lower mobility scores and more physically active patients at baseline (Table 8.4). The estimated difference between ParkFit and controls was largest in the most sedentary patients (estimated group difference 34%, 95% Confidence Interval (CI) 10 to 64%), women (40%, CI=10 to 80%), and patients older than 67 (38%, CI=13 to 68%) (Table 8.4). The ParkFit program was effective in changing physical fitness in different subgroups (Table 8.4). Quality of life changed only in patients with lower disease severity (-1.7, CI=-3.4 to -0.05%) (Table 8.4).

DISCUSSION

We aimed to evaluate the trial experience with the ParkFit program, as a basis to facilitate future implementation into clinical practice. Both therapists and patients were positive about the intervention. Almost all therapists wished to use the ParkFit program in other patients, and 73% of patients would recommended the program to other patients. Subgroup analyses revealed that the program was effective in almost all subgroups. The most sedentary patients, women, patients with lower disease severity, shorter disease duration and elderly patients appeared to benefit relatively most. The different elements of the ParkFit program were offered as a 'total package' to achieve a behavioral change. Since therapists were educated to offer this multifaceted program and we evaluated the program likewise, we cannot conclude whether specific elements were more or less effective. However, the results of the questionnaire gave some insight in the perceived success of the various components. Specifically, therapists reported education and the coaching sessions as main tools of the ParkFit program, while most patients reported the Activity Monitor as the most useful tool. Clearly, these three elements deserve optimal attention when delivering the ParkFit program in clinical practice. Future work is needed to decide which component is most effective in increasing physical activity levels, and if any component of the ParkFit program will also be effective when used in isolation.

The program had an excellent compliance: 85% of patients in the ParkFit program completed the total intervention (van Nimwegen M and Speelman AD et al., BMJ 2012, in press). Our results concerning adherence are comparable with previous short-term programs (up to 6 months)⁹³ but remarkably higher compared with previous long-term programs (up to 14 months).²⁶⁴ In an exercise program of six months aiming to reduce fall risk in PD, 54% of patients completed at least 75% of the sessions.⁹³ Another study of group exercise in PD found an attendance rate of 73% during 14 months.²⁶⁴ Several aspects of our program could have contributed to its high adherence. First, the individually tailored character of the intervention – with activities that participants enjoyed – makes participation more palatable compared with exercise in general.²⁵⁸

Since patient and therapist jointly chose one or more (sport) activities, patients were allowed to follow their own wishes, adjusted to the individual situation. Second, the disease-specific knowledge of the therapists could explain the high adherence. The intervention was delivered solely by experienced physiotherapists participating in the Dutch ParkinsonNet.¹⁵ ParkinsonNet networks were specifically developed to improve the PD-specific expertise of health professionals, and to increase patient volumes per therapists.¹⁵ Probably, due to these specific elements, therapists were able to adequately anticipate on perceived barriers of PD patients, and this could have improved patients' adherence. Most patients who withdrew from the intervention did so just after baseline inclusion (4.7%). After about six months, another 5% of patients had stopped with the program. Apparently, once patients participate and perceive no 'starting' problems, there are hardly no reasons to stop with the intervention. This suggests that the program is feasible and achievable for patients. Besides the excellent compliance of patients, almost all involved therapists delivered the intervention for two years and completed both the interview and the questionnaire. This shows great enthusiasm and interest with the ParkFit program.

Multivariate regression showed that larger changes in levels of physical activity were associated with less baseline physical activity. The major part of the explained variance was explained by baseline physical activity. This could be a simple regression to the mean effect, but it could also suggest that poor daily participation in exercise is no reason to withhold patients a physical activity program such as ParkFit. Furthermore, better mobility was associated with greater increases in physical activity after two years. Moreover, therapists reported that patients without comorbidities and cognitive disturbances were more easy to stimulate towards an active lifestyle. Therefore, physiotherapists should take poor baseline mobility, physical limitations, baseline physical activity levels, and cognitive functioning of patients into account before starting a behavioral change program, for example by engaging the immediate caregiver into the program. Perhaps, patients should receive treatment (e.g. by increasing dopaminergic medication, or by offering physiotherapy strategies such as cueing) prior to participation.

Subgroup analyses showed significant differences for almost all subgroups between patients in the ParkFit program and controls. In the subgroups of women, patients with lower disease severity and patients with a shorter disease duration, the benefits from the ParkFit program seem to be greater. However, these results should be interpreted with caution, because the study was not set up to compare subgroups and had insufficient power to reliably detect differences. As such, the present results serve only as hypothesis-generating, which call for further confirmation in new studies. This work could focus on some promising hypotheses that came from our current research, suggesting that specific subgroups may benefit more than others. Specifically, further research should focus on the effects of ParkFit-like interventions in women, patients with lower disease severity and patients with a shorter disease duration.

The ParkFit program was now offered solely by physiotherapists with PD-specific expertise, which likely helped to overcome any barriers imposed by the physical limitations. The question is whether adding professionals from other disciplines might help to improve the quality of the behavioral change program. One example that came from the interviews was a psychologist, who could address the cognitive issues associated with PD, but who also adds specific expertise to change behavior. One could also consider adding sport instructors, since they have specific knowledge about coaching, counseling, sports and exercise. It will be interesting to examine the possible role of such sport instructors within the ParkFit program. For example, we anticipate that patients with greater disease severity will require more specific knowledge of a specialized physiotherapist, while patients in earlier stages could be coached solely by a sport instructor.

CONCLUSION

Our analysis of the ParkFit program yielded several suggestions for improvement: 1) improve education for therapists with respect to theories about behavioral change; 2) formulate concrete and specific examples of exercise goals; and 3) pay more specific attention to patients with comorbidities, cognitive dysfunction and a lack of motivation during education. Sedentary behavior is a major public health problem, and physical activity can have various specific benefits for patients with PD. We therefore recommend further implementation of this program into everyday clinical practice.

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CHAPTER 09

SUMMARY



This chapter summarizes the main findings of this thesis and focused on the assessment and benefits of physical activity in PD and how PD patients can increase their level of physical activity using a multifaceted behavioral change program.

CHAPTER 2 THE BENEFITS AND RISKS OF PHYSICAL ACTIVITY

The potential benefits and risks of increased physical activity in PD were explored in Chapter 2. This perspective article identified the following 10 potential benefits of an active lifestyle in PD patients: 1) prevention of cardiovascular complications, 2) slowing or arrest of osteoporosis development, 3) improved cognitive function, 4) prevention or treatment of depression, 5) improved sleep, 6) decreased constipation, 7) decreased fatigue, 8) improved functional motor performance, 9) improved drug efficacy, and 10) optimization of the dopaminergic system (possibly resulting in modification of the disease course). This chapter also concluded that there is still a lack of evidence about the benefits of exercise in patients with PD. Most evidence for the beneficial effects of exercise is on cardiovascular mortality and morbidity, cognitive dysfunction and mood. The best available evidence that supports the avoidance of a sedentary lifestyle is based on studies in healthy individuals and in patients with other neurodegenerative diseases. Besides the benefits of exercise, there could be an increased risk of falls, fall-related fractures, and an increased risk of cardiovascular complications.

Compelling theoretical reasons support the importance of avoiding a sedentary lifestyle and promoting physical activity for patients with, or at risk of developing, PD. However, there is still a lack of adequate knowledge about the benefits of exercise in patients with PD.

CHAPTER 3 PREVALENCE AND RISK FACTORS OF OSTEOPOROSIS

In Chapter 3, one specific health benefit of an active lifestyle was described, which was the positive effect on bone mass. Bone loss is regarded as more common in PD than in the general population. Several factors may be involved in the development of bone loss. Moreover, osteoporosis is an important risk factor for fractures. In Chapter 3, the prevalence of osteoporosis in sedentary PD patients was investigated. Furthermore, the possible risk factors that are associated with bone loss in sedentary patients were studied in 191 PD patients in an early stage of the disease (Hoehn and Yahr stage 1 to 2.5). The results demonstrated that the prevalence of osteoporosis and osteopenia was 53.2% in patients with an early stage of PD. These results were consistent with previous studies about osteoporosis in PD. Female gender, weight loss and

low vitamin D levels were identified as significant risk factors for decreased bone mineral density. Furthermore, vitamin D concentrations were significantly lower in comparison with sex and age-matched controls without PD.

Over 50% of sedentary PD patients have an abnormal bone mineral density. Female gender, weight loss and low vitamin D levels were identified as risk factors for decreased bone mineral density in PD.

CHAPTER 4 PATHOPHYSIOLOGY AND TREATMENT OF OSTEOPOROSIS

In this chapter, the pathophysiological mechanisms of bone loss and treatment of osteoporosis were described by reviewing the existing literature. PD patients have a lower bone mineral density compared to age-matched controls. PD patients also have a high risk of falls and – consequently – of sustaining osteoporotic fractures. The reduction of bone mineral density is multifactorial in origin, and includes reduced mobility, vitamin D deficiency, hyperhomocysteinemia (caused by use of levodopa), vitamin B12 or folic acid deficiency, malnutrition or low body weight, and decreased muscle strength. A few studies demonstrated that treatment with bisphosphonates, vitamin D and calcium can increase the bone mineral density in PD patients. Screening for osteoporosis should be considered in PD patients more often and therapeutic interventions should be initiated for those patients with proven osteoporosis. An appropriate treatment of osteoporosis could reduce the risk of fractures in PD patients, but the (cost-)effectiveness of this approach remains to be examined.

Reduced bone mineral density in PD is multifactorial in origin, including reduced mobility, vitamin D deficiency, hyperhomocysteinemia, vitamin B12 or folic acid deficiency, malnutrition or low body weight, and decreased muscle strength.

CHAPTER 5 AMBULATORY MONITORING

The assessment of physical activity in daily life is complex. Several methods have been proposed to assess physical activity levels or energy expenditure including ambulatory monitors. The use of activity monitors for long-term monitoring of walking distance is still limited. To evaluate whether an ambulatory monitor could estimate walking distance in PD patients, a simple activity monitor (Dynaport activity monitor) was validated in PD patients in Chapter 5. This device

measures accelerations of the lower trunk using tri-axial accelerometers and is placed in a belt positioned on the lower back between the posterior superior iliac spines. The results demonstrated that the precision of the activity monitor to estimate short walking distance (ranging between 21 and 27 meters) was good. However, the precision to estimate long walking distances (up to 1097 meters) was less adequate, with a wide range of agreement (-43% to 41%). The use of this monitor for clinical purposes is therefore limited. If this monitor is used as a screening tool, the actual walking distance might be the measured distance plus or minus 40%.

The accuracy of ambulatory activity monitoring (using tri-axial accelerometers mounted on the lower back) for long walking distances is insufficiently adequate. Therefore, the use of this type of ambulatory monitor for this clinical purpose is limited.

CHAPTER 6 CARDIOVASCULAR RESPONSES IN PD

Patients with PD are physically less active than controls. Autonomic dysfunction may contribute to this sedentary lifestyle. Specifically, an altered cardiovascular response to physical effort may limit physical activities. Therefore, in Chapter 6 the cardiovascular responses to a submaximal exercise test in sedentary PD patients and sedentary controls were assessed. The study demonstrated that PD patients had a lower estimated $\text{VO}_{2\text{max}}$ compared to controls (22 ml/min/kg versus 33 ml/min/kg). Moreover, more than half of the sedentary PD patients were unable to adequately increase their heart rate during a submaximal exercise test while almost all controls had an adequate heart rate increase. This inadequate increase in heart rate during exercise may be caused by cardiac sympathetic denervation leading to autonomic dysfunction. The lower resting heart rate and lower systolic blood pressure observed in those patients may be an additional indication for this symptomatic denervation of the heart.

Half of the PD patients have an inadequate heart rate increase during submaximal exercise, most likely caused by cardiac sympathetic denervation leading to autonomic dysfunction. This knowledge should be used when interpreting the outcome of exercise tests to screen the suitability of candidates for exercise interventions.

CHAPTER 7 PROMOTION OF PHYSICAL ACTIVITY

The evidence for the possible positive effects of exercise on several health outcomes indicates that an active lifestyle in PD patients could be beneficial. The sedentary lifestyle observed in patients with PD can be explained by physical limitations and mental changes, warranting an individually tailored, disease-specific physical activity intervention. Chapter 7 describes the ParkFit trial, a multicentre, randomized controlled trial in which a multifaceted, behavioral program, the ParkFit program, was compared with a matched general physiotherapy intervention. The ParkFit program was designed to achieve a sustained increase in the level of physical activity. The intervention was based on theories and models of behavioral change, and on widely used behavioral change techniques with proven effectiveness. Both groups were compared for the change in physical activity over a course of two years (primary outcome LASA physical activity questionnaire (LAPAQ), secondary outcomes of physical activity were a diary and accelerometer). Secondly the influence of a changed lifestyle on the number of falls, quality of life (PDQ-39) and physical fitness (six minute walk test) was investigated. We included 586 patients, 299 in the ParkFit group and 289 in the control group.

The results showed that the overall time spent in physical activities was comparable between the two groups (difference 7%; confidence interval, -3 to 17%; $p=0.19$). Three of our secondary outcomes indicated greater physical activity in patients allocated to the ParkFit program. This was demonstrated both subjectively (with activity diaries, difference 30%; $p<0.001$) and objectively (with an ambulatory activity monitor, difference 12%; $p<0.001$). Moreover, physical fitness increased in ParkFit patients, but not in controls (difference 4.8 meters; $p=0.05$). Quality of life did not differ between ParkFit and controls (difference -0.9 points; $p=0.14$). The number of patients with one or more falls was comparable in both groups: 184 (62%) in ParkFit and 191 (67%) in controls.

Our study showed that the ParkFit behavioural change program did not increase overall physical activity, as measured with the LAPAQ. Analysis of the secondary endpoints justifies further work into the possible merits of behavioural change programs to increase physical activities in daily life. The ParkFit program improved fitness over a 2-year period, without causing more falls.

CHAPTER 8 EVALUATION OF THE BEHAVIORAL CHANGE PROGRAM

The ParkFit program improved physical activities in sedentary PD patients based on positive findings of the secondary outcomes of the ParkFit study (Chapter 7), so implementation in clinical practice seems justified. In Chapter 8, we evaluated elements that are relevant for the future implementation of this program; specifically, we assessed the following three elements: 1) experiences of patients and physiotherapists (investigated using interviews and questionnaires); 2) factors associated with changed physical activity level; and 3) exploratory subgroup analyses to identify differential effects in subgroups of patients based on baseline physical activity level, age, gender, disease severity, disease duration, and mobility.

Data of 255 (85%) patients and 116 (97%) physiotherapists were collected. Both patients and therapists were positive about the intervention. Almost all therapist (90%) wanted to use the ParkFit program in other patients and 73% of patients would recommend the program to other patients. No major hurdles were reported for further implementation. The most important suggestions included a need for (more) education about coaching and behavioral change techniques, and (more) advice about increasing physical activity in specific groups of patients (i.e. patients with e.g. co-morbidities).

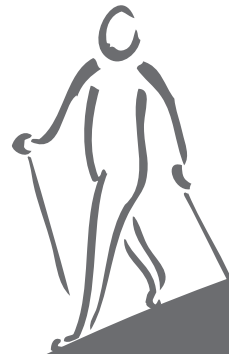
Less baseline physical activity and better mobility were associated with larger changes in physical activity over two years ($R^2=48\%$). Exploratory subgroup analyses revealed that the program was effective in almost all subgroups. In women, most sedentary patients, and patients with lower disease severity, the estimated size was largest.

The ParkFit program was effective in almost all specific subgroups. Therapists and patients experienced no major hurdles for further implementation. This knowledge can be used for further implementation into everyday clinical practice.

CHAPTER

10

GENERAL DISCUSSION AND FUTURE PERSPECTIVES



Several issues related to physical activity and exercise in PD have been answered by the studies described in this thesis. Below, these results are discussed and placed into a broader context. It is clear that there are still many areas of uncertainty that require further research, and some suggestions for this research agenda are also given below.

IS PHYSICAL ACTIVITY EFFECTIVE FOR PD PATIENTS?

Although the number of studies on exercise or physical activity increases, there is still a lack of evidence about the benefits of exercise in patients with PD, as described in Chapter 2. The most recent exercise studies provided some evidence in support of exercise programs in PD. A six week treadmill intervention in 20 patients with PD showed improvements in fatigue and quality of life, but not in walking capacity, as compared to a control group (usual care with advice to maintain current levels of physical activity).¹²⁶ Executive function improved in a group of 19 PD patients directly after 30 minutes passive leg cycling.²⁶⁵ Furthermore, a review of forced exercise in animal models and preliminary data on humans with PD has become available, underscoring the potential of forced exercise to influence cognition, metabolism, and, potentially, the progression of neurodegenerative disease.²⁶⁶

In general elderly populations, physical activity and exercise are associated with improved bone health.⁵⁶ The effect of exercise on bone mass in patients with PD has not yet been studied (Chapter 2 and 4). There is an indication for a complex interaction between various factors that can contribute to bone loss in PD. Optimal management of osteoporosis calls for an extensive risk assessment of all of these factors, including medication use, level of immobilization, muscle strength and nutritional status. Furthermore, the high incidence of vitamin D deficiency is particularly interesting (Chapter 3). Until now, the influence of vitamin D deficiency on the pathogenesis of PD or the possibility that PD itself leads to vitamin D deficiency is not clearly understood. However, it is important to be aware of vitamin D deficiency in PD patients, because of the possible effects on bone mineral density and muscle strength. Therefore, pending further evidence, it would appear prudent to perform regular measurements of vitamin D in older PD patients, starting early on in the course of their disease. Treatment of osteoporosis should be similar as for non-parkinsonian patients with osteoporosis and osteopenia and should start with bisphosphonates, vitamin D and an adequate intake of calcium.^{185 187-189} Furthermore, the general benefits of physical activity on bone loss in healthy adults can also be expected in PD patients. The question is if the high-impact exercises, that are effective in adults in combination with weight-bearing exercises⁵⁷, are also suitable for PD patients because of their high risk of falling.³¹ This now needs to be taken to the test.

The aim of the ParkFit study (Chapter 7) was to increase the level of physical activity in sedentary PD patients. Overall time spent on physical activities (measured with the LAPAQ) was comparable between patients in the ParkFit program and patients allocated to the control intervention. The LAPAQ yields a total sum score for outdoor and household activities, more detailed post hoc analyses of the nature of the physical activities showed that ParkFit patients significantly increased their outdoor activities (difference 24%; confidence interval 10 to 40%; $p < 0.001$), while they reduced their household activities (difference 16%; confidence interval -27 to -3%; $p = 0.02$). As a result, the net volume of indoor and outdoor activities was not significantly different between both groups. The question is whether PD patients who increased their outdoor activities, actually reduced their household activities. Several aspects could explain this observation. First, the time spent on household activities was really reduced in ParkFit patients because they spent more time outdoors. Alternatively, it is possible that patients who became more active outdoors no longer regarded household activities as physical activities, leading to underreport. Regardless, ParkFit patients did increase their outdoor activities, and this was a welcome finding as outdoor activities are likely associated with greater aerobic challenges.

Furthermore, in the ParkFit study the relationship between physical activity and specific health benefits was investigated in a post hoc analysis. Small but statically significant correlations were found between the change in level of physical activity and changes in mobility, quality of life, and disease severity: the subgroup of patients with the greatest increase in physical activity also showed better quality of life, lower disease severity scores and relatively greater mobility. The observed increase in outdoor activities and sports was 24%, but in terms of health benefits only physical fitness significantly increased. These findings support the hypothesis that physical activity is accompanied by health benefits. However, the results have to be interpreted with caution since the direction of these relations is unclear; for example, patients with only minimal changes in disease severity could have been able to increase physical activity more easily.

The lack of evidence for health outcomes in the ParkFit study could possibly be explained by a low intensity of activities. Patients become more active, but probably the intensity of the activities is not sufficient for health benefits to be picked up. There is evidence that aerobic physical activities which improve cardiorespiratory fitness are beneficial for cognitive function in healthy older adults.⁵¹ The question is whether PD patients can continue to participate in intensive aerobic physical activities for prolonged periods of time, and whether such greater efforts will translate into tangible clinical effects. Furthermore, if intensive aerobic activities are required to examine these effects, PD patients must be able to increase their heart rate during physical effort. The question is whether this is suitable for every PD patient, in light of their inadequate heart rate increase during submaximal exercise as described in Chapter 6. Another concern is that PD patients become only partially more physically active (by example, participating in fitness classes for two hours a week),

but during the rest of the time such patients may still spend a lot of time being sedentary, which in turn is related to all-cause cardiovascular disease and mortality.^{267 268} The influence of single exercise sessions or divided exercise sessions on health outcomes needs to be further investigated.

THE ASSESSMENT OF PHYSICAL ACTIVITY

The assessment of physical activity in daily life is complex. Several methods have been proposed to assess physical activity levels or energy expenditure including questionnaires, diaries and ambulatory monitors. In the ParkFit study, we selected a physical activity questionnaire (LAPAQ) as our primary outcome measure (Chapter 7). This questionnaire is a validated instrument to measure habitual physical activity¹¹² and as such, it was closely related to the goals of the ParkFit intervention, namely promotion of physical activities.¹¹² A disadvantage of physical activity questionnaires could be the overestimation of activities or delivery of socially desirable answers by the respondents.²⁶⁹ People tend to over-report physical activity, for example household activities, and to underestimate sedentary activities like watching television.^{270 271} The ParkFit study showed that a multifaceted behavioural change program does not promote overall physical activities in sedentary PD patients, as measured with LAPAQ. However, two of our secondary outcomes did suggest greater physical activity in patients allocated to the ParkFit program. This was demonstrated both subjectively (with activity diaries) and objectively (with an ambulatory activity monitor). Both the LAPAQ and the diary are subjective instruments, but only the diary showed increased activity levels. One possible explanation for this discrepancy is the fact that the diary merely includes strenuous activities, while the LAPAQ questionnaire reflects the net sum of all physical activities (including household activities). However, it was reassuring to see that the post hoc findings from our primary outcome (namely an increased time spent on outdoor and sport activities, with a 24% difference in favor of ParkFit patients compared to controls) were confirmed by these two secondary outcome measures, both in terms of direction of the effect (showing benefits for the ParkFit group) and magnitude of the effect (expressed as a percentage difference). Specifically, the activity monitor showed a 12% difference in favor of ParkFit, and the activity diary showed a 30% difference in favor of ParkFit.

Overall, this study shows (again) that physical activity is a complex behavior: it includes sports as well as non-sports activities and it can be characterized by purpose (occupational or leisure), type (cycling, fitness or soccer), intensity (light, moderate or vigorous) and duration. Taken together, the outcomes of the ParkFit study offered converging evidence for a beneficial effect of the ParkFit program on (outdoor) physical activities, but only if the LAPAQ is divided into outdoor and sport activities and household activities. Further research should focus on comprehensive, valid and reliable instruments to accurately measure all of the aspects of

physical activity behavior, specifically in patients with chronic diseases as they perform more light and moderate activities which are easy to overestimate when using questionnaires and difficult to detect with activity monitors.

Activity monitoring has potential as a practical tool to study activity levels in older patients.²⁷² Many different types of ambulatory monitors are available.²⁷³ In Chapter 5, a simple activity monitor was validated for use as a tool to assess walking distances in PD patients. Specifically, this ambulatory monitor measures accelerations of the lower trunk using tri-axial accelerometers and is placed in a belt positioned on the lower back between the posterior superior iliac spines. The results showed that the ambulatory monitor can be used to measure short walking distances (up to 27 meters), but the tool had a less accurate precision for longer walking distances (up to 1097 meters). Besides accelerometry, Global Positioning Systems (GPS) seem to be a promising approach for understanding physical activity behavior at the population level.²⁷⁴ Future research is needed on the use of ambulatory monitors in specific groups, such as patients with PD who experience specific types of gait problems (for example, hypokinetic gait, freezing of gait, or dyskinetic gait induced by medication). Furthermore, different types of activities like cycling or more static activities (like weight-bearing exercises or household activities like washing windows) should ideally be assessed using such ambulatory monitors.

In case of aerobic training, data are often expressed as a percentage of maximal oxygen intake. In Chapter 6, the cardiovascular responses of PD patients to a submaximal exercise test and the estimated VO_2 max were compared to controls. More than half of the PD patients were unable to adequately increase their heart rate, which may be caused by cardiac sympathetic denervation leading to autonomic dysfunction. This cardiac sympathetic denervation may have several consequences. It leads to a lower heart rate and cardiac contractility,²¹³ which causes a lower cardiac output during exercise, which is associated with shortness of breath²¹⁷ and fatigue.²¹⁸ This may limit PD patients during daily activities and might force them to lead a more sedentary lifestyle.¹⁷ In an early disease stage, PD patients should therefore be screened for exercise behavior, and be examined to identify whether any limitations in exercise performance are secondary to cardiac sympathetic denervation and autonomic dysfunction. Further research should focus on a reliable submaximal screening tool to assess cardiorespiratory fitness in PD patients with autonomic dysfunction in clinical practice. Furthermore, the observed cardiac sympathetic denervation and autonomic dysfunction could have therapeutic consequences, as the use of beta blockers may aggravate the inadequate heart rate response to exercise. Beta blockers should therefore be prescribed with caution, certainly when patients are referred for exercise programs.

IS PHYSICAL ACTIVITY PROMOTION FEASIBLE IN PD PATIENTS?

The first reason to recommend the ParkFit program to PD patients is that the ParkFit study (Chapter 7) showed that older sedentary patients with a chronic disease like PD can increase their level of physical activity based on the secondary outcomes (Chapter 7), and that this could increase physical fitness without causing more falls. Although the evidence for health benefits was weak, there is substantial evidence that older adults who are less active than recommended by guidelines can achieve health benefits.²⁰¹ Our participants were on average less sedentary in comparison with patients who were not willing to participate,⁸⁷ so those people that may have benefited most from exercise declined to participate. Future work should focus on patients that are more sedentary than our population. Second, the experiences of patients and therapists in the ParkFit program were encouraging (Chapter 8). Specifically, almost all therapists said they would use the ParkFit program in other patients after the trial, and reported no major hurdles for further implementation. Ninety percent of the patients reported benefits due to the intervention and have recommended the program to other patients. Furthermore, the program showed an excellent attendance rate: 85% of the patients in the ParkFit program completed the total intervention, despite the long trial duration of two years. Therefore, we recommend further implementation of the ParkFit program.

In general, age, gender, health status, and fear of falling are associated with exercise behavior.⁹⁶ In PD patients, two studies investigated the determinants of physical activity.^{17 275} Self-efficacy was associated with regular exercise in community-dwelling PD patients.²⁷⁵ Furthermore, physical inactivity was associated with worse walking performance, more disability in daily life, and greater disease severity.¹⁷ In Chapter 8, we tried to identify factors associated with increased activity levels in PD and to identify group(s) of patients who increased their activity level the most. Multivariate regression showed that a larger change in the level of physical activity was strongly associated with less time spent on physical activity at baseline. Once again, this underscores the need for a proactive approach towards patients with a very sedentary lifestyle, and who now declined to participate in the ParkFit study.

Although patients with severe apathy, cognitive impairment or depression were not included in the ParkFit study (Chapter 7), therapists reported that patients with cognitive disturbances were more difficult to coach towards an active lifestyle. It remains unclear if the ParkFit program is also suitable for those patients. Future research and education of physiotherapists should focus on coaching patients with co-morbidities, cognitive dysfunction and a lack of motivation.

The success of behavioural change programs depends probably not only on the barriers PD patients experience, but also on self-efficacy. Self-efficacy, rather than disability, is strongly associated with whether community-dwelling PD patients exercise regularly.²⁷⁵ A strength of the

ParkFit study is that not only patients who were highly motivated to increase their physical activity were included, and that the ParkFit program was individually tailored. Future work should now focus on the most effective (individually tailored) programs for PD patients with different barriers and different levels of self-efficacy to become physically active. Physical therapists should include strategies in their coaching to increase self-efficacy and take into account poor baseline mobility, physical limitations, baseline physical activity levels, and cognitive functioning of patients before starting a behavioral change program in PD patients, for example by engaging the immediate caregiver into the program. Perhaps, patients should receive treatment (e.g. by increasing dopaminergic medication, or by offering physiotherapy strategies such as cueing) prior to participation.

The development of appropriate measurements to detect various barriers, including cognitive functioning, to become physically active in PD is needed. Furthermore, future work should also decide which component of the ParkFit program was most effective, and evaluate if any component would also have been effective when used in isolation, and also evaluate which component is most effective in different types of patients.

The ParkFit study is by far one of the largest randomized controlled trials about physical activity in PD patients. Compared with other studies about physical activity, both in PD and other chronic diseases, most available trials have some methodological problems such as a short-term follow-up and a low number of patients.^{68 276} The ParkFit study tackled these problems. What sets the ParkFit study apart is: (1) the long term follow-up period of two years; (2) the large number of participants included in the study; (3) the challenging combination of both physical limitations and cognitive impairments patients with PD are faced with; (4) the pragmatic nature and generalizability of the study; the intervention was delivered by not less than 154 different physiotherapists, and (5) the low dropout rate of 7.7%.

OVERALL CONCLUSION

The aim of this thesis was to obtain better insight into the benefits, risks and measurements of physical activity and exercise in PD, and to develop an approach to stimulate PD patients to a sustained, active lifestyle. We have shown that sedentary PD patients were not able to increase their overall level of physical activity with an individualized behavioral change program. However, the secondary endpoints suggest that patient did increased physical activity and improved fitness, without causing more falls. Although the ParkFit program suggest a sustained behavioral change in sedentary PD patients, changing unhealthy behavior still remains a challenge for patients, therapists and researchers. The evidence about the merits of physical activity in patients with PD is still limited. The long-term health benefits of physical activity should be studied in more detail, with a focus on the optimal dosage, intensity, frequency and duration that is needed to achieve clinically meaningful health benefits.

CHAPTER

NEDERLANDSE SAMENVATTING

11



Dit hoofdstuk geeft een samenvatting van de belangrijkste bevindingen van dit proefschrift. Het concentreert zich op de metingen en voordelen van fysieke activiteit bij patiënten met de ziekte van Parkinson en hoe patiënten met de ziekte van Parkinson hun niveau van fysieke activiteit kunnen verhogen met behulp van een gedragsveranderingsprogramma.

HOOFDSTUK 2 DE VOORDELEN EN RISICO'S VAN FYSIEKE ACTIVITEIT BIJ DE ZIEKTE VAN PARKINSON

In Hoofdstuk 2 zijn de voordelen en risico's van meer fysieke activiteit bij de ziekte van Parkinson onderzocht. Tien potentiële voordelen van een actieve leefstijl bij patiënten met de ziekte van Parkinson zijn geïdentificeerd namelijk: 1) de preventie van cardiovasculaire complicaties; 2) het vertragen of tegenhouden van osteoporose (botontkalking); 3) het verbeteren van de cognitieve functie; 4) de preventie of behandeling van depressie; 5) het verbeteren van het slapen; 6) het verminderen van constipatie; 7) het verminderen van vermoeidheid; 8) het verbeteren van de functionele mobiliteit; 9) het verbeteren van de doelmatigheid van de parkinsonmedicatie; en 10) het optimaliseren van het dopaminerge systeem. Ondanks dat er veel onderzoek gedaan wordt naar de voordelen van een actieve leefstijl, bestaat er nog steeds een gebrek aan bewijs over de voordelen hiervan bij de ziekte van Parkinson. Het beste bewijs over de positieve effecten van fysieke activiteit bestaat voor hart- en vaatziekten, cognitief functioneren en stemming. Naast de positieve aspecten van fysieke activiteit is het ook van belang om in de gaten te houden of actievare patiënten niet meer gaan vallen, vaker valgerelateerde fracturen hebben of vaker cardiovasculaire complicaties ondervinden.

Hoewel er veel onderzoek gedaan wordt is er nog steeds weinig bewijs over de voordelen van fysieke activiteit bij patiënten met de ziekte van Parkinson. Op basis van verschillende theoretische gronden is het echter wel belangrijk om een actieve leefstijl bij patiënten met, of met het risico op, de ziekte van Parkinson te stimuleren.

HOOFDSTUK 3 PREVALENTIE EN RISICOFACTOREN VAN OSTEOPOROSE

Een van de gezondheidsvoordelen van een actieve leefstijl is het positieve effect op de botmassa. Het verlies van botmassa komt vaker voor bij mensen met de ziekte van Parkinson dan in de algemene populatie. Er zijn verschillende factoren die betrokken zijn bij dit verlies aan botmassa. Daarnaast is osteoporose een belangrijke risicofactor voor het krijgen van fracturen. In Hoofdstuk 3 is de prevalentie van osteoporose en de mogelijke factoren die geassocieerd zijn met verlies van botmassa onderzocht bij 191 inactieve patiënten met de ziekte van Parkinson.

De resultaten laten zien dat 53.2% van de patiënten met de ziekte van Parkinson osteoporose hadden. Mensen die minder wegen en een laag vitamine D niveau hebben, hebben meer kans op een lagere botdichtheid. Daarnaast hebben vrouwen meer kans op een lagere botdichtheid. De vitamine D concentratie werd onderzocht tussen de 191 inactieve patiënten met de ziekte van Parkinson en een controlegroep zonder de ziekte van Parkinson. De vitamine D concentratie bleek lager te zijn bij mensen met de ziekte van Parkinson in vergelijking met de groep zonder de ziekte van Parkinson.

Meer dan 50% van de inactieve patiënten met de ziekte van Parkinson hebben een abnormale botdichtheid. Mensen die minder wegen en een laag vitamine D niveau hebben, hebben meer kans op een lagere botdichtheid. Daarnaast hebben vrouwen meer kans op een lagere botdichtheid. De vitamine D concentratie bleek lager te zijn bij mensen met de ziekte van Parkinson in vergelijking met een controlegroep zonder de ziekte van Parkinson.

HOOFDSTUK 4 PATHOFYSIOLOGIE EN BEHANDELING VAN OSTEOPOROSE

In Hoofdstuk 4 is de pathofysiologie en behandeling van osteoporose onderzocht doormiddel van een literatuurstudie. De resultaten van het literatuuronderzoek laten zien dat de vermindering van de botdichtheid veel verschillende factoren kent. Deze factoren zijn: 1) verminderde mobiliteit; 2) tekort aan vitamine D; 3) hyperhomocysteenemie (een verhoogde waarde van het aminozuur homocysteïne in het bloed); 4) tekort aan vitamine B12 of foliumzuur; 5) ondervoeding of een laag lichaamsgewicht; en 6) verminderde spierkracht. De behandeling met bisfosfonaten (geneesmiddel ter preventie van osteoporose), vitamine D en calcium verhogen de botdichtheid bij patiënten met de ziekte van Parkinson. Het screenen van patiënten met de ziekte van Parkinson op osteoporose zou vaker overwogen moeten worden en een therapeutische behandeling moet gestart worden bij die patiënten met bewezen osteoporose. Een adequate behandeling van osteoporose zou het risico op fracturen kunnen verminderen, maar de (kosten-) effectiviteit van deze aanpak moet onderzocht worden.

Een verlaagde botdichtheid bij de ziekte van Parkinson is multifactoriaal en bestaat uit een verminderde mobiliteit, vitamine D tekort, hyperhomocysteenemie, vitamine B12 of foliumzuur tekort, ondervoeding of een laag lichaamsgewicht en een verminderde spierkracht.

HOOFDSTUK 5 METEN VAN FYSIEKE ACTIVITEIT MET EEN ACTIVITEITENMONITOR

Het meten van fysieke activiteit in het dagelijks leven is lastig. Er zijn verschillende methodes beschikbaar om het niveau van fysieke activiteit of energieverbruik te meten waaronder activiteitenmonitors. Het gebruik van activiteitenmonitors bij het langdurig meten van fysieke activiteit of het meten van de gelopen afstand is nog beperkt. In Hoofdstuk 5 is een simpele activiteitenmonitor die de gelopen afstand kan schatten onderzocht bij patiënten met de ziekte van Parkinson. Deze monitor wordt gedragen in een riem op de rug en maakt gebruik van tri-axiale accelerometers. De resultaten laten zien dat deze monitor korte afstanden (tussen de 20 en 27 meter) precies kan schatten, maar dat het schatten van lange afstanden (maximaal 1097 meter) minder precies is. De afwijking van de werkelijk gelopen afstand ligt tussen de -42% en 41%. Hierdoor is het gebruik van deze monitor in de praktijk beperkt. Als de monitor gebruikt wordt als screeningsmethode, zal de werkelijk gelopen afstand de gemeten afstand min of plus 40% zijn.

De precisie van de activiteitenmonitor voor het schatten van lange afstanden is onvoldoende adequaat. Daarom is het gebruik van deze activiteitenmonitor voor klinische doeleinden beperkt.

HOOFDSTUK 6 CARDIOVASCULAIRE REACTIES BIJ PATIËNTEN MET DE ZIEKTE VAN PARKINSON

Patiënten met de ziekte van Parkinson zijn minder fysiek actief in vergelijking met gezonde controles. Autonome dysfunctie draagt mogelijk bij aan deze inactieve leefstijl. Mogelijk beperken veranderende cardiovasculaire reacties tijdens fysieke inspanning het ondernemen van fysieke activiteiten. In Hoofdstuk 6 zijn de cardiovasculaire reacties van patiënten met de ziekte van Parkinson tijdens een submaximale inspanningstest op de fiets vergeleken met gezonde controles. Patiënten met de ziekte van Parkinson bleken een lagere geschatte maximale zuurstofopname te hebben vergeleken met gezonde controles (22 ml/min/kg versus 33 ml/min/kg). Daarnaast was meer dan de helft van de patiënten niet in staat hun hartslag adequaat (een hartslag boven de 120 slagen per minuut) te verhogen tijdens de submaximale inspanningstest, terwijl bijna alle gezonde controles hier wel toe in staat waren. Deze inadequate verhoging van de hartslag tijdens inspanning wordt mogelijk veroorzaakt door autonome dysfunctie.

De helft van de patiënten met de ziekte van Parkinson heeft een inadequaat verhoging van de hartslag tijdens submaximale inspanning, waarschijnlijk veroorzaakt door cardiale sympatische denervatie die leidt tot autonome dysfunctie. Deze kennis moet gebruikt worden bij de interpretatie van uitkomsten van inspanningstests tijdens het screenen van bruikbare patiënten voor bewegingsprogramma's.

HOOFDSTUK 7 RESULTATEN VAN DE PARKFIT STUDIE

In Hoofdstuk 7 wordt de ParkFit studie beschreven. De ParkFit studie richtte zich op de vraag of patiënten met de ziekte van Parkinson met een inactieve leefstijl in staat zijn middels een bewegingsbevorderingsprogramma hun niveau van fysieke activiteit te verhogen. Vervolgens werd onderzocht wat de mogelijke voordelen of nadelen van meer bewegen waren. Patiënten die deelnamen aan het onderzoek werden willekeurig verdeeld over twee fysiotherapeutische programma's. Het ParkFit programma richtte zich op het bevorderen van een actieve leefstijl. De patiënten stelden samen met hun coach een beweegplan op met persoonlijke doelstellingen voor korte en lange termijn. Daarnaast ontvingen ze een activiteitenmonitor die hen visueel stimuleerde fysiek actiever te worden. Het controleprogramma richtte zich op het verbeteren van de kwaliteit van leven door verbeteren of behouden van zelfstandigheid, veiligheid en welbevinden tijdens bewegen.

In totaal werden er 586 patiënten twee jaar lang gevolgd en de verandering in het niveau van fysieke activiteit werd tussen de twee groepen vergeleken. De resultaten laten zien dat de tijd die besteed werd aan fysieke activiteit vergelijkbaar was tussen de twee groepen (verschil: 7%; 95% betrouwbaarheidsinterval -3 tot 17%; $p=0.19$). Analyses van de secundaire uitkomstmaten lieten echter wel een toename zien van fysieke activiteit bij patiënten die het ParkFit programma hadden gevolgd. Zowel op basis van een beweegdagboek (verschil van 30%; $p<0.001$), een activiteitenmonitor (verschil van 12%; $p<0.001$), als op de 6 minuten wandeltest (verschil van 4.8 meter; $p=0.05$) waren patiënten in het ParkFit programma significant verbeterd ten opzichte van de patiënten in het controleprogramma. Kwaliteit van leven gemeten met de PDQ-39 verschilde niet tussen beide groepen (verschil van -0.9 punten; $p=0.14$). Het aantal mensen dat één of meerdere keren viel, was vergelijkbaar tussen de twee groepen: ParkFit 62% en controles 67%.

Het ParkFit programma had geen invloed op het niveau van fysieke activiteit van mensen met de ziekte van Parkinson. Echter, de secundaire uitkomstmaten lieten een toename in het activiteiten-niveau zien evenals een verbetering in fitheid, zonder dat mensen meer gingen vallen.

HOOFDSTUK 8 EVALUATIE VAN HET PARKFIT PROGRAMMA

In Hoofdstuk 8 hebben we de verschillende elementen van het ParkFit programma geëvalueerd die relevant zijn voor toekomstige implementatie van het programma in de praktijk. Hiervoor zijn er vier verschillende elementen gemeten: 1) de ervaringen van patiënten en therapeuten met het programma middels vragenlijsten en interviews; 2) factoren die geassocieerd zijn met een verandering van het niveau van fysieke activiteit; en 3) analyses om effecten in verschillende subgroepen van patiënten te inventariseren; de indeling in subgroepen was gebaseerd op de volgende variabelen: niveau van fysieke activiteit op baseline; leeftijd; geslacht; ziekte ernst; ziekte duur; en mobiliteit van de patiënt.

Data van 255 patiënten (85%) en 116 (97%) fysiotherapeuten werden geanalyseerd. Zowel patiënten en therapeuten zijn positief over de interventie. Bijna alle therapeuten (90%) geven aan het ParkFit programma ook graag bij andere patiënten te willen gebruiken, 73% van de patiënten zouden het ParkFit programma aanbevelen aan andere patiënten. Aanbevelingen voor verdere implementatie zijn: 1) de behoefte aan (meer) scholing op het gebied van coaching en gedragsveranderingstechnieken; en 2) (meer) advies over het verhogen van het niveau van fysieke activiteit in specifieke groepen patiënten (bijvoorbeeld patiënten met comorbiditeiten).

Een lager niveau van fysieke activiteit op baseline en een hoger niveau van mobiliteit waren geassocieerd met een hogere toename van fysieke activiteit gedurende twee jaar ($R^2=48\%$). De subgroepanalyse laat zien dat het programma effectief is in bijna alle subgroepen. De meest inactieve patiënten, vrouwen, patiënten met een lagere baselinescore op de UPDRS, patiënten met een korte ziekte duur en oudere patiënten lijken het meeste voordeel te hebben van het programma.

Het ParkFit programma verhoogde het niveau van fysieke activiteit in bijna alle subgroepen van patiënten. Therapeuten en patiënten hadden geen grote belemmeringen ervaren voor verdere implementatie van het ParkFit programma.

CHAPTER 12

DANKWOORD



DANKWOORD

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CHAPTER

13

13.1 REFERENCES

13.2 LIST OF PUBLICATIONS


13.3 CURRICULUM VITAE

13.4 DISSERTATIONS OF THE PARKINSON CENTRE NIJMEGEN



13.1

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13.2

LIST OF PUBLICATIONS

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13.3

CURRICULUM VITAE

Arlène D. Speelman was born in Epe, the Netherlands, on the 25th of September 1983.

She finished secondary education at the Ulenhof College in Doetinchem in 2001. She continued to study physiotherapy at the HAN University of Applied Sciences in Nijmegen, where she received her Bachelor of Science in 2005. Thereafter, she decided to start studying Biomedical Sciences, and during her master she specialized in the field of Clinical Human Movement Sciences at the Radboud University Nijmegen in the Netherlands. She concluded her masters with two internships at the department of Neurology of the Radboud University Nijmegen Medical Center, where she studied physical activity in Parkinson's disease patients. After graduating in 2008, she gained a research position at the department of Neurology of the Radboud University Nijmegen Medical Center where she studied physical activity and physical fitness in patients with Parkinson's disease. In 2011 she won the Ralph S. Paffenbarger Jr. Poster Award of the 21st international Puijo Symposium "physical exercise, ageing and disability – current evidence" in Kuopio, Finland. Currently, she is project coordinator Elderly and Cancer at the Comprehensive Cancer Center South in Eindhoven, the Netherlands.

13.4

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