PROMOTION OF PHYSICAL ACTIVITY IN PARKINSON'S DISEASE

THE CHALLENGE TO CHANGE BEHAVIOR

MARLIES VAN NIMWEGEN
PROMOTION OF PHYSICAL ACTIVITY IN PARKINSON’S DISEASE

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Promotion of physical activity in Parkinson’s disease feasibility and effectiveness. Thesis, Radboud University Nijmegen, the Netherlands

Design: IS – Ontwerp • Ilse Schrauwers • www.isontwerp.nl

Cover concept and movement-illustrations: Nynke Hester Bakker

Printing: Ipskamp Drukkers B.V • www.ipskampdrukkers.nl

ISBN: 978-94-6191-598-6

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There are two primary choices in life; to accept conditions as they exist, or accept the responsibility for changing them.

Denis Waitley
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CHAPTER 01
GENERAL INTRODUCTION & AIMS OF THIS THESIS
PARKINSON’S DISEASE

Parkinson’s disease (PD) is one of the most common neurodegenerative diseases. The prevalence is estimated at around 1.3% to 1.5% for people above the age of 60 years. Ageing is a major risk factor for PD; due to the growing elderly population, the prevalence will increase sharply in the next decades.

PD is characterized by motor symptoms including bradykinesia, tremor, rigidity, gait disturbances and postural instability. In addition to these symptoms, a wide variety of non-motor symptoms like depression or apathy is present in almost all patients; examples include autonomic dysfunction, depression, fatigue, cognitive decline, and sleep disturbances. All these symptoms markedly impair the quality of life, and with disease progression, most patients experience severe disability. People with PD carry a relatively heavy illness burden compared with those suffering from other chronic conditions: only people with high spinal cord injury (among the conditions leading to physical impairments) and people with depression (among the conditions leading to mental impairments) scored lower on quality of life.

The underlying causes of PD are still largely unknown, but the changes in the brain and resulting pathophysiology are becoming quite clear. It is widely appreciated that dopaminergic neurons from the pars compacta of the substantia nigra degenerate progressively, resulting in a mounting central dopamine deficiency in various dopaminergic circuitries. Levodopa, combined with a peripheral dopa decarboxylase inhibitor (benserazide or carbidopa), can correct this dopamine deficiency and remains to date the most effective therapy. An increasing number of other dopaminergic drugs is also available to alleviate the symptoms of PD. For a selected subgroup of patients, deep brain surgery is a therapeutic option.

As the disease progresses, non-dopaminergic brain areas become progressively involved in the neurodegenerative process. This leads to emergence of debilitating symptoms and signs that fail to respond adequately to dopamine replacement therapy or deep brain surgery. In addition to the medical management approaches, allied health interventions and specialized Parkinson nurses are increasingly deployed to treat both the dopaminergic and non-dopaminergic symptoms of PD. The evidence to support the merits of these interventions is gradually growing and treatment guidelines (partially based on evidence, partially on practical clinical experience) for some of these allied healthcare interventions have been developed; for example, the use of physiotherapy is described in Textbox 1. Integrating all 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.
**PHYSICAL ACTIVITY AS A MEDICINE?**

Although medical treatment with levodopa substantially improves the quality of life and functional capacity, PD remains an incurable disease that results in considerable and progressive disability for almost all affected patients. Therefore, new and better treatment approaches are needed to suppress the symptoms and signs of PD, and to perhaps slow down or even arrest the otherwise relentless disease progression. This thesis examines whether promotion of physical activities could represent such an intervention.

There are several reasons to assume why more physical activity might be beneficial for PD patients. First, physical activity could have potential disease-specific effects, for example by improving cognitive dysfunction and mood. Second, recent studies have shown that exercise can have a beneficial effect on the neurodegenerative process in rodent models of PD. Specifically, studies in rats and mice with experimental parkinsonism 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. Of course, extrapolation of these experimental findings to patients requires extreme caution. However, the results have fuelled speculation that exercise might perhaps be used to modify the course of PD by acting directly on the neurodegenerative process. Taken together, these symptomatic and presumed disease-modifying effects raise hope that exercise could be used as a ‘medicine’ in patients with PD. Exercise as a medicine, it sounds both easy and simple, but it is not, as we shall see in this thesis.

Sedentary behavior is a major public health problem and it is one of the highest risk factors for death in developed countries. Changing a sedentary lifestyle is difficult, even for healthy people, and to increase physical activity in old persons or in patients with one or multiple chronic conditions is even harder. This is particularly true for PD patients who typically experience a combination of both physical limitations and mental changes, which creates considerable barriers to become physically active. A critical question that is addressed in this thesis is whether people with PD can achieve an enduring increase in their physical activities in daily life. And even when such a sustained change in lifestyle is possible, it needs to be demonstrated whether this change can improve disease-specific symptoms and prevent development of co-morbid complications.

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**TEXTBOX 1**

**PHYSIOTHERAPY IN PD**

Even with optimal medical treatment, patients with PD experience a decline of body function and mobility. This can lead to inactivity and social isolation, resulting in a reduced quality of life. To reduce these motor impairments, physiotherapy can be effective. The evidence-based guideline for physiotherapy in PD describes specific treatment areas. The objective of physiotherapy is to improve the patient’s independence, safety and well-being.

In the Netherlands, specialized physiotherapy for patients with PD - as well as other healthcare professions such as speech & language therapy or occupational therapy - is available in regional professional networks, known as ParkinsonNet. Each ParkinsonNet network consists of a small number of healthcare professionals who have been specifically trained to treat PD patients according to evidence-based recommendations. To further improve the quality of care, ParkinsonNet aims to improve the accuracy of referrals by neurologists, and to increase the patient volume per therapist. Moreover, collaboration and communication between the participating health professionals is stimulated. 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.

---

**BENEFITS OF PHYSICAL ACTIVITY**

Living an active lifestyle promotes health. The benefits of regular physical activity are extensive and it prevents people from chronic diseases such as cardiovascular disease, diabetes, cancer, hypertension, obesity and osteoporosis. Moreover, physical activity may improve specific symptoms such as sleep impairment, depression, and constipation. Several biological mechanisms may be responsible for the benefits associated with physical activity: for example, habitual physical activity has been shown to improve vascular function and cholesterol levels, to reduce blood pressure and body weight, to prevent bone loss associated with aging, and to increase cardiac function. Because of the benefits associated with physical activity and exercise, international guidelines state that every adult “should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all days of the week.” There are no reasons to assume that similar health benefits will not apply to chronic patients as well.

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* 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.
ACHIEVING A BEHAVIORAL CHANGE: A CHALLENGE

Despite the seemingly well-known health benefits of physical activity, almost half of the Dutch adults do not meet the international guidelines for healthy physical activity. Why is it so difficult to live an active life? Why is it easier to choose the alternative – physically inactive – option? Why is simply informing people about the potential health benefits of physical activity not enough to attain a sustained behavioral change? Everything that people can do for themselves is often more important than what conventional medical management can offer, but even this fact is for many people not enough to change their unhealthy lifestyle. Apparently, making healthy changes is easier said than done. Even when people are strongly motivated, adopting a new, healthy habit – and even more importantly, breaking an old one – proves very difficult.

Considerable research has been aimed at identifying factors and tools for clinicians that contribute to a successful lifestyle change. As a first step, knowledge about the health risks and benefits of the specific behavior is vital: if people lack knowledge about how their habits affect their health, they have little reason to change these habits at all. Furthermore, according to social cognitive theories, behavior is based on two types of expectations: (1) self-efficacy expectations, which are the individuals’ beliefs in their capabilities to perform a course of action to attain a desired outcome; and (2) outcome expectations, which are the beliefs that a certain consequence will be produced by personal action. The stronger someone believes both in his or her abilities and the positive outcomes of the behavior, the more likely it is that he or she will change the unhealthy behavior. The transtheoretical model (TTM) has been used to understand the stages that people progress through when they change behavior. The model assumes that individuals move through different stages: precontemplation; contemplation; preparation; action; and maintenance. The TTM shows that behavioral change does not occur in a linear manner and that it is a dynamic process.

When trying to achieve an enduring behavioral change, both knowledge about this behavioral change process and specific strategies such as goal setting, problem-solving techniques and motivational interviewing is needed. Physical activity promoting programs including such elements were effective in sedentary people, in patients with chronic heart failure, and in patients with COPD.

Although an active lifestyle has extensive benefits, an increased risk for falls is a potential other side of the same coin. This concern is especially true for people with PD who have a much higher risk of falling compared to age matched controls. One of the most common causes of falls in PD appears to be freezing of gait; other falls may result from insecure transfers or changes in posture, or when performing more than one activity at the same time. Promoting physical activity inevitably increases the number of daily circumstances when patients are engaged in such hazardous activities, and as such greater mobility may paradoxically increase the risk of falls. In contrast, fall risks are presumably minimal for patients who are sitting on a chair all day, although one might argue that because of de-conditioning, particularly these patients are susceptible to fall once they do need to make a transfer or walk. Whether or not promoting physical activities leads to more or fewer falls really needs to be tested.

AIMS OF THIS THESIS

Physical activity levels of patients with PD are still unclear, and so are their determinants. Consequently, a disease-specific intervention program considering the complexity of PD and their physical activity behavior is lacking. This thesis is dedicated to the relationship between PD and physical activity behavior, and aims to clarify some uncertainties about physical activity in PD.

In Chapter 2, we examine the level of physical activity in patients with PD. Patients with PD are likely to become physically inactive, because of their motor, mental and emotional problems. However, specific studies on the actual volume of physical activity in PD are scarce, and the available results are conflicting. In this chapter, we quantify daily physical activities in PD patients, and analyze the associated determinants.

Since there is a lack of specific interventions that accommodate the complexity of PD and the physical activity behavior of PD patients, we developed such a PD-specific program (the ParkFit program). The ParkFit program is a physiotherapy intervention that aims to increase physical activity levels over a period of two years in sedentary patients with PD. The intervention is based on models of behavioral change, and contains different behavioral change techniques. To evaluate its effectiveness, we designed a multicentre, randomized controlled trial comparing ParkFit with a matched general physiotherapy intervention. Primary endpoint for this ParkFit trial was the time spent on physical activity per week. The ParkFit program as well as the design of the trial are described in Chapter 3.

Multivariable selection methods are frequently used to determine factors associated with an outcome, for example in Chapter 2 when analyzing determinants of physical activity in PD. However, it is well known that different studies often lead to different models. By using the data described in Chapter 2, we show in Chapter 4 that these conflicting results are partly due to the fact that the final model is usually not unique.

The ParkFit study intended to include sedentary patients, based on a physical activity screening questionnaire. It was uncertain whether these self-reported sedentary patients could also be
identified as being sedentary when tested objectively for daily physical activity using quantitative ambulatory accelerometry. In Chapter 5, we therefore measured the daily physical activity levels of ParkFit patients by using an ambulatory accelerometer.

The results of the ParkFit trial are described in Chapter 6. Primary aim of the trial is to investigate whether the ParkFit program leads to increased physical activity levels that persist for two years. Physical activity levels will be measured every six months using an interview-based 7-day recall. To investigate whether increased levels of activity might be beneficial for patients, physical fitness and quality of life are assessed, as well as the number of falls.

To further facilitate implementation of the ParkFit program into everyday clinical practice, we also evaluated the trial experience with the ParkFit program. These results are described in Chapter 7.

Finally, Chapter 8 summarizes this thesis and Chapter 9 discusses the main findings. Moreover, future challenges are described.
ABSTRACT

BACKGROUND

Patients with Parkinson’s disease (PD) are likely to become physically inactive, because of their motor, mental and emotional symptoms. However, specific studies on physical activity in PD are scarce, and results are conflicting. Here, we quantified daily physical activities in a large cohort of PD patients and another large cohort of matched controls. Moreover, we investigated the influence of disease-related factors on daily physical activities in PD patients.

METHODS

Daily physical activity data of PD patients (n=699) were collected in the ParkinsonNet trial, and of controls (n=1,959) in the Longitudinal Aging Study Amsterdam (LASA); data were determined using the LAPAQ, a validated physical activity questionnaire. In addition, variables that may affect daily physical activities in PD were recorded, including motor symptoms, depression, disability in daily life, and co-morbidity.

RESULTS

Patients were physically less active; a reduction of 29% compared to controls (95% CI, 10-44%). Multivariate regression analyses demonstrated that greater disease severity, gait impairment, and greater disability in daily living were associated with fewer daily physical activities in PD (R²=24%).

CONCLUSION

In this large study, we show that PD patients are about one third less active compared to controls. While disease severity, gait, and disability in daily living predicted part of the inactivity, a portion of the variance remained unexplained, suggesting that additional determinants may also affect daily physical activities in PD. Because physical inactivity has many adverse consequences, work is needed to develop safe and enjoyable exercise programs for patients with PD.
Controls
Controls were derived from the Longitudinal Aging Study Amsterdam (LASA), a prospective study of persons aged 55 to 85 years old (1995-1996)\textsuperscript{53}. This cohort forms a nationally representative sample of the older Dutch population and thus creates a good control group. After exclusion of participants older than 80 years, data of 1,959 controls were available for the analyses. Mean age was 65.8 ± 7.0 years and 921 subjects were men (47.0\%) (Table 2.1). Full ethical approval has been granted for the study and all respondents gave informed consent at the start of the study.

Daily physical activities in patients and controls
In both groups, daily physical activities were measured with the LASA Physical Activity Questionnaire (LAPAQ)\textsuperscript{55}. The LAPAQ covers frequency and duration of different activities during the previous two weeks\textsuperscript{55} \textsuperscript{56}. Activities covered in the LAPAQ include: walking outside, cycling, gardening, light and heavy household activities, and a maximum of two sport activities. To consider different levels of intensity of activities, a metabolic equivalent value (MET) was assigned to each activity to calculate the number of kilocalories spent per day per kilogram of body weight\textsuperscript{57}. In addition, types of different activities (‘inside’ and ‘outside the house’) were specified. The LAPAQ was initially designed as an interview-based physical activity questionnaire; in the LASA study, data was collected this way. A self-completed version was used in the ParkinsonNet trial. To reduce recall bias, the time window was limited to one week. A random sample of the ParkinsonNet trial population (n=76) completed the questionnaire, and was also interviewed similar to the controls. The subgroup was comparable to the total PD population (Table 2.1).

### TABLE 2.1
CHARACTERISTICS OF THE PARTICIPANTS

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total population</td>
<td>Random sample</td>
</tr>
<tr>
<td>N</td>
<td>699</td>
<td>76</td>
</tr>
<tr>
<td>Men</td>
<td>409 (58.5%)</td>
<td>44 (57.9%)</td>
</tr>
<tr>
<td>Age</td>
<td>68.6 ± 7.7</td>
<td>67.6 ± 8.2</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>5.3 (± 4.7)</td>
<td>3.9 (± 3.7)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>385 (55.1%)</td>
<td>26 (34.2%)</td>
</tr>
<tr>
<td>Medium</td>
<td>112 (16.0%)</td>
<td>16 (21.1%)</td>
</tr>
<tr>
<td>High</td>
<td>150 (21.5%)</td>
<td>25 (32.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>52 (7.4%)</td>
<td>9 (11.8%)</td>
</tr>
<tr>
<td>Partner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>522 (74.7%)</td>
<td>54 (71.1%)</td>
</tr>
<tr>
<td>No</td>
<td>131 (18.6%)</td>
<td>13 (17.1%)</td>
</tr>
<tr>
<td>Missing</td>
<td>46 (6.7%)</td>
<td>9 (11.8%)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>77 (11.0%)</td>
<td>7 (9.2%)</td>
</tr>
<tr>
<td>2</td>
<td>327 (46.8%)</td>
<td>36 (47.4%)</td>
</tr>
<tr>
<td>3</td>
<td>243 (34.8%)</td>
<td>25 (32.9%)</td>
</tr>
<tr>
<td>4</td>
<td>34 (4.9%)</td>
<td>7 (9.2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>18 (2.6%)</td>
<td>7 (9.2%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%).

DISEASE RELATED FACTORS ASSOCIATED WITH DAILY PHYSICAL ACTIVITIES IN PD
In the ParkinsonNet trial, a wide range of variables was assessed: disease severity (H&Y stages and motor section of the unified Parkinson’s Disease Rating Scale\textsuperscript{58}), fear of falling (Falls Efficacy Scale-International\textsuperscript{59}), anxiety and depression (Hospital Anxiety and Depression Scale\textsuperscript{60}), mobility (timed up and go test\textsuperscript{61}), freezing of gait (Freezing of Gait questionnaire\textsuperscript{62}), walking speed (6-meter walk test), disability in daily life (Self-assessment Parkinson’s Disease Disability Scale\textsuperscript{63}), co-morbidity (cumulative illness rating scale\textsuperscript{64}), and “faller status” (≥ 1 fall in the preceding year). Patient characteristics included gender, age, education level and marital status. We studied the influence of these disease-related factors on daily physical activities. We classified six dimensions to analyze all factors: demographics (gender, age, education level, and marital status); health status/disease severity (H&Y, UPDRS, CIRS, and time since diagnosis); walking performance/mobility (TUG, FOGQ, and walking speed); fear of falling, anxiety and depression (HADS and FES-I); disability in daily life (SPDDS); and faller status.
ANALYSES

Data of daily physical activities in both groups were summarized with medians and 25th and 75th percentiles. Since the LAPAQ scores were skewed, linear logarithmic transformation was applied for all subsequent analyses. Differences between patients and controls in minutes per day as well as in kilocalories per day were evaluated using linear regression analyses, with adjustment for gender, age, education level and marital status. Furthermore, linear regression analysis with forward variable selection was performed to study the association between the dimensions mentioned above and daily physical activities. First, we used a stepwise selection procedure to identify additional variables that contributed significantly. In addition, we used a hierarchic approach whereby in each subsequent step of the selection procedure, an F-test was carried out for each dimension that was not yet in the model. First, the demographic variables were included in the model. The dimension with the smallest F-value was then included, provided that it was statistically significant. The selection procedure was stopped when the F-test of none of the remaining dimensions was significant. A two-sided P value of less than 0.05 was considered to indicate statistical significance. In general, selection procedures provide a model, but they do not guarantee that the model is unique. Therefore, we evaluated whether the resulted model was optimal and unique by calculating the explained variance (R²) for all possible alternative models.

RESULTS

DAILY PHYSICAL ACTIVITIES IN PD COMPARED TO CONTROLS

Patients spent 111 minutes per day (interquartile range 58 – 206) on daily physical activities, compared to 150 minutes for controls (interquartile range 89 – 232). This amount lead to a 29% reduction in patients versus controls (95% CI, 10 to 44%; p<0.01). Patients also spent 29% less kilocalories on daily physical activities (95% CI, 11 to 43%; p<0.01). After adjustment for age, gender, education level and marital status, the difference between patients and controls was 24% (95% CI, 3 to 40%; p<0.05). In contrast to the control group, the patient population included subjects younger than 55 years of age. Therefore, we performed an additional analysis excluding patients younger than 55 years old, which showed comparable results.

In a sub analysis, we specified the nature of activities. Median time spent to 'outdoor and sports activities' did not differ between patients and controls (95% CI, 3 to 40%; p<0.05). Patients also spent significantly less time to activities inside the house (62%, 95% CI, 45 to 83%; p<0.01).

DISEASE RELATED FACTORS ASSOCIATED WITH DAILY PHYSICAL ACTIVITIES IN PD

Univariate relationships

Univariate regression analyses were performed to investigate the relation between the various disease related factors and daily physical activities in minutes per day (Table 2.2). All disease-related factors were significantly correlated with daily physical activities, except for ‘time since diagnosis’. Compared to men, women with PD were 80% more active. Furthermore, time spent to daily physical activities decreased significantly with age (-3% for each year) and with disease severity (-3% for each point on the UPDRS). Figure 2.1 shows that the time spent to daily physical activities decreased when disease severity increased. Additionally, patients without falls in the preceding year spent 32% more time to daily activities compared to fallers. Greater fear of falling, co-morbidity, and depression and anxiety were associated with fewer daily physical activities in PD.

Multivariate relationships

Stepwise model selection resulted in a model with four variables: gender, co morbidity, mobility, and disability in daily life (Table 2.2). This model explained 22% of the variance. However, when we checked whether this model was unique, we found ten additional models...
TABLE 2.2
REGRESSION COEFFICIENTS (%) AND 95% CONFIDENCE INTERVALS FOR UNIVARIATE AND
MULTIVARIATE ANALYSES BETWEEN DAILY PHYSICAL ACTIVITIES AND THE EXPLANATORY FACTORS

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate Regression (95% CI’s)</th>
<th>Multivariate Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-3 (-5, -2) *</td>
<td></td>
</tr>
<tr>
<td>Gender (woman versus men)</td>
<td>80 (44, 125) *</td>
<td>101 (65, 141)</td>
</tr>
<tr>
<td>Education level (low, medium, high)</td>
<td>-5 (-17, 9)</td>
<td></td>
</tr>
<tr>
<td>Marital status (partner versus no partner)</td>
<td>6 (-20, 39)</td>
<td></td>
</tr>
<tr>
<td>Health status/Disease severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;Y Stage</td>
<td>-34 (-43, -23) *</td>
<td>*</td>
</tr>
<tr>
<td>UPDRS III (0 – 108)</td>
<td>-3 (-4, -2) *</td>
<td></td>
</tr>
<tr>
<td>CIRS (0 – 56)</td>
<td>-28 (-38, -17) *</td>
<td>-18 (-29, -9)</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>-2 (-4.5, 0.3)</td>
<td></td>
</tr>
<tr>
<td>Walking performance/Mobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUG (time in seconds)</td>
<td>-10 (-13, -8) *</td>
<td>-7 (-10, -4)</td>
</tr>
<tr>
<td>FOGQ§ (0 – 20)</td>
<td>-19 (-28, -10) *</td>
<td></td>
</tr>
<tr>
<td>Walking speed (speed in m/s)</td>
<td>184 (50, 389) *</td>
<td></td>
</tr>
<tr>
<td>Fear of Falling, Anxiety and Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FES-I§ (16 – 64)</td>
<td>-65 (-74, -52) *</td>
<td>*</td>
</tr>
<tr>
<td>HADS depression (0 – 21)</td>
<td>-7 (-9, -4) *</td>
<td></td>
</tr>
<tr>
<td>HADS anxiety (0 – 21)</td>
<td>-4 (-7, -1) *</td>
<td></td>
</tr>
<tr>
<td>Disability in daily life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPDDS§ (24 – 120)</td>
<td>-82 (-87, -73) *</td>
<td>-63 (-75, -45)</td>
</tr>
<tr>
<td>Faller status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faller status (no versus yes)</td>
<td>32 (6, 65) *</td>
<td>*</td>
</tr>
</tbody>
</table>

H&Y Stage = Hoehn and Yahr stage; UPDRS = Unified Parkinson’s Disease Rating Scale; CIRS = cumulative illness rating scale; TUG = timed up and go test; FOGQ = Freezing of Gait questionnaire; FES-I = Falls Efficacy Scale-International; HADS = Hospital Anxiety and Depression Scale; SPDDS = Self-assessment Parkinson’s Disease Disability Scale. § = linear logarithmic transformation was applied; the coefficients presented here indicate the effect of doubling of the score: e.g. when fear of falling increased by a factor 2, daily physical activities decreased by 65%. * = significant relationship between the independent factor and daily physical activities.

TABLE 2.3
MODELS WITH THEIR EXPLAINED VARIANCE (R2); ALL MODELS WERE ADJUSTED FOR DEMOGRAPHIC CHARACTERISTICS

<table>
<thead>
<tr>
<th>One Dimension</th>
<th>Two Dimensions</th>
<th>Three Dimensions</th>
<th>Four Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL</td>
<td>19 Walking, ADL</td>
<td>23 Severity, Walking, ADL</td>
<td>24</td>
</tr>
<tr>
<td>Walking</td>
<td>18 Severity, ADL</td>
<td>21 Foa &amp; Anxiety, Walking, ADL</td>
<td>23</td>
</tr>
<tr>
<td>Severity</td>
<td>15 Severity, Walking</td>
<td>20 Walking, Falls, ADL</td>
<td>23</td>
</tr>
<tr>
<td>Falls</td>
<td>15 Foa &amp; Anxiety, ADL</td>
<td>20 Severity, Foa &amp; Anxiety, ADL</td>
<td>22</td>
</tr>
<tr>
<td>Foa &amp; Anxiety</td>
<td>10 Falls, ADL</td>
<td>19 Severity, Falls, ADL</td>
<td>21</td>
</tr>
</tbody>
</table>

Classified dimensions: Severity = Health status/disease severity; Walking = Walking performance/Mobility; Foa & Anxiety = Fear of falling, anxiety and depression; ADL = Disability in daily life; Falls = Faller status.

leading to 21% explained variance. In addition, the model with three variables (gender, mobility, and disability in daily life) had an explained variance of 21%. All models with five or more variables explained at least 20% of the variance, whereas the percentage explained variance of the full model was 24%. We evaluated the possible collinearity in the full model. The largest collinearity index was 3.9 and the largest variance inflation factor (VIF) was 2.6. Only SPDDS and FES-I had a VIF exceeding 2.

Multivariate relationships: hierarchic approach
As we could not find a reasonably unique model in the multivariable approach, we used a hierarchic variable selection to identify dimensions which were associated with daily physical activities. Demographic characteristics were first included in the multivariate regression model and explained a small portion of the variance (R2 = 9%). The subsequent model selection procedure for dimensions of health resulted in a model with the dimensions walking performance/mobility, disability in daily life, and health status/disease severity. These dimensions, in addition to demographics, jointly explained 24% of the variance in LAPAQ scores (Table 2.3). Adding more dimensions into the model did not increase the explained variance. This final model was not unique: Table 2.3 shows that various other models yielded only slightly lower R2.
DISCUSSION

Patients with PD are widely presumed to follow a sedentary lifestyle, due to their physical, cognitive and emotional impairments. We now provide new evidence to underpin this assumption, based on analyses of time spent to daily physical activities in a large cohort of PD patients and another large cohort of controls. The loss of time spent to activities was most obvious in patients with greater disease severity.

Our results showed that PD patients were 29% less active compared to controls. In a previous study of 24,000 subjects aged 65 years and older, similarly reduced activity levels (by about 23%) were found for patients with a chronic disease such as musculoskeletal disorders and vascular or heart diseases. The 29% reduction observed for PD patients in the present study might even be greater in comparison with healthy controls since our cohort did not include severely affected PD patients. Moreover, the LASA study, which we used as a control group, showed that about 60% of the population had a chronic disease. Direct comparison for comorbidity between the two groups was not possible as the LASA study only recorded broad categories and did not subdivide in specific disorders. Although it would be interesting incorporating fall histories in the analysis, data of fall history was not available for the control group. Future studies are required to investigate the influence of these factors.

It is important to consider the methods use to assess physical activity in the present and other studies. We used a validated interview-based physical activity questionnaire, which is a subjective method of measuring physical activity. This might have resulted in an overestimation of the reported physical activities. However, this possible overestimation likely applies equally to both patients and controls, so it is unlikely that this influenced our results. Another possibility is that patients underestimated their activities due to memory problems. However, patients with severe cognitive impairment (MMSE <24), were excluded, so this is unlikely to explain the physical inactivity observed in PD patients. Other studies circumvented such problems by using objective measures of physical activity; these studies did not find differences between patients and controls. Although these activity monitors have been well validated and shown to be reliable for a range of activities, some specific activities such as gardening and cycling are difficult to quantify. This may be one reason for the discrepancy with our results.

We also investigated the determinants associated with daily physical activities in PD patients. One factor was gender. Univariate regression analysis showed that women with PD were 80% more active than men. This is in contrast with observations in non-PD populations. The LAPAQ assessed a broad range of activities, including walking outside, cycling, gardening, light and heavy household activities, and a maximum of two sport activities. When we removed the household activities from the total activity score, men appeared to be more physically active than women (p<0.01). The same effect was found in the control group. This suggests that women spent more time to daily activities because the LAPAQ records household activities. Another study found comparable results for older women: two thirds of them reached recommended levels of physical activity when domestic activities were included in the assessment, but only 21% when these domestic activities were excluded.

We also found several additional determinants associated with daily physical activities. Specifically, inactivity in PD was associated with worse walking performance, more disability in daily life, and greater disease severity. These factors identified in this study for PD, are comparable to other studies who investigated the determinants of physical inactivity in older persons. Our results concerning the determinants of daily physical activities in PD have to be interpreted with some caution, for several reasons. First, the final model was not unique, because various different combinations of determinants yielded almost the same percentage of explained variance. A model with two dimensions (i.e. walking performance and disability in daily life) was as good as a model with three dimensions (additionally including either disease severity, fear of falling, anxiety and depression, or faller status).

Second, in all models, the unexplained variance remained large. Our final model explained 24% of the variance. Adding more variables into the model did not increase the explained variance. This suggests that additional factors are responsible for the variability in LAPAQ scores in PD. Because we secondary analyzed data from two previous trials, various factors were not investigated. One such factor is fatigue, which may be an independent contributor to physical inactivity in PD. Moreover, social cognitive theories propose that behavioral factors are associated with physical activity. Earlier work showed that a model which included self-efficacy and outcome expectations, explained 64% of the variance in exercise behavior in older adults. Other studies found that (lack of) interest in physical activity, knowledge about the benefits of exercise, and social supports also predicted exercise behavior. In the literature, many other possible determinants have been suggested, ranging from income and socioeconomic status up to seasonal effects. Further work therefore remains necessary to identify ‘all’ determinants, as a basis for future therapeutic interventions.

Although we showed that physical inactivity was most obvious in patients with greater disease severity, not all PD patients with advanced disease were completely sedentary. This suggests that even PD patients in later stages of the disease might be stimulated to become more active. Participating in regular physical activity would be particularly useful for PD patients, because exercise may help to prevent cardiovascular events, diabetes mellitus, and osteoporosis. Moreover, in older subjects, physical activity was reported to suppress typical PD symptoms such as depression and cognitive decline. In addition, preclinical evidence in animals with...
experimental parkinsonism suggests that exercise may directly alter the neurodegenerative process in PD\(^7\). A meta-analysis has found exercise to be effective at improving physical functioning, health-related quality of life, strength, balance, and gait speed for people with PD\(^7\). It is therefore important for PD patients to avoid a sedentary lifestyle. Simply informing people about the health benefits of physical activity is likely insufficient to attain a sustained behavioral change. Motivational aspects are especially important because such behavioral interventions could target motivation to increase levels of physical activity. We are now taking this to the test in the ParkFit trial, a large exercise study involving 586 PD patients randomized to receive a behavioral change program aimed to increase daily physical activity levels. The ParkFit trial uses motivational strategies and personal health coaches to induce a lasting increase in exercise behavior for patients with PD; the first results are expected in 2012\(^2\).

**ACKNOWLEDGEMENTS**

The ParkinsonNet trial was supported by ZonMw (947-04-357), the Netherlands Organization for Scientific Research, the Dutch Parkinson’s Disease Society, the National Parkinson Foundation, and De Stichting Robuust. The Longitudinal Aging Study Amsterdam is largely supported by a grant from the Netherlands Ministry of Health, Welfare, and Sports, Directorate of Nursing Care and Older Persons. This study was sponsored by the MJ Fox Foundation and the National Parkinson Foundation. All sources of funding had no further involvement.
DESIGN AND BASELINE CHARACTERISTICS OF THE PARKFIT STUDY

A RANDOMIZED CONTROLLED TRIAL EVALUATING THE EFFECTIVENESS OF A MULTIFACETED BEHAVIORAL PROGRAM TO INCREASE PHYSICAL ACTIVITY IN PARKINSON PATIENTS

BMC NEUROLOGY 2010;10:70

Marlies van Nimwegen, Arlène D Speelman, Katrijn Smulders, Sebastiaan Overeem, George F Borm, Frank J G Backx, Bastiaan R Bloem, and Marten Munneke

on behalf of the ParkFit study group
ABSTRACT

BACKGROUND

Many patients with Parkinson’s disease lead a sedentary lifestyle. Promotion of physical activities may beneficially affect the clinical presentation of PD, and perhaps even modify the course of PD. However, because of physical and cognitive impairments, patients with PD require specific support to increase their level of physical activity.

METHODS

We developed the ParkFit Program: a PD-specific and multifaceted behavioral program to promote physical activity. The emphasis is on creating a behavioral change, using a combination of accepted behavioral motivation techniques. In addition, we designed a multicentre randomized clinical trial to investigate whether this ParkFit Program increases physical activity levels over two years in sedentary PD patients. We intended to include 700 sedentary patients. Primary endpoint is the time spent on physical activities per week, which will be measured every six months using an interview-based 7-day recall.

RESULTS

In total 3453 PD patients were invited to participate. Ultimately, 586 patients – with a mean (SD) age of 64.1 (7.6) years and disease duration of 5.3 (4.5) years – entered the study. Study participants were younger, had a shorter disease duration and were less sedentary compared with eligible PD patients not willing to participate.

CONCLUSION

The ParkFit trial is expected to yield important new evidence about behavioral interventions to promote physical activity in sedentary patients with PD. The results of the trial are expected in 2012.

INTRODUCTION

Parkinson’s disease is a progressive neurological disorder characterized by both motor symptoms (such as bradykinesia and postural instability) and non-motor symptoms (such as depression and cognitive impairment). Both motor and non-motor symptoms can result in reduced physical activity. Observations in non-parkinsonian populations suggest that participating in regular physical activity has preventive effects (e.g. cardiovascular events, diabetes mellitus, dementia) and positive symptomatic effects (on depression, sleep disturbances, health-related quality of life). Studies in PD patients concluded that brief physiotherapy interventions can improve flexibility, balance and muscle strength. In addition, preclinical evidence in animals with experimental parkinsonism raised the possibility that physical activity may directly alter the neurodegenerative process.

A critical question remains how PD patients can be stimulated best to achieve an enduring increase in their physical activities in daily life, in order to prevent co-morbid complications and to improve symptoms. Simply informing subjects about the health benefits of physical activity is not enough to attain a sustained behavioral change. The challenges to induce a lasting change in exercise behavior are particularly great for neurological patients. To change lifestyle, behavioral programs should focus on appropriate supervision, social support from spouses and caregivers, and the individual’s preferences and needs. Achieving an enduring behavioral change also calls for specific strategies such as goal setting, problem-solving techniques and motivational interviewing. Physical activity promoting programs including such elements were effective in sedentary people, patients with chronic heart failure, and patients with COPD. Stimulated by these observations, we developed the ParkFit program: a multifaceted intervention to promote physical activity in sedentary patients with PD. In addition, we developed the ParkFit trial to investigate whether this program affords increased physical activity levels that persist for two years. The trial will also search for possible health benefits and risks of increased physical activity. Here, we describe the study design and baseline characteristics of this ParkFit trial.

METHODS

STUDY DESIGN

The ParkFit trial is a multicentre, randomized controlled trial comparing two arms: physiotherapy with specific emphasis on promoting a physically active lifestyle (ParkFit Program); and matched physiotherapy with specific emphasis on safety and quality of performing daily activities (ParkSafe Program) (Figure 3.1). Trial duration is two years. Full ethical approval has been granted for the study (CMO Regio Arnhem-Nijmegen). The study is registered at clinicaltrials.gov (nr NCT00748488).
PATIENTS

We started with all patients who visited their neurologist in 2007, 2008 or 2009 in 32 participating community hospitals. Eligibility criteria were: (a) PD, according to the UK Brain Bank Criteria; (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 ≤3. 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.

THE INTERVENTION

After baseline assessment, patients were randomly assigned to the ParkFit or ParkSafe Program. In both groups, patients receive high quality physiotherapy: both interventions are delivered exclusively by experienced therapists who participate in the Dutch ParkinsonNet. Patients in both treatment arms are offered an equal maximum number of treatment sessions (i.e. 35 sessions of 30 minutes a year, Table 3.1). Therapists contact patients at least every six months to investigate if there are new aims.

![Figure 3.1: Design of the ParkFit Study](image)

### Table 3.1

<table>
<thead>
<tr>
<th>Year</th>
<th>Intensity</th>
<th>ParkFit</th>
<th>ParkSafe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>Maximum of 19 physical therapy sessions</td>
<td>Maximum of 35 physical therapy sessions</td>
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<tr>
<td></td>
<td>based on problems and disabilities as perceived by each individual patient</td>
<td>based on problems and disabilities as perceived by each individual patient</td>
<td></td>
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<tr>
<td></td>
<td>16 coaching sessions</td>
<td>16 coaching sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to identify and focus on individual beliefs and aims to promote a physically active lifestyle</td>
<td>to identify and focus on individual beliefs and aims to promote a physically active lifestyle</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>Maximum of 23 physical therapy sessions</td>
<td>Maximum of 35 physical therapy sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>based on problems and disabilities as perceived by each individual patient</td>
<td>based on problems and disabilities as perceived by each individual patient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 coaching sessions</td>
<td>12 coaching sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to identify and focus on individual beliefs and aims to promote a physically active lifestyle</td>
<td>to identify and focus on individual beliefs and aims to promote a physically active lifestyle</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific Elements</th>
<th>ParkFit Brochure</th>
<th>ParkSafe Brochure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Education about benefits of physical therapy</td>
<td>• Education about benefits of physical therapy</td>
<td></td>
</tr>
<tr>
<td>• Identifying aims of physical therapy</td>
<td>• Identifying aims of physical therapy</td>
<td></td>
</tr>
<tr>
<td>• Education about the benefits of physical activity</td>
<td>• Education about the importance of safety when performing daily activities</td>
<td></td>
</tr>
<tr>
<td>• Identifying barriers to engage physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Setting goals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recruiting social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sign a health contract to support patients in initiating and maintaining physical activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• A logbook to describe and monitor the specific goals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical therapist</th>
<th>Physical therapist</th>
</tr>
</thead>
<tbody>
<tr>
<td>who treat the patient in order to obtain the aims of the individual projected treatment plan</td>
<td>who treat the patient in order to obtain the aims of the individual projected treatment plan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal Activity Coach</th>
<th>Goal setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>who guide patients towards a more active lifestyle</td>
<td>creating goals to increase the level of physical activity in order to obtain the half-year-goals as formulated in the health contract</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ambulatory Activity Monitor</th>
<th>Bi-annual newsletter</th>
</tr>
</thead>
<tbody>
<tr>
<td>gives visual feedback about the level of physical activity during the day</td>
<td>specific information about physical activity, general information about Parkinson’s disease, and general entertainment in order to facilitate compliance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bi-annual newsletter</th>
<th>Bi-annual newsletter</th>
</tr>
</thead>
<tbody>
<tr>
<td>specific information about physical activity, general information about Parkinson’s disease, and general entertainment in order to facilitate compliance</td>
<td>specific information about physical activity, general information about Parkinson’s disease, and general entertainment in order to facilitate compliance</td>
</tr>
</tbody>
</table>
**ParkFit Program**

Widely used behavioral change techniques, with demonstrated effectiveness\(^{21,28}\) and based on models of behavioral change\(^{23,24}\), are combined in the ParkFit Program to stimulate patients to increase their physical activity levels.

1) **Brochure ParkFit**

Patients receive a brochure covering specific strategies to promote a behavioral change. These strategies include: education about the benefits of physical activity, advice about suitable activities, identifying and overcoming any perceived barriers to engage in physical activity, setting goals, and recruiting social support.\(^{23,25,26}\) Part of the educational workbook is a health contract: a written agreement signed by the patient and physiotherapist to support them in initiating and maintaining physical activities.\(^{41}\) A logbook monitors the specific goals.

2) **Personal Activity Coach**

Physiotherapists serve as personal activity coaches who guide patients towards a more active lifestyle, during specific coaching sessions. Their task is to educate patients about the beneficial effects of physical activity. Patients are additionally stimulated to participate in group exercise to experience the beneficial effects of physical activity and to receive social support from fellow patients.\(^{31}\) For safety reasons, all patients are encouraged to receive a preventive sports medical screening.

3) **Goal setting**

Patient and coach create activity goals in order to obtain the 6-month-goals (as formulated in the health contract). Goals have to be realistic, concrete and individualized and have to be formulated in a systematic way, based on behavioral change theories.\(^{41}\)

4) **Ambulatory Activity Monitor with visual feedback**

Patients receive a personal ambulatory monitor with automated visual feedback showing the amount of actually delivered daily physical activity, recorded by a triaxial accelerometer.\(^{87,88}\) Additionally, a personalized website shows the activity history.\(^{87}\) Previous work showed that feedback from pedometers increases physical activity levels in COPD patients\(^{89}\), sedentary workers\(^{90}\), and patients with diabetes mellitus.\(^{21}\)

5) **Physiotherapy**

The ParkFit Program also includes a maximum of 19 physiotherapy sessions in year 1 and 23 in year 2. Based on individual disabilities, therapist and patient jointly formulate treatment aims based on the evidence-based guideline of physiotherapy for PD.\(^{21}\)

**ParkSafe Program**

The ParkSafe Program includes physiotherapy interventions from the physiotherapy guideline for PD\(^{11}\) to stimulate patients to move more safely, e.g. by improving the quality of transfers, but without explicit emphasis on reaching a physically active lifestyle.

1) **Brochure ParkSafe**

Patients receive a brochure with information about the benefits of physiotherapy.\(^{11}\) Specific emphasis is given to the importance of safety when performing daily activities.

2) **Physiotherapy**

Patients receive an individualized physiotherapy program. We maximized the total number of sessions at 35/year, to avoid large differences in number of treatment sessions between the two arms (patients in the ParkFit arm receive 35 annual sessions: 19 physiotherapy plus 16 coach sessions). 35 sessions is considered sufficient for patients in Hoehn and Yahr stage ≤3. Physiotherapist and patient jointly formulate the aims of the projected treatment plan, based on individual problems and disabilities. The aims of the physiotherapy sessions in both treatment arms are derived from the guideline for physiotherapy in PD.

**IMPLEMENTATION**

**Training for physiotherapists**

All participating physiotherapists were specifically trained to treat patients in both treatment arms and informed about the aim of the study. Special attention was given to models of behavioral change,\(^{23,24}\) to specific strategies of coaching sedentary patients,\(^{26,92}\) and to the technique of setting realistic, concrete and individualized goals.\(^{41}\) Throughout the trial, therapists continuously register the individual treatment sessions.

**OUTCOME MEASURES**

**Baseline characteristics**

Blood pressure, height, body weight, education and employment are assessed at baseline as well as alcohol use, smoking history and lifetime physical activity.\(^{11}\) Participants in the ParkFit Program also completed a questionnaire about attitude, social support and self-efficacy towards physical activity.

**Primary endpoint: level of physical activity**

Primary endpoint is the level of physical activity, as measured with a 7-day recall, based on an interview-based physical activity questionnaire, the LAPAQ.\(^{11}\) Patients are asked to list their daily amount of activity (frequency and duration), so total time spent on physical activity (in hours per day) will be calculated. A MET-value will be used to calculate the number of kilocalories spent per day per kilogram of body weight.\(^{14}\) The LAPAQ is completed during a face-to-face interview.
We assume that patients will increase their level of physical activity during the first months of intervention and then maintain this level. Therefore, main endpoint is the level of physical activity during the entire follow-up period (i.e. the mean of 6, 12, 18 and 24 months).

Secondary endpoints (Table 3.2)
Secondary measures include: (a) physical fitness, measured with the six minute walk test (6MWT); (b) quality of life, measured with the PDQ-39; and (c) level of physical activity in time and kilocalories per week, measured with the same tri-axial accelerometer that is used as feedback-tool in the ParkFit Program. The level of physical activity is additionally measured with a physical activity diary.

Additional measures
Patients who increased their amount of physical activity will be compared with patients unable to achieve this, to assess specific health consequences. Disease progression (UPDRS motor section, 9-hole peg board test), mobility (Timed Up and Go test), quality of sleep (SCOPA-sleep), anxiety and depression (HADS), fatigue (Fatigue Severity Scale), and cognitive functioning (Table 2 for test battery) are assessed. Additionally, physical fitness is measured with the Åstrand-Ryhming test. Bone mineral density (dual energy X-ray absorptiometry, DXA) is determined in a subgroup of 300 patients. PD medication and medical costs (combined with the EQ-5D) are assessed, as well as the number of falls (as an index of safety). Patients are asked whether their falls occurred during exercise and about the consequences of falls (e.g. injuries). Information about other adverse events is collected systematically at each physical assessment.

Blinding
To avoid bias due to more positive expectations of patients towards the outcomes of the ParkFit Program, patients were initially informed about the fact that there are two intervention groups, each with a beneficial intervention. To ensure blinding during assessments, patients are assessed by trained assessors who are unaware of group allocation. Patients are explicitly asked to not share their experiences with the program during the assessments.

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 15% (with coefficient of variation of 110%) between both treatment arms, the study 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 0.85). This is also the power when the correlations are at least 0.60 and at most

### Table 3.2
AN OVERVIEW OF PATIENT ASSESSMENTS

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Visit &amp; Questionnaires</th>
<th>6 months Visit &amp; Questionnaires</th>
<th>12 months Visit &amp; Questionnaires</th>
<th>18 months Visit &amp; Questionnaires</th>
<th>24 months Visit &amp; Questionnaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Activity</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LAPAQ</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Activity Monitor</td>
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<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Activity Diary</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Physical Fitness</td>
<td></td>
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<tr>
<td>6 MWT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Åstrand-Ryhming test</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>PDQ-39</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Health Effects</td>
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<tr>
<td>UPDRS III</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Nine hole peg board test</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Timed up and go test</td>
<td>x</td>
<td>x</td>
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<tr>
<td>DXA</td>
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<td>SCOPA-sleep</td>
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<td>HADS</td>
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<tr>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td>Cognitive testing battery*</td>
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<td>PD medication</td>
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<td>Medical costs &amp; EQ-5D</td>
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<tr>
<td>Number of falls (monthly)</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td>Determinants</td>
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<td>Blood pressure</td>
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<tr>
<td>Height</td>
<td>x</td>
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<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>x</td>
<td></td>
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<tr>
<td>Education</td>
<td></td>
<td></td>
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<td>Employment</td>
<td></td>
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<tr>
<td>Alcohol use</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Smoking</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Lifetime physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attitude, SS &amp; SE**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Including tests for spatial working memory, intra- and extra-dimensional shift performance, paired associate learning performance, phonemic and semantic word fluency, and complex figure drawing

** Only patients in the ParkFit Program
0.95, respectively. The power is based on two-sided 95% confidence intervals. We assumed that patients would take part in exercise groups with on average eight participants and that the corresponding ICC would be 0.1. Based on a previous trial of physiotherapy for PD involving the national ParkinsonNet networks\(^1\), we expect a drop-out rate of 10%.

Randomization
A minimization algorithm is used to randomize patients, with the factors region, Hoehn & Yahr stage, age, gender and current level of physical activity.

Statistical analyses
All participants who really started with their program, will be included in the primary analysis. The results after 6, 12, 18 and 24 months will be evaluated using a linear mixed model with random nested factors ‘patient’ and ‘exercise group’. Fixed factors will be treatment arm, LAPAQ score at baseline, month, month*treatment (interaction), and the factors region, H&Y stage, age, gender and bone density assessment. In an additional analysis, the influence of H&Y stage, age, gender and level of previous sports activities on the success of the treatment will be evaluated by including the interaction terms between treatment and each of these variables in the model. Multiple imputation analyses will be used to evaluate the impact of missing values on the outcome. Throughout, 95% confidence intervals will be calculated.

RESULTS
INCLUSION PROCEDURE
Selection of patients ran from September 2008 to January 2010. A total number of 4479 patients received a screening questionnaire; 587 (13.1%) did not respond, 439 (9.8%) were excluded because there was doubt about the diagnosis (Figure 3.2). After invitation for participation, 1766 patients were excluded based on our exclusion criteria, and 1101 eligible patients were excluded because they were not willing to participate. Finally, 586 patients signed informed consent. The number of enrolled patients is less than the power calculation required. However, the power remains over 80% because only 60% of patients participates in exercise groups with an average group size of only three, whereas our power calculation assumed that all patients would participate in exercise in groups of eight patients.

BASELINE CHARACTERISTICS
The most relevant baseline characteristics of included patients are presented in Table 3.3 and compared with the characteristics of the complete cohort of PD patients and the cohort of patients who were eligible but not willing to participate. Study participants were younger, had a shorter disease duration and were less sedentary compared with eligible patients not willing to participate.

**FIGURE 3.2**
FLOW CHART OF THE INCLUSION PROCEDURE

Legend: * No Parkinson’s disease = patient is diagnosed with parkinsonism or patient declared to have no gratifying and sustained response to dopaminergic therapy; ** 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.
Several lines of evidence suggest that regular participation in physical activity could be important for patients with PD. The ParkFit trial was designed to evaluate a multifaceted program to achieve an enduring increase in physical activity in PD patients. The intervention is based on accepted motivational and behavioral change models, which will now be employed for the first time in PD.

We carefully monitored the characteristics of all invited patients as well as eligible patients who were not willing to participate. The results demonstrate that among all PD patients who were invited, 64% indeed had a sedentary lifestyle. The results further demonstrate that eligible PD patients not willing to participate were on average somewhat more sedentary in comparison with the participants of the study. Should our study shows a beneficial effect of the ParkFit behavioral change program, efforts must be made to also reach out to this subgroup of sedentary patients. A critical issue in rehabilitation studies is the choice for an appropriate control condition, and we have selected a program that emphasized safety of movement (according to evidence-based guidelines), rather than the quantity of movements. Both intervention programs are matched for intensity, and are delivered by the same therapists. We have taken several measures to avoid bias between both treatment arms, rendering both groups comparable except for the focus on physical activities. Because the same therapists participate in both programs, differences in their personalities should not differ between the two treatment arms. A possible drawback is contamination. Furthermore, personal preference for a specific program can possibly introduce variation between therapists. We strive to avoid this by: (1) specific training, informing all therapists about the aim of the study and the do’s and don’ts in both treatment arms. They have signed a contract and agreed to keep both programs separate. (2) The tools used in ParkFit are not freely available. Since all patients receive their own Activity Monitor and brochure, therapists cannot give these tools to patients allocated to ParkSafe. (3) During the trial, therapists are being visited and observed during one or more sessions. A standardized checklist of prescribed interventions will be completed to investigate if contamination is at play. (4) Each therapist will be interviewed, between 3 to 6 months after start of the program. The aim is to investigate how therapists put the program into practice, and to re-emphasize the do’s and don’ts of both programs. (5) About every two months, the research team contacts each therapist to ask them about their individual aims in both treatment arms. Again, it is emphasized that coaching towards a more physically active lifestyle is not allowed in ParkSafe. (6) Yearly, a ‘booster’ session is planned for therapists to discuss possible problems and to re-emphasize the do’s and don’ts.

A strong element of the ParkFit trial is the availability of our national ParkinsonNet networks, which allows us to administer the interventions in both treatment arms by therapists with documented experience in treating PD patients. The ParkFit trial is one of the largest and longest lifestyle intervention trials in PD, and is the first one to focus on behavioral change as an intermediate to achieve a sustained increase in physical activity levels.

The endpoints of this trial cover several complementary domains. A prerequisite is that patients will actually increase their physical activity levels. To document this, we have selected the time spent on physical activities per week as primary endpoint. We choose the LAPAQ as primary outcome measure instead of the Activity Monitor because a questionnaire covers a wider range of activities. We also want to see whether physical activity affords any symptomatic relief of PD. To this end we have included a battery of additional endpoints (including quality of life) that measure possible health benefits for patients. Safety is also an issue, because physical activity may theoretically predispose patients to falls. Therefore, this will also be documented in this study. Furthermore, costs will be recorded, although we have no specific a priori reason to expect drastic increases or reductions in costs associated with the interventions of this trial.

### Table 3.3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete cohort of PD patients</th>
<th>Eligible patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not willing to participate</td>
<td>Willing to participate</td>
</tr>
<tr>
<td>N</td>
<td>3453</td>
<td>1101</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>59.0</td>
<td>53.4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.1 (7.2)</td>
<td>67.2 (7.1)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6.2 (5.7)</td>
<td>6.0 (6.6)</td>
</tr>
<tr>
<td>Ability to walk (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>814 (23.7)</td>
<td>232 (21.3)</td>
</tr>
<tr>
<td>Slow but independently</td>
<td>1747 (50.8)</td>
<td>556 (51.0)</td>
</tr>
<tr>
<td>Independently with walking aid</td>
<td>605 (17.6)</td>
<td>302 (27.7)</td>
</tr>
<tr>
<td>With help of someone</td>
<td>112 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Wheelchair bounded</td>
<td>158 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Level of physical activity (min/week)</td>
<td>144.8 (196.7)</td>
<td>40.1 (61.1)</td>
</tr>
</tbody>
</table>
In conclusion, the ParkFit trial is expected to yield important new knowledge about behavioral interventions for patients with PD to change their sedentary lifestyle. If the ParkFit Program shows good treatment compliance and beneficial symptomatic effects, future trials could identify which components of our multifaceted approach are most effective. In addition, positive results may have implications for different neurological disorders where beneficial effects of physical activity may be expected. The results of the ParkFit trial are scheduled for 2012.

ACKNOWLEDGEMENTS

This research is supported by grants from ZonMw, The Netherlands Organization for Health Research and Development (75020012), and the Michael J Fox Foundation for Parkinson’s research. Furthermore, health insurer VGZ financially supported the ParkFit study. Professor Bastiaan R. Bloem was supported by a NWO VIDI grant (016.076.352).

We would like to thank the local coordinators of the participating general hospitals:
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 (Eilkeriek 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); E. Berger (‘t Lange Land Ziekenhuis en Medisch Centrum Haaglanden); A.G.G.C. Korten (Laurentius Ziekenhuis); M. Westerink (Maastad Ziekenhuis); M. Aramideh (Medisch Centrum Alkmaar); R. Rundervoort (Medisch Centrum Haaglanden); F.A. Rooy (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. Labooyre (Tergooiziekenhuizen); F.J.W. Opstelten (VieCuri Medisch Centrum); A.M.G. Sas (Westfriesgasthuis); P.J. Nederveen (Westfriesgasthuis); J. Lion (Ziekenhuis Bernhoven); and C. Jansen (Ziekenhuis Gelderse Vallei) for their participation in the ParkFit study group.

Furthermore, we would like to thank J.W. Custers and P.J. van der Wees (Royal Dutch Society for Physiotherapy), S.I. Detaille and V. Peters (Seneca, Expertise Centre for Sport, Work and Health, HAN University of Applied Sciences), M.T. Hopman (Department of Physiology, Radboud University Nijmegen Medical Centre), M.W.A. Jongert (TNO Netherlands Organization for Applied Scientific Research), Y.P.T. Kamsma (University Medical Center Groningen), S.H.J. Keus (Departments of Physiotherapy and Neurology, Leiden University Medical Centre; Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Centre), G. Kwakkel (VU University Medical Center), H. Leutscher (Disability Sports Netherlands), W. Oerlemans (HAN University of Applied Sciences), C.J.M. van Santen (Society of Exercise Therapists Cesar and Mensendieck), N.H.M.J. van Velthoven (Netherlands Olympic Committee * Netherlands Sports Federation), A.M.J. van de Wert (Netherlands Institute for Sport en Physical Activity), and T. Wolff (Parkinson Vereniging) for their participation in the ParkFit advisory board.
CHAPTER 04
MULTIVARIABLE ANALYSES OFTEN HAVE MULTIPLE SOLUTIONS, ALL OF WHICH SHOULD BE REPORTED

SUBMITTED
Marlies van Nimwegen, Arlène D Speelman, and George F Borm
ABSTRACT

BACKGROUND

When variable selection methods are used to determine the factors that are associated with an outcome, the selected model may not be unique. In general, as the number of factors increases, the number of models that fit the data also increases. To illustrate this, we describe a study that seeks to identify factors associated with the level of physical activity in patients with Parkinson’s disease (PD).

METHODS

This example was based on a fairly large data set of 699 patients. Multivariable linear regression was used to evaluate the relationship between patients’ physical activity level and a number of individual and disease-related factors. To evaluate to what extent the model was unique, we calculated the percentage explained variance ($R^2$) of all possible models.

RESULTS

The forward selection method resulted in a model with four variables ($R^2=22%$); the model with all fourteen variables explained 24% of the variance. We identified ten models, each with four variables, that each explained 21% of the variance; numerous other models had only a slightly lower $R^2$. In addition, the best-fitting model with three variables also had an explained variance of 21%.

CONCLUSION

Several models seem appropriate to describe the relationship between the independent factors and the physical activity level in PD. We propose that all models with approximately the same fit should be reported in addition to the final model that results from the variable selection procedure. Such an approach would show the uncertainty of the results of the model selection in the same way that confidence intervals present the uncertainty of a quantitative outcome. Presenting all models makes it possible to evaluate the extent to which the best-fitting models overlap and aids in comparing and pooling the results of different studies. This approach depicts the uncertainty of the results and avoids unnecessary discussions when investigators find other models.

INTRODUCTION

Variable selection methods are frequently used to generate a multivariable model to determine which factors may predict or influence a certain disease or a specific outcome. However, the final model may include variables that should not have been selected, whereas other important variables may have been inappropriately excluded. Moreover, several additional models may fit the data almost as well as the selected model, suggesting that the selected model is not unique. Several reasons may explain this uncertainty.

First, the final selected model depends on the statistical variable selection procedure. For example, a model obtained through forward selection may differ from a model obtained through backward selection or stepwise selection; additional selection methods may lead to other models. Additionally, the final selected model depends on inclusion or exclusion criteria. Therefore, even when the same selection method is used, the final selection models may vary. For example, using forward selection, a model generated using an inclusion criterion of $p<0.05$ will be different from a model generated using an exclusion criterion of $p<0.01$. Moreover, as larger data sets tend to lead to models with more variables, the size of the data set also influences the final model.

Even when exactly the same methods and criteria are used, the reproducibility of the results may still be of concern. This possibility may be in part due to differences between data sets, but also to the nature of multivariable data. When the independent variables are either strongly associated with the outcome or are not associated with the outcome, selecting a model may be straightforward. However, there may also be variables that are weakly associated with the outcome. Therefore, it may be impossible to make an unambiguous distinction between variables with a true or spurious association with the outcome. In addition, because several variables may measure the same or overlapping constructs, it may be difficult to make a selection. Consequently, a unique model may be practically impossible to identify.

Good statistical practice requires a measure of the precision or reliability of the statistical analysis to be reported. For that purpose, p-values and confidence intervals are reported, showing a range of results that are compatible with the data. In this study, we suggest a similar approach for the selection of multivariable models. We propose that reports should investigate whether the result of the selection procedure is unique, or if other models lead to approximately the same fit. In the latter case, the additional models should also be presented. This approach demonstrates the reliability of the model selection procedure.

To illustrate this approach, we describe a study that seeks to identify factors associated with the level of physical activity in patients with Parkinson’s disease (PD).
PD is a progressive neurological disease. Although medical treatment substantially improves patients’ quality of life and functional capacity, PD remains an incurable disease. Recent studies using rodent models have shown that exercise may have a beneficial effect in the management of PD. However, patients with PD are heavily inclined toward a sedentary lifestyle. Consequently, it is a challenge to encourage patients to become more active. Information pertaining to the patients’ physical activity level is needed to develop appropriate ‘exercise advice’. Data were derived from the ParkinsonNet trial, a randomized trial evaluating the impact of community-based networks of professional physiotherapists (ParkinsonNet) on healthcare costs and health outcomes. The trial has been approved by the appropriate ethics committee and all persons gave their informed consent prior to inclusion in the study.

Multivariable linear regression was used to evaluate the relationship between patients’ physical activity level and a number of individual and disease-related factors. Physical activity was measured using an interview-based questionnaire, specifically, the LASA Physical Activity Questionnaire (LAPAQ). The independent variables included gender, age, education level, marital status, disease severity (Hoehn and Yahr [H&Y]), and the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS), cognitive function (mini mental state examination [MMSE]), fear of falling (Falls Efficacy Scale-International [FES]), anxiety and depression (Hospital Anxiety and Depression Scale [HADS]), mobility (Timed Up and Go Test [TUG]), freezing of gait (Freezing of Gait Questionnaire [FOGQ]), disability in daily life (Self-Assessment Parkinson’s Disease Disability Scale [SPDDS]), co-morbidity (Cumulative Illness Rating Scale [CIRS]), and ‘faller status’ (≥ 1 fall in the preceding year versus no fall).

A two-sided p-value ≤ 0.01 was used as a threshold for inclusion in the model. We choose p ≤ 0.01 because the data set was rather large (699 patients). Therefore, even an irrelevant variable could result in statistical significance. For example, in univariate analyses, variables reaching significance at p ≤ 0.05 were found, even when the percentage of explained variance (R²) was only 1%. In addition, many variables were statistically tested for inclusion in the model; therefore, an adjustment of the significance level, for example a Bonferroni correction, could be appropriate. To the best of our knowledge, no guidelines exist describing how or whether to carry out such an adjustment. A small p-value may be appropriate when one is interested in excluding irrelevant variables at the cost of missing some variables that are only weakly associated with the outcome. When one wants to capture all potential variables at the cost of capturing spurious associations, a larger p-value may be appropriate.

To evaluate to what extent the model was unique, we carried out the all subset selection method, i.e. we calculated the percentage explained variance (R²) of all possible models. In this way, we identified all models with an R² similar to the R² of the model obtained from the forward selection procedure.

Methods

The forward selection method resulted in a model with four variables: gender, co-morbidity, mobility, and disability in daily life. This model explained 22% of the variance. Although this R² value indicated a poor fit, additional variables were unlikely to contribute to a better fit because the model with all fourteen variables explained only 24% of the variance.

To identify models with a comparable fit, we calculated the percentage explained variance (R²) of all other possible models. Table 4.1 shows a selection of these results. The second column in the table lists the variables in the models. The third column shows the accompanying R². We identified ten models, each with four variables, that each explained 21% of the variance; numerous other models had only a slightly lower R². In addition, the best-fitting model with three variables (gender, mobility, and disability in daily life) also had an explained variance of 21%. Because a difference of 1% is well within the error margin of the R² (the standard error of R² is approximately 2.5%), there is no evidence that the models with 22% explained variance are better compared to the models with an R² of 21%. As a result, several models seem appropriate to describe the relationship between the independent factors and the physical activity level.

Table 4.2 shows the details of the best fitting models. The coefficients of the variables are quite similar across models, suggesting that the results are stable and robust. Regression models become particularly unstable when the number of variables in the model is high (‘overfitting’), or when multicollinearity is present. Because the number of variables included in the analysis was limited compared to the number of observations, overfitting may not be an issue. In addition, the variance inflation factors were all less than 2.6, meaning that there was no indication of multicollinearity.

As some of the independent variables had a correlation of greater than 0.5 and may measure overlapping constructs, we repeated the analysis with only seven variables: gender, age, educational level, marital status, UPDRS, MMSE and CIRS. These variables measure different constructs and all have correlations of less than 0.25. The full model with these seven variables had an R² of 15%. Forward selection led to a model with four variables, including gender, age, UPDRS and CIRS, and had an R² of 13%. In addition, several models had an R² greater than 12%, including one model with three variables and four models with four variables (results not shown).
### Table 4.1
PERCENTAGE OF EXPLAINED VARIANCE ($R^2$) OF A SELECTION OF MODELS

<table>
<thead>
<tr>
<th>Nr of variables</th>
<th>Variables in the model</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SPDDS</td>
<td>0.12</td>
</tr>
<tr>
<td>2</td>
<td>Gender, SPDDS</td>
<td>0.17</td>
</tr>
<tr>
<td>3</td>
<td>Gender, TUG, SPDDS</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Gender, CIRS, SPDDS</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Gender, Age, SPDDS</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Gender, CIRS, TUG</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Gender, TUG, FES</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Gender, H&amp;S, SPDDS</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Gender, Mental Status, SPDDS</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Gender, FES, SPDDS</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Gender, TUG, FES</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Gender, TUG, SPDDS</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Gender, Education, SPDDS</td>
<td>0.17</td>
</tr>
<tr>
<td>4</td>
<td>Gender, CIRS, TUG, SPDDS</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Gender, TUG, FOGQ, SPDDS</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Gender, Age, TUG, SPDDS</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Gender, Education, TUG, SPDDS</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Gender, Mental Status, TUG, SPDDS</td>
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</tr>
<tr>
<td></td>
<td>Gender, HADS, TUG, SPDDS</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Gender, H&amp;S, TUG, SPDDS</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Gender, TUG, Faller, SPDDS</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Gender, CIRS, TUG, SPDDS</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Gender, TUG, FES, SPDDS</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Gender, Age, CIRS, SPDDS</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Gender, CIRS, FES</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Gender, H&amp;S, CIRS, SPDDS</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>Gender, CIRS, TUG, FOGQ, SPDDS</td>
<td>0.22</td>
</tr>
<tr>
<td>6</td>
<td>Gender, Age, CIRS, TUG, FOGQ, SPDDS</td>
<td>0.23</td>
</tr>
<tr>
<td>14</td>
<td>Gender, Age, Mental Status, Education, H&amp;S, UPDRS, CIRS, MMSE, HADS, TUG, FOGQ, Faller, FES, SPDDS</td>
<td>0.24</td>
</tr>
</tbody>
</table>

SPDDS = Self-Assessment Parkinson’s Disease Disability Scale; TUG = Timed Up and Go Test; CIRS = Cumulative Illness Rating Scale; FES = Falls Efficacy Scale-International; H&S = disease severity; UPDRS = Unified Parkinson’s Disease Rating Scale (motor section); FOGQ = Freezing of Gait Questionnaire; MMSE = Mini Mental State Examination; Faller = ≥1 fall in the preceding year versus no fall; HADS = Hospital Anxiety and Depression Scale.

### Table 4.2
DETAILS OF SOME OF THE BEST-FITTING MODELS THAT DESCRIBE THE LEVEL OF PHYSICAL ACTIVITY

<table>
<thead>
<tr>
<th>$R^2$</th>
<th>Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21</td>
<td>8.6+0.71<em>Gender -0.078 * TUG -1.2</em>SPDDS</td>
</tr>
<tr>
<td>0.19</td>
<td>9.9+0.67<em>Gender -0.23</em>CIRS -1.6*SPDDS</td>
</tr>
<tr>
<td></td>
<td>11.3+0.65<em>Gender -0.024</em>Age -1.6*SPDDS</td>
</tr>
</tbody>
</table>

Models with four variables

<table>
<thead>
<tr>
<th>$R^2$</th>
<th>Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.22</td>
<td>8.5+0.74<em>Gender -0.20</em>CIRS -0.073<em>TUG -1.1</em>SPDDS</td>
</tr>
<tr>
<td>0.21</td>
<td>9.5+0.73<em>Gender -0.083 * TUG +0.16</em>FOGQ -1.5*SPDDS</td>
</tr>
<tr>
<td></td>
<td>9.6+0.71<em>Gender -0.016 * Age -0.66</em>TUG -1.2*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.9+0.68<em>Gender -0.097 * Education -0.080</em>TUG -1.2*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.3+0.75<em>Gender -0.18 * Mental Status -0.075</em>TUG -1.2*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.8+0.70<em>Gender -0.092 * HADS -0.078</em>TUG -1.3*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.6+0.71<em>Gender -0.099 * H&amp;S -0.072</em>TUG -1.1*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.4+0.71<em>Gender -0.077 * TUG -0.079</em>Faller -1.1*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.2+0.70<em>Gender -0.015 * MMSE -0.078</em>TUG -1.2*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.6+0.70<em>Gender -0.003 * UPDRS -0.073</em>TUG -1.1*SPDDS</td>
</tr>
<tr>
<td></td>
<td>8.7+0.72<em>Gender -0.075 * TUG -0.12</em>FES -1.1*SPDDS</td>
</tr>
</tbody>
</table>

TUG = Timed Up and Go Test; SPDDS = Self-Assessment Parkinson’s Disease Disability Scale; CIRS = Cumulative Illness Rating Scale; FOGQ = Freezing of Gait Questionnaire; HADS = Hospital Anxiety and Depression Scale; H&S = disease severity; Faller = ≥1 fall in the preceding year versus no fall; MMSE = Mini Mental State Examination; UPDRS = Unified Parkinson’s Disease Rating Scale (motor section); FES = Falls Efficacy Scale-International.
DISCUSSION

In the literature, it is well-documented that multivariable regression analysis may result in several models that fit the data equally well.\textsuperscript{102-114} We illustrated this with an example based on a fairly large data set of 699 patients. While we used forward selection, other methods, including backward selection and hierarchical selection, will lead to similar results.

As some of the fourteen variables measured overlapping constructs, for example H&Y and UPDRS that both measure the severity of the disease, we repeated the analysis with seven independent variables that mostly measure different constructs. However, this approach did not lead to a unique model either.

Apart from manually preselecting the variables that are included in the model selection procedure, also statistical methods can be used, for example principal components analysis. However, whatever method is used to reduce the number of variables prior to the model selection, the results are often not unique and other variables or combination could have been chosen as well. Moreover, an elaborate search leading to an apparently unique solution may be misleading and appear to be a ‘fishing expedition’ for statistically pleasing results. The results of such an approach may even be less reliable than the results of a more straightforward approach.

The purpose of our paper was neither to determine if multivariate regression leads to multiple solutions nor to show the best approach for variable selection. We wanted to illustrate that one model should not be solely reported as ‘the’ solution. When an analysis leads to multiple solutions, we propose that all models with approximately the same fit be reported. Therefore, we kept the analysis straightforward in this example. We presented an example of linear regression and used $R^2$ as a criterion to select alternative models. In the case of logistic regression, a similar approach could be used with the Nagelkerke $R^2$ or the $c$ statistic as a criterion for model fit. The latter may be particularly useful when the aim of the study is to develop a diagnostic decision rule because the $c$ statistic is equal to the area under the ROC curve.

We propose that when variable selection is used to generate a multivariable regression model, the model should be analyzed to determine if it is unique and unambiguous. Additional models that fit the data equally well should be reported. Our proposal is based on two arguments. First, a statistical analysis requires an estimate of its precision and reliability. For example, when an analysis estimates the difference between two means, one cannot conclude that this estimated value is exactly the ‘true’ difference. Therefore, it is advisable to report a confidence interval. Confidence intervals contain all values for the difference that fit the data, one of those values is probably the ‘true’ value. When comparing two means, a 95% confidence interval may be reported with a half width of approximately two times the standard error. Similarly, when the aim of an analysis is to obtain a multivariable model, not only a single result, but a range of models that fit the data should be reported. When the difference between two means is evaluated, a 95% confidence interval may be reported, with a half width of approximately two times the standard error. For multivariable models, the range of alternative models that should be presented is less obvious. In cases of linear regression, all models that have an $R^2$ within two standard errors from the $R^2$ of the best-fitting model could be reported. However, in our example, this approach would lead to 16 models with three variables and over 100 models with four variables. A stricter criterion that reports models with an $R^2$ within one standard error would still lead to two models with three variables and approximately 40 models with four variables. In our analysis that utilized seven variables, 14 models with three variables and 27 models with four variables had an $R^2$ that was within two standard errors of the $R^2$ of the best model. Hence, it may not always be feasible or even useful to present such an extensive list. However, it may be of interest to present additional models as additional information on the Internet.

Our second argument for presenting all models with approximately the same fit is to improve systematic reviews. Presenting a range of results when no unique model is found may help when comparing and summarizing the results of different studies in systematic reviews. This strategy avoids unnecessary discussions about discrepancies between the results of studies, as a number of the models with a fit that is comparable to the best model may be similar across studies. The ranges of well-fitting models for studies presented in a systematic review could be compared in the same way as confidence intervals are compared in forest plots.

In summary, several models seem appropriate to describe the relationship between the independent factors and the physical activity level in patients with PD. We propose tables similar to Tables 4.1 and 4.2 to be included in the reports of multivariable analyses using variable selection methods. Such tables depict the uncertainty of results and avoid unnecessary discussions when other investigators find other models.

ACKNOWLEDGEMENTS

Part of this research was supported by ZonMw (The Netherlands Organization for Health Research and Development (75020012)) and The Michael J Fox Foundation for Parkinson’s research.
CHAPTER

QUANTIFYING DAILY PHYSICAL ACTIVITY AND DETERMINANTS IN SEDENTARY PATIENTS WITH PARKINSON’S DISEASE

SUBMITTED
Manon L Domtje, Mathieu H G de Greef, Arlène D Speelman, Marlies van Nimwegen, Wim P Krijnen, Ronald P Stolk, Yvo P T Kamsma, Bastiaan R Bloem, Marten Munneke, and Cees P van der Schans
ABSTRACT

BACKGROUND
Although physical activity is beneficial for Parkinson’s disease patients, many do not meet the recommended levels. The range of physical activity among sedentary PD patients is unknown, as are factors that determine this variability. Hence, we aimed to (1) assess daily physical activity in self-identified sedentary PD patients; (2) compare this with criteria of a daily physical activity guideline; and (3) identify determinants of daily physical activity.

METHODS
Daily physical activity of 586 self-identified sedentary PD patients in the ParkFit study was measured with a tri-axial accelerometer for seven consecutive days. Physical fitness and demographic, disease-specific, and psychological characteristics were assessed. Daily physical activity was compared with the 30-minute activity guideline. A linear mixed-effects model was estimated to identify determinants of daily physical activity.

RESULTS
Accelerometer data of 467 patients who fulfilled all criteria revealed that >98% of their day was spent on sedentary to light-intensity activities. Eighty-two percent of the participants were ‘physically inactive’ (0 days/week of 30-minute activity); 17% were ‘semi-active’ (1-4 days/week of 30-minute activity). Age, gender, physical fitness, and scores on the Unified Parkinson’s Disease Rating Scale explained 69% of the variability in daily physical activity.

CONCLUSION
Performance-based measurements confirmed that most self-identified sedentary PD patients are ‘physically inactive’. However, the variance in daily physical activity across subjects was considerable. Higher age, being female, and lower physical capacity were the most important determinants of reduced daily physical activity. Future therapeutic interventions should aim to improve daily physical activity in these high-risk patients, focusing specifically on modifiable risk factors.

INTRODUCTION
Physical activity, which includes exercise as well as daily physical activities,23 is important for patients with Parkinson’s disease. Although physical activity will not cure the disease, it may positively affect functional capacity, physical fitness, health, and several dimensions of quality of life. Recommendations state that PD patients should perform at least 30 minutes of physical activity (≥ moderate intensity) per day (in bouts of minimal 10 minutes). This should be done for at least five days per week.10

Research suggests that many PD patients do not meet this recommendation.15, 21, 115, 122, 125 However, it is not clear how far the actual daily physical activity of patients is below the recommended level, what the range in physical activity is across patients, and which factors determine differences in daily physical activity across patients. This is important to know, because it could have implications for the way physical activity levels can be enhanced.

A number of related factors have been suggested in the literature to account for differences, including disease-related features,21, 115 demographics, psychological characteristics and physical fitness. 32, 115, 124, 125

However, it remains unknown how these factors specifically contribute to the variability in daily physical activity among PD patients who do not meet the recommended level of physical activity. PD patients below the recommended level of daily physical activity were included in the ParkFit study, a randomized controlled trial that examined the effects of a multifaceted behavioral program on physical activity behavior.22 This screening was initially done with a specifically developed questionnaire. Subsequently, actual daily physical activity was quantified with an accelerometer. Compared to questionnaires, such performance-based measurements can provide more accurate and detailed information about the diversity, duration, and intensity of physical activities during the day.

The primary aim of this study was to produce for the first time a performance-based description of daily physical activity in self-identified sedentary PD patients. Second, by comparing these results with criteria of the daily physical activity guideline,21 we examined whether these patients were really ‘physically inactive’ (in the sense of failing to meet the recommended level of physical activity once a week) or ‘semi-active’ (in the sense of meeting the recommended level of physical activity one to four days per week).21 Third, we aimed to identify determinants of daily physical activity in these patients.

METHODS

STUDY DESIGN
All subjects in the present study are participants in the ParkFit trial,42 and their baseline data were used here. The ParkFit trial is a multicenter, randomized controlled trial whose aim is to increase physical activity levels in sedentary PD patients.22 The study complied with principles outlined in the Declaration of Helsinki and was approved by the local ethics committee. All participants gave their written informed consent.
STUDY SAMPLE

The ParkFit trial recruited patients from 32 community hospitals between September 2008 and January 2010. All of these patients had received chronic care from a neurologist. Patients were included if they were diagnosed with idiopathic PD, were rated with a Hoehn and Yahr (HY) stage ≤3,24 and were between 40 and 75 years of age. Also, to be included candidate subjects had to report that they do not meet the recommended level of daily physical activity (i.e., moderate-intensity physical activity for >150 minutes per >3 times/week or vigorous-intensity physical activity for >60 minutes for >3 times/week). Included PD patients are referred to throughout this study as being ‘self-identified sedentary’ to make it clear that their initial status was determined by perceived daily physical activity, not objectively measured activity. Exclusion criteria concerned marked cognitive impairment (Mini-Mental State Examination [MMSE] score of <24),19 inability to complete Dutch questionnaires, severe comorbidities that interfered with daily functioning, receiving daily institutionalized care, and previously deep brain surgery.

MEASUREMENTS

Demographic and disease-specific characteristics

Demographic and disease-specific characteristics were assessed with self-report questionnaires and by trained assessors. The modified HY scale,30 and the motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS)31,32 were used to assess the severity of the disease. Cognition was measured with the MMSE.127

Daily physical activity

Daily physical activity was performance-based measured with a tri-axial accelerometer for movement registration (TracmorD, Philips New Wellness Solutions, Lifestyle Incubator, The Netherlands). This small device can be worn as a necklace, attached to a belt, or in a pocket. It converts activity counts via algorithms into energy expenditure in kcal per minute. It is a valid device for predicting energy expenditure in daily life, with correlations with the doubly labeled water technique ranging from .54 to .91.88 128 127 Although the accelerometer was not specifically validated for PD patients, no extensive problems with validity in this specific population were expected. No unambiguous evidence exists to indicate that patients expend more energy than healthy subjects to achieve the same movements, or that patients’ resting energy is elevated.46 130 Several literature-based decisions were made with regard to preprocessing the accelerometer data.131 Patients were asked to wear the accelerometer every day for a period of two weeks, a ‘day’ being 24 hours. ‘Non-wearing time’ was defined as a period of at least 60 consecutive minutes of zero’s, with a maximum of 2 minutes larger than 0.2 kcal.47 132 Subtracting non-wearing time from 24-hours resulted in the ‘wearing time’. To determine the minimal wearing time per day acceptable for a valid measurement, we used the ’70/80’ rule.67 131 132 A measurement was deemed valid if the patient wore the accelerometer for at least 80% of the ‘wearing day’. ‘Wearing day’ was defined as the length of time in which at least 70% of the subject sample was wearing the accelerometer. Only the last seven consecutive valid days were included for data analysis.

Daily physical activity was expressed as mean total energy expenditure per day (in kcal), which was calculated by dividing the sum of energy expenditure (in kcal) of the last seven consecutive valid days by seven for each participant. This consisted of sedentary to light-intensity activities (0-3.5 kcal/minute), moderate-intensity activities (3.5-7 kcal/minute), and vigorous-intensity activities (>7 kcal/minute) per day.124

Psychological characteristics

Depression and generic anxiety were measured with the Hospital Anxiety and Depression Scale (HADS).135 The scale consists of two subscales (depression and anxiety), which have seven items each. Scores on the subscales range from 0 to 21; higher scores indicate more symptoms. Only patients who were randomized to the intervention group (N=299) of the original ParkFit trial completed the Self-Efficacy for Exercise Scale (SEE),136 which assessed their self-efficacy toward physical activity. The SEE consists of nine items that rate the degree of confidence in performing regular physical activity across a range of circumstances (range: 0-10). A higher score indicates a higher level of exercise self-efficacy.

Physical fitness

Physical fitness was measured with the 6-minute walk test (6-MWT).127 138 This submaximal test measures the distance (in meters) a patient is able to walk for a period of 6 minutes.

DATA ANALYSIS

Descriptive statistics were used to characterize the participants and their daily physical activity outcomes. To calculate prevalence rates for physically active, semi-active and physically inactive patients,131 132 we collected data on the patients’ daily physical activity. The activity had to be (1) performed for at least 10 consecutive minutes, with allowable interruptions of maximally 2 minutes; and (2) either moderate intensity (3.5-7 kcal/minute) or vigorous intensity (> 7 kcal/minute).139 Patients were classified as ‘physically active’ if they were physically active for a minimum of 30 minutes/day (in bouts of ≥ 10 minutes), if the intensity of the activity was moderate or vigorous, and if they performed this activity for a minimum of 5 days/week. Patients were classified as ‘semi-active’ if they were moderately to vigorously active (30 min/day) for 1-4 days/week, and as ‘physically inactive’ if they were active for zero days/week. For exploratory reasons, we calculated prevalence rates based on the total number of minutes of moderate- to vigorous-intensity activities per day for ‘physically active’, ‘semi-active’ and ‘physically inactive’ patients. Average bout-length was assessed as well.
The first step for identifying determinants of daily physical activity was to calculate correlations (Spearman’s rho) between mean total energy expenditure and demographics, disease-specific characteristics, physical fitness and psychological characteristics. The second step was to analyze differences in mean total energy expenditure between men and women, HY stages, and education levels by using Mann-Whitney/Kruskall Wallis tests. The final step was to fit a linear mixed-effects model by using maximum likelihood. All analyses were performed in the statistical programming language R and SPSS (17.0); p-values of <0.05 were considered significant.

RESULTS

STUDY SAMPLE

Of the 3453 PD patients who were invited to participate in the ParkFit trial, 1766 were excluded. Of those excluded, 1263 did not qualify because they met or exceeded the physical activity guideline. Of the remaining 1687 eligible patients, 1101 were not willing to participate. In total 586 were randomized into the ParkFit trial. Of these, 119 patients (20%) were excluded from the present study based on accelerometry-data preprocess decisions (see Methods). In total, 467 patients (80%) had valid accelerometry measurements (≥659 minutes/day) on at least seven consecutive days. There were no significant differences in age (Mann-Whitney U=26388; p=0.40); gender (Chi²=1.44; p=0.23); body mass index (BMI) (Mann-Whitney U=27292; p=0.76); HY stage (Chi²=1.82; p=0.77); or disease duration (Mann-Whitney U=27186; p=0.72) between patients with insufficient (<7 valid days) and sufficient (≥7 valid days) accelerometer data. Patient characteristics of the study sample (N=467) are presented in Table 5.1.

DESCRIPTION OF PERFORMANCE-BASED DAILY PHYSICAL ACTIVITY

The median (IQR) time PD patients wore the accelerometer was 997 (234) minutes/day (16.6 hours/day). The median (IQR) of the mean total energy expenditure per day was 463.8 kcal (271.7). Figure 5.1 presents a histogram of the distribution of the mean total energy expenditure from the study sample as well as the estimated density for the total population. This figure shows a relatively large variance in daily physical activity within the sample of self-identified sedentary patients.

Continuous variables were not normally distributed, except for self-efficacy. ADL, Activities of Daily Living; BMI, Body Mass Index; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range, MMSE=Mini-Mental State Examination; SD, standard deviation; SEE, Self-Efficacy for Exercise Scale; UPDRS-III, Unified Parkinson’s Disease Rating Scale, motor part; 6-MWT, 6 Minute walk test.
Mean total energy expenditure was categorized according to the intensity of physical activity: sedentary to light, moderate, and vigorous intensity (Table 5.2). The median time spent on physical activities at a minimum of moderate intensity was approximately 12 minutes/day (≈1% of measured time). With regard to moderate- to vigorous-intensity physical activities, the median of the average bout length was 1.6 minutes. The median of the maximum bout length was 6 minutes. Sixty percent of the participants failed to achieve an activity session of at least 10 minutes.

**ACTUAL DAILY PHYSICAL ACTIVITY COMPARED TO THE PHYSICAL ACTIVITY GUIDELINE**

Eighty-two percent of the participants were classified as physically inactive, and 17.3% as semi-active (Table 5.2). Prevalence rates differed when it was based on the total number of minutes of moderate- to vigorous-intensity activity, rather than on the recommended 10-minute bouts of activity: 53.5% of the patients were categorized as physically inactive, 31.7% as semi-active, and 14.8% as physically active.
TABLE 5.3
CORRELATIONS WITH MEAN TOTAL ENERGY EXPENDITURE PER DAY

<table>
<thead>
<tr>
<th></th>
<th>Mean total energy expenditure per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spearman’s rho</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.34</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.11</td>
</tr>
<tr>
<td>UPDRS, motor function</td>
<td>-0.26</td>
</tr>
<tr>
<td>Time since diagnosis (months)</td>
<td>-0.03</td>
</tr>
<tr>
<td>Daily Levodopa equivalent dose (mg)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cognition (MMSE)</td>
<td>0.12</td>
</tr>
<tr>
<td>Anxiety (HADS-A)</td>
<td>0.08</td>
</tr>
<tr>
<td>Depression (HADS-D)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Self-efficacy (SEE)</td>
<td>0.08</td>
</tr>
<tr>
<td>Physical fitness (6-MWT)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

BMI, body mass index; UPDRS, Unified Parkinson’s Disease Rating Scale; MMSE, Mini-mental state examination; HADS, Hospital Anxiety and Depression Scale; SEE, Self-Efficacy for Exercise Scale; 6-MWT, 6-Minute walk test.

* Correlation is significant at the 0.05 level (two-tailed); ** Correlation is significant at the 0.01 level (two-tailed).

TABLE 5.4
LINEAR MIXED-EFFECTS MODEL*

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Value</th>
<th>SE</th>
<th>T</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>868.43</td>
<td>119.45</td>
<td>7.27</td>
<td>&lt; .001</td>
<td>634.39 - 1102.48</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-6.70</td>
<td>1.30</td>
<td>-5.17</td>
<td>&lt; .001</td>
<td>-9.26 - -4.15</td>
</tr>
<tr>
<td>Gender (0=male, 1=female)</td>
<td>-60.95</td>
<td>20.36</td>
<td>-2.99</td>
<td>.003</td>
<td>-100.93 - -20.98</td>
</tr>
<tr>
<td>Distance at 6-MWT (m)</td>
<td>-46</td>
<td>13</td>
<td>-3.61</td>
<td>&lt; .001</td>
<td>-71.7 - -20.70</td>
</tr>
<tr>
<td>UPDRS, motor function (0-108)</td>
<td>-2.32</td>
<td>.94</td>
<td>-2.47</td>
<td>.014</td>
<td>-4.16 - -0.47</td>
</tr>
<tr>
<td>Within group standard error</td>
<td>149.21</td>
<td></td>
<td></td>
<td></td>
<td>145.32 - 153.21</td>
</tr>
</tbody>
</table>

| Dependent variable was mean total energy expenditure in kcal/day. SE, Standard error; 6-MWT, 6-Minute walk test; UPDRS, Unified Parkinson’s Disease Rating Scale.

DETERMINANTS OF DAILY PHYSICAL ACTIVITY

As presented in Table 5.3, age, BMI, and the motor part of the UPDRS were negatively correlated to mean total energy expenditure (p<0.05). Cognition and physical fitness were positively correlated to mean total energy expenditure (p<0.01). Men (mean [SD] 541.9 [209.7] kcal/day) were more physically active than women (mean [SD] 447.6 [198.8] kcal/day) (Mann-Whitney U = 16825.0; p<.001). Patients with a spouse (mean [SD] 524.1 [213.4] kcal/day) were more physically active than those without a spouse (mean [SD] 429.3 [174.8] kcal/day) (Mann-Whitney U = 9441.0; p<.001). Patients with more severe PD (higher HY stage) were less physically active than patients with less severe PD (lower HY stage) (Chi²=12.4; p=.002).

To estimate a linear mixed-effects model for predicting mean total energy expenditure, we used variables that were significantly different in mean total energy expenditure (gender, spouse, HY) and variables that were significantly correlated to mean total energy expenditure (age, BMI, UPDRS, MMSE and distance on the 6MWT). The best model found according to minimum Akaike information criterion (AIC) had all coefficients significant, including age, gender, distance on the 6-MWT, and the motor part of the UPDRS (R²=0.69) (Figure 5.4).

DISCUSSION

The present study demonstrates that daily physical activity of self-identified sedentary PD patients varies widely, but the majority of their time is associated with sedentary to light-intensity physical activities. Using a performance-based assessment of daily physical activities, we report for the first time that most self-identified sedentary PD patients (82%) can indeed be classified as physically inactive and a smaller proportion (17%) as semi-active. Higher age, being female, more motor problems, and less physical fitness were the most important determinants of reduced daily physical activity.

Variability in daily physical activity is always present to a greater or lesser extent both in healthy adults and in chronically ill patients.139 Our results show that, even among a selected subcategory of self-identified sedentary PD patients, however, the variability in daily physical activity is still considerable. Although the majority (82%) failed to meet the daily recommended level of 30 minutes activity, even for one day per week, some (17%) did achieve the recommended level for one to four days per week. This suggests that even self-identified sedentary PD patients are capable of performing at least some physical activity. This is important new information for designing physical activity promotion programs for inactive PD patients. Even if these patients cannot meet the recommended level of physical activity, some activity is still considered to be better than none.140
The results of our study show that performing moderate-intensity activity for a minimum of 10 consecutive minutes was problematic for self-identified sedentary PD patients; the median length of their activity sessions was only 1.6 minutes. The majority (61%) of our participants failed to perform a single 10-minute session in a week. When data were collected on each minute of activity performed at a moderate to vigorous intensity, we found that more patients (46.5%) performed 30 minutes of activity per day than when data were collected on only 10-minute sessions of activity (18%). Further research should clarify whether 10-minute bouts (which are currently recommended) are really necessary to produce health effects in PD patients.

The present study showed that self-identified sedentary PD patients spent the largest part of their day engaging in sedentary to light-intensity physical activities (98.3%). This is in line with another study showing that patients with advanced PD were sedentary (lying/sitting) for 76.7% of the time. Also healthy adults and older people have been shown to spend most of their day on sedentary to light-intensity physical activities. The pattern of sedentary behavior in PD patients might be different, however, compared to that of healthy adults. The participants in the present study spent only 1% of the measured time on activities performed at a moderate to vigorous intensity, which translates to approximately 12 minutes per day. This is comparable to patients with chronic obstructive pulmonary disease (COPD); COPD patients spent, on average, 7.0-13.2 minutes per day performing moderate- to vigorous-intensity physical activities. By contrast, healthy adults perform moderate-intensity activities for 34 minutes per day, on average, or 17 minutes per day when bouts of minimally 10 minutes are taken into account.

Daily physical activity in self-identified sedentary PD patients is associated with several factors. Our findings corroborate those resulting from the survey of Bauman et al. (2002), who summarized factors often associated with physical activity. Higher age, higher BMI, and more motor problems were associated with less daily physical activity, as was gender (females), lacking a spouse, and severe disease. Conversely, better cognition and higher levels of physical fitness were associated with more daily physical activity. Our results showed that the variability in daily physical activity was mainly explained by age, gender, motor problems and physical fitness. The linear mixed-model showed that as age increases by one year, daily physical activity decreases by 6.7 kcal per day. Women spent 61.0 kcal/day less on daily physical activities than men. One point higher on the motor part of the UPDRS results in a decrease of 2.3 kcal/day spent on daily physical activities. An improvement of one meter on the 6MWT results in an increase in daily physical activity of 0.5 kcal/day. In other patient populations (e.g., heart failure patients and candidates for lung transplantation), physical fitness is also an important predictor of daily physical activity. Our findings illustrate that daily physical activity is related in part to factors that cannot be changed (age, gender), but also in part to factors that are modifiable (physical capacity such as motor problems and physical fitness). Several studies show that the physical capacity of PD patients can be improved by exercise. For example, an 8-week pole-striding exercise program can improve motor problems in PD patients. Furthermore, physical exercise improves aerobic capacity, muscular strength, balance, gait, physical performance and activities of daily living. However, more research is needed to support the suggestion that these improvements lead to actual increase in daily physical activities, because the direction of the relationship between physical capacity and daily physical activity could not be defined based on our results. When interpreting the present results, it should be noted that only self-identified sedentary patients were included. Therefore, the results may not be representative of the total PD population. In addition, approximately 65% of the self-identified sedentary patients were reluctant to participate in the ParkFit trial, possibly introducing selection bias. Since the present study used the baseline data of the ParkFit trial, daily physical activity of reluctant patients was not part of our analysis. Finally, due to the relatively small sample size, caution must be taken in generalizing the results of this study to all sedentary PD patients.

CONCLUSION
Self-identified sedentary PD patients spent the majority of their time being sedentary or performing light-intensity physical activities. The variability in physical activity is considerable and can be, in part, explained by age, gender, and physical capacity. Higher age, being female, having more motor problems, and being less physically fit are the most important determinants of reduced daily physical activity. Age and gender cannot be modified by experimental intervention, but physical capacity can. We suggest that future therapeutic interventions aim to improve daily physical activity in these high-risk patients by focusing, in particular, on modifiable risk factors.

ACKNOWLEDGEMENTS
We thank Mark Massa for his contribution to the data analysis. We would like to thank T. Roordink, M. Gerrits and W. Trompers for their contribution during data collection.
CHAPTER

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

BRITISH MEDICAL JOURNAL 2012; IN PRESS
Marlies van Nimwegen, Arlène D. Speelman, Sebastiaan Overeem, Bart P. van de Warrenburg, Katrijn Smulders, Manon L. Donjé, 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 Parkinson’s disease (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, randomized 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 (LASA Physical Activity Questionnaire, LAPAQ). 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

Parkinson’s disease (PD) is a common neurodegenerative disease, characterized by motor symptoms2 and a wide variety of non-motor symptoms like depression or apathy.3 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 healthcare interventions have been developed.4-7 In recent years, a number of physiotherapy programs have been tested in patients with PD.8-14 Reviews and meta-analyses generally found evidence to support ‘exercise’ as being beneficial with regard to physical functioning, strength, balance and gait speed.15-17 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.15-18 Promoting physical activity may also improve specific symptoms of PD, such as insomnia, depression or constipation.19 Furthermore, rodent work suggests that physical activity might counter neurodegeneration in experimental parkinsonism.20-22 An individually tailored, disease-specific training program is needed to improve physical activity in PD.23 We developed such an intervention (the ParkFit program) based on models of behavioral change24-26 and containing established behavioral change techniques.27,28 To evaluate this program, we designed a randomized controlled trial (RCT) comparing ParkFit with a matched control intervention.29

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.29

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 Criteria;2 (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 week;2; and (d) Hoehn and Yahr stage ≤3. Exclusion criteria were: (a) MMSE <24, (b) unable to complete Dutch questionnaires; (c) comorbidity 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.42

Primary endpoint was the LASA Physical Activity Questionnaire (LAPAQ), 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).55 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.55 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:55 (1) physical fitness, as measured with the 6-minute walk test55 at 12 and 24 months (i.e. average of all measurements); (2) quality of life, as measured with the PDQ-3955 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);55 and (4) physical activity, measured objectively every six months with an ambulatory activity monitor (i.e. average of all measurements).55 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) 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.133 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.135 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.13 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.42

ParkFit program
The ParkFit program was designed specifically to achieve a sustained increase in physical activity levels, based on theories and models of behavioral change13 14 and on effective behavioral change techniques.15 38 41 Important elements were: (a) activity coaches, who guided each patient towards a more active lifestyle during monthly personal coaching sessions; (b) educatio
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 activi-
ties.48 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.11

Control intervention

The control intervention consisted of a general physiotherapy program aimed at safety of move-
ments, according to the evidence-based guideline.11 Patients received an identical brochure as
ParkFit patients, but now with information about the benefits of physiotherapy and safety of move-
ments. 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 inter-
ventions 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 co variables. 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 com-
pared 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 inter-
vention studies that aimed to change activity behavior in Parkinson’s disease patients. Moreover,
prior behavioral 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 group,15, 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 fea-
sible. 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.50 Significant risk reductions have been observed with 45-150
minutes/week of brisk walking.155 Additionally, women who walked or exercised vigorously for
at least 2.5 hours/week had a 30% lower risk of coronary heart disease.155 Conversely, the risk
of cardiovascular disease was higher among women who spent >12 hours/day lying down or
sleeping.115 This suggests that a 2-hour increase in physical activities might help to prevent car-
diovascular 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 ap-
proximately eight patients leads to an ICC of 0.1. Based on a previous trial of physical therapy
in PD,116 we expected a drop-out rate of 10%.

RESULTS

BASELINE CHARACTERISTICS

586 patients were included (Figure 6.1). 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 6.1).

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, con-
trols 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 physia-
therapist 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 6.1
SCREENING, RANDOMIZATION, AND COMPLETION OF THE PRIMARY OUTCOME MEASURE

TABLE 6.1
BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Demographics &amp; Clinical Characteristics</th>
<th>ParkFit (n = 299)</th>
<th>Controls (n = 287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.1 (7.9)</td>
<td>65.9 (7.2)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>194 (65%)</td>
<td>188 (65%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 (4.5)</td>
<td>27.6 (4.0)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.0 (4.5)</td>
<td>5.5 (4.6)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.1 (1.7)</td>
<td>28.1 (1.7)</td>
</tr>
<tr>
<td>Modified Hoehn and Yahr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (2.3%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>1.5</td>
<td>7 (3.3%)</td>
<td>10 (3.5%)</td>
</tr>
<tr>
<td>2</td>
<td>221 (73.9%)</td>
<td>223 (77.7%)</td>
</tr>
<tr>
<td>2.5</td>
<td>48 (16.1%)</td>
<td>36 (12.5%)</td>
</tr>
<tr>
<td>3</td>
<td>16 (5.4%)</td>
<td>14 (4.9%)</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>33.1 (11.3)</td>
<td>32.3 (9.5)</td>
</tr>
<tr>
<td>Daily levodopa equivalent dose (mg)</td>
<td>458 (362)</td>
<td>499 (414)</td>
</tr>
<tr>
<td>Level of physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAPAQ (hours per week)</td>
<td>12.8 (20.3)</td>
<td>13.8 (23.9)</td>
</tr>
</tbody>
</table>

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.

* 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 6.2
EFFECT OF THE INTERVENTION (IN HOURS PER WEEK) ON THE LEVEL OF PHYSICAL ACTIVITY MEASURED WITH THE LASA PHYSICAL ACTIVITY QUESTIONNAIRE (LAPAQ)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ParkFit</th>
<th>Controls</th>
<th>Estimated difference (CI)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>299</td>
<td>12.8 (8.3-20.3)</td>
<td>287</td>
<td>13.6 (8.3-23.9)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>285</td>
<td>12.2 (9.2-20.5)</td>
<td>277</td>
<td>14.2 (8.5-22.0)</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>281</td>
<td>12.5 (7.2-21.1)</td>
<td>277</td>
<td>12.4 (7.2-17.9)</td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>277</td>
<td>12.3 (7.0-19.0)</td>
<td>271</td>
<td>12.3 (6.8-19.1)</td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td>273</td>
<td>12.5 (6.3-18.4)</td>
<td>267</td>
<td>12.0 (7.0-18.3)</td>
<td></td>
</tr>
</tbody>
</table>

Data reflect median (IQ-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 6.2).

Secondary endpoints
Both the activity diary and the activity monitor data suggested increased levels of physical activity in ParkFit patients (Table 6.3). Additionally, ParkFit patients increased their physical fitness compared to controls (4.8 meters; 95% CI 0.1 to 9.6; p=0.05) (Table 6.3). 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=22, 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.

DISCUSSION
This RCT shows that a multifaceted behavioral 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.

**Table 6.3**
EFFECT OF THE INTERVENTION ON THE SECONDARY OUTCOME MEASURES

|                          | N     | ParkFit | N     | Controls | Estimated
difference (CI)* | p     |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity Diary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (hrs per week)</td>
<td>297</td>
<td>5.5 (3.1-10.3)</td>
<td>282</td>
<td>6.3 (3.3-10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>275</td>
<td>1.3</td>
<td>273</td>
<td>0.5</td>
<td>30% (17% to 43%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Activity Monitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (kcal per day)</td>
<td>273</td>
<td>453 (368-618)</td>
<td>269</td>
<td>462 (346-604)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>254</td>
<td>38.7</td>
<td>258</td>
<td>-14.2</td>
<td>12% (7% to 16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Quality of Life (PDQ-39)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>297</td>
<td>26.0 (13.7)</td>
<td>286</td>
<td>26.2 (13.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>278</td>
<td>0.1</td>
<td>276</td>
<td>1.7</td>
<td>-0.9 (2.1 to 0.3)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Physical fitness (6MWT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (distance in m)</td>
<td>298</td>
<td>391.6 (87.5)</td>
<td>283</td>
<td>392.9 (84.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>255</td>
<td>8.4</td>
<td>253</td>
<td>-1.6</td>
<td>4.8 (0.1 to 9.6)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data reflect mean (SD) or median (IQ-range); * estimated (relative) difference, based on analysis of covariance; PDQ-39 = Parkinson’s Disease Questionnaire. 6MWT = 6-minute walk test.
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.55,150 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.152 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.77–152 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)157 but also in the United Kingdom.157

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.161 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.160 On the other hand, accelerometers as used in our study can reliably measure activities such as indoor and outdoor walking.150 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;159–152 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. 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. As discussed above, our study also highlights the challenges of selecting the appropriate outcomes for a complex intervention such as a behavioral 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. 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 behavioral 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 behavioral 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 behavioral 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.

ACKNOWLEDGEMENTS

This study was primarily funded by ZonMw (The Netherlands Organization for Health Research and Development (75020012)) and The Michael J Fox Foundation for Parkinson’s research. Additional financial support was provided by VGZ (health insurance company); Glaxo Smith Kline; and National Parkinson Foundation. We thank all patients and physiotherapists for participation. We would like to thank T. Roordink, M. Gerrits, W. Trompers, M. Weijers, A. Vinke, K. van Geel, M. Post, J. Mulder, T. Remijn, Y. Cornelissen, and I. Wijnhaven for their contribution during recruitment and data collection. We thank Mark Massa and Wim Lemmens for their contribution to the data analysis. We thank Bert de Swart and the HAN University of Applied Sciences for organizing the temporary participation of many students in the project team of the study. We thank all students for their contribution during the data collection.

Furthermore, we would like to thank J.W. Custers and P.J. van der Wees (Royal Dutch Society for Physotherapy), S.I. Detaille and V. Peters (Seneca, Expertise Centre for Sport, Work and Health, HAN University of Applied Sciences), M.T. Hopman (Department of Physiology, Radboud University Nijmegen Medical Centre), M.W.A. Jongeri (TNO Netherlands Organization for Applied Scientific Research), Y.P.T. Kamsma (University Medical Center Groningen), S.H.J. Keus (Departments of Physical Therapy and Neurology, Leiden University Medical Centre; Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Centre), G. Kwakkel (VU University Medical Center), H. Leutscher (Disability Sports Netherlands), W. Oerlemans (HAN University of Applied Sciences), C.J.M. van Santen (Society of Exercise Therapists Cesar and Mensendieck), N.H.M.J. van Velthoven (Netherlands Olympic Committee “ Netherlands Sports Federation), A.M.J. van de Wert (Netherlands Institute for Sport and Physical Activity), and T. Wolff (Parkinson Vereniging) for their participation in the ParkFit advisory board.

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 (Elderliek Ziekenhuis); A.J.W. Boon (Erasmus Medisch Centrum); E. van Wensen and F.E. Strijks (Gelre Ziekenhuizen); G.A. van Meer (Greene Hart Ziekenhuizen); A. Mosch (HagaZiekenhuis); J.P. ter Bruggen (Jeroen Bosch Ziekenhuis); M.F. Roesi (Kennemer Gasthuis); E. Berger (‘t Lande Land Ziekenhuis and Medisch Centrum Haaglanden); A.G.C. Karten (Laurentius Ziekenhuis); M. Westerink (Maasstad Ziekenhuis); M. Aramideh (Medisch Centrum Alkmaar); R. Rundervoort (Medisch Centrum Haaglanden); F.A. Roayer (Orbis Medisch Centrum); D.J. Kamphuis (Reinier de Graaf Groep); G.J. de Jong (Sint Franciscus Gasthuis); L. van Haaf (Franciscus Ziekenhuis); K. Lemmen (Slingeland Ziekenhuis); Th.J.M. Breuer (St. Anna Ziekenhuis); J.M.J. Krul and P.M. Labooyne (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 07

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 Munnèze
We conclude that the ParkFit program was effective in almost all specific subgroups. Therapists

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 implementati-

on 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 wors-

ens with disease progression. Reversing sedentary lifestyles could have various ge-

nic benefits, including increased survival and lower risks of chronic diseases as cardio-

vascular disease, diabetes, and cancer. Promoting physical activity may also improve specific symptoms of PD, such as insomnia, depression, and constipation. Moreover, recent work suggests that physical activity may counter neurodegeneration in experimental parkinsonism. 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. 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 individually tailored. 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. The ParkFit program was solely delivered by experienced physiotherapists who participate in the Dutch ParkinsonNet. 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 imple-
molation of the ParkFit program into clinical practice could now be considered. To facili-
tate 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 associ-

ated 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 7.1. Ethical approval has been granted for the study and all patients signed informed consent. The full study protocol has been described elsewhere.42

**PARKFIT PROGRAM**

The ParkFit program was specifically designed to achieve a sustained increase in the level of physical activity and was based on theories and models of behavioral change33 34 and on behavioral change techniques with proven effectiveness.35 38 41

**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.41 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.

---

**TABLE 7.1**

**BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Demographics &amp; Clinical Characteristics</th>
<th>ParkFit (n = 299)</th>
<th>Controls (n = 287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.1 (7.9)</td>
<td>65.9 (7.2)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>194 (65%)</td>
<td>188 (65%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 (4.5)</td>
<td>27.6 (4.0)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.0 (4.5)</td>
<td>5.5 (4.6)</td>
</tr>
<tr>
<td>MMSE (points)</td>
<td>28.1 (1.7)</td>
<td>28.1 (1.7)</td>
</tr>
<tr>
<td>Modified Hoehn and Yahr</td>
<td>1.7 (2.3%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>1.5</td>
<td>7 (2.3%)</td>
<td>10 (3.5%)</td>
</tr>
<tr>
<td>2</td>
<td>221 (73.9%)</td>
<td>223 (77.7%)</td>
</tr>
<tr>
<td>2.5</td>
<td>48 (16.1%)</td>
<td>36 (12.5%)</td>
</tr>
<tr>
<td>3</td>
<td>16 (5.4%)</td>
<td>14 (4.9%)</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>33.1 (11.3)</td>
<td>32.3 (9.5)</td>
</tr>
<tr>
<td>Daily levodopa equivalent dose (mg)</td>
<td>458 (362)</td>
<td>499 (414)</td>
</tr>
</tbody>
</table>

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.

**Activity Monitor**

All patients received a personal ambulatory monitor. 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.

**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.
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 LASA Physical Activity Questionnaire (LAPAQ). 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 indentified variables that could be associated with this change in ‘outdoor physical activity’ as measured with the LAPAQ.

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 7.2). 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 7.2).

**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 7.3). 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 (R²=38%) (Table 7.3).

**TABLE 7.2**

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

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=255)</th>
<th>Physiotherapists (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>77%</td>
<td>94%</td>
</tr>
<tr>
<td>Goal setting (short term)</td>
<td>60%</td>
<td>88%</td>
</tr>
<tr>
<td>Goal setting (long term)</td>
<td>59%</td>
<td>83%</td>
</tr>
<tr>
<td>Coaching sessions</td>
<td>71%</td>
<td>93%</td>
</tr>
<tr>
<td>Activity Monitor</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>Sport sessions</td>
<td>58%</td>
<td>74%</td>
</tr>
</tbody>
</table>

**TABLE 7.3**

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

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

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 7.4
EFFECT SIZES OF THE PRIMARY AND SECONDARY OUTCOME MEASURES IN ALL PATIENTS AND FOR SUBGROUPS OF PATIENTS BETWEEN PARKFIT AND CONTROLS

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

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.

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 recommend 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) but remarkably higher compared with previous long-term programs (up to 14 months). In an exercise program of six months aiming to reduce fall risk in PD, 54% of patients completed at least 75% of the sessions. Another study of group exercise in PD found an attendance rate of 73% during 14 months. 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.163 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.11 ParkinsonNet networks were specifically developed to improve the PD-specific expertise of health professionals, and to increase patient volumes per therapists.17 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 any 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 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 co morbidities, 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.

ACKNOWLEDGEMENTS

We thank all patients and physiotherapists for participation. We would like to thank I. Boers, D. Drijkoningen, G. Kastenberg-van Spijker, and J. Tra for their contribution during data collection. Furthermore, we would like to thank T. Roordink, M. Gerrits and W. Trompers for their contribution.

This study was primarily funded by ZonMw (The Netherlands Organization for Health Research and Development (75020012)) and The Michael J Fox Foundation for Parkinson’s research. Additional financial support was provided by VGZ (health insurance company); Glaxo Smith Kline; and National Parkinson Foundation.
CHAPTER 2
PHYSICAL INACTIVITY IN PARKINSON’S DISEASE
Patients with Parkinson’s disease are widely presumed to follow a sedentary lifestyle, due to their physical, cognitive and emotional impairments. Nevertheless, only a few studies have thus far examined physical activity in PD, and the results were inconsistent. In Chapter 2, we provided new evidence to demonstrate the presence of physical inactivity in PD. Daily physical activity levels of patients with PD were compared with controls; data were obtained using a validated physical activity questionnaire (LASA Physical Activity Questionnaire (LAPAQ)).

The results showed that patients were physically less active; a reduction of 29% in daily physical activities was found (95% CI, 10% to 44%). The loss of time spent on activities was most obvious in patients with greater disease severity. We also investigated the influence of disease-related factors on daily physical activities in patients with PD. Multivariate regression analyses demonstrated that greater disease severity, gait impairment, and greater disability in daily living were associated with daily physical activities in PD ($R^2=24\%$).

Patients with PD are less active compared with controls. This reduction is in part related to greater disease severity, more severe gait impairment, and greater disabilities in daily living.

CHAPTER 3
DESIGN AND INTERVENTION OF A RANDOMIZED CONTROLLED TRIAL TO PROMOTE PHYSICAL ACTIVITY IN PATIENTS WITH PARKINSON’S DISEASE
Participating in regular physical activity reduces the risk of chronic diseases such as cardiovascular diseases, type 2 diabetes mellitus, osteoporosis and obesity. Moreover, promotion of physical activities may beneficially affect the clinical presentation of PD, and perhaps even modify the course of PD. However, changing a sedentary lifestyle is difficult; to increase physical activity in old persons or in patients with a chronic disease may be even harder. We developed a multifaceted intervention to promote physical activity in sedentary patients with PD (the ParkFit program). We designed a multicentre, randomized controlled trial comparing the ParkFit program with a matched general physiotherapy intervention.

The ParkFit intervention program was based on theories and models of behavioral change and on widely used behavioral change techniques with proven effectiveness. Important elements of the program were: (a) the physiotherapist as activity coach who guided each individual patient towards a more active lifestyle during monthly personal coaching sessions; (b) a brochure with
education 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) stimulating patients to participate in group exercises to experience social support from peers; and (f) an ambulatory monitor with automated feedback. Chapter 3 described the ParkFit program and the design of this large randomized controlled trial. The primary outcome of the trial was the change in physical activity over the course of two years measured with the LAPAQ, an interview-based 7-day recall. The trial would also search for possible health benefits and risks of increased physical activity in PD.

CHAPTER 3

**SUMMARY**

- Education about the benefits of physical activity and suitable activities for PD patients.
- Identifying and overcoming any perceived barriers to engage in physical activity.
- Systematic goal setting, using a health contract and logbook.
- Stimulating patients to participate in group exercises to experience social support from peers.
- An ambulatory monitor with automated feedback.

The ParkFit trial evaluates a new, multifaceted intervention program to achieve an enduring increase in physical activity specifically in patients with PD. The intervention is based on motivational and behavioral change models, which are employed for the first time in patients with PD.

CHAPTER 4

**MULTIVARIABLE ANALYSES OFTEN HAVE MULTIPLE SOLUTIONS; AN EXAMPLE**

When we used forward variable selection to identify factors that were related to the level of physical activity in Parkinson’s disease patients (Chapter 2), we found a model with four variables. This model explained 22% of the variance in physical activity. Although this R² value indicated a poor fit, additional variables were unlikely to contribute to a better fit; the model with all variables explained only 24% of the variance. In Chapter 4, we showed that several other models seemed equally appropriate to describe the relationship between the independent factors and the physical activity level. As a consequence, it was impossible to determine one ‘best’ combination of independent factors explaining physical activity in patients with PD.

Several models seem appropriate to describe the relationship between ‘personal and disease related factors’ and physical activity levels in PD patients. When the purpose of a multivariable analysis is to identify which combination of independent factors explains a certain outcome, the ‘best-fitting’ model, as well as all other models with a comparable percentage declared variance, should be reported.

CHAPTER 5

**QUANTIFYING LEVELS OF INACTIVITY IN PARKINSON’S DISEASE PATIENTS AND ITS DETERMINANTS**

Questionnaires are widely used to measure daily physical activity in large populations. However, due to their subjective character, they might result in an under- or overestimation of the performed physical activities. The ParkFit study intended to include sedentary patients, based on a physical activity screening questionnaire. It was not clear whether these self-reported sedentary patients also had objective evidence for a sedentary lifestyle, as determined using quantitative accelerometry measurements. The aim of this study was to objectively assess physical activity behavior of all sedentary participants of the ParkFit study. Physical activity behavior was measured over seven days using a linear triaxial accelerometer which was worn as a necklace, on the belt or in the pocket. Determinants of daily physical activity were additionally identified.

In total, 467 patients (80%) had valid accelerometry measurements on at least seven consecutive days. Median total energy expenditure was 464 kilocalories per day and participants spent 12 minutes per day on moderate or vigorous intensive activities. Consequently, none (except for one) of the participants met the recommendations for healthy physical activity (i.e. moderate-intensity cardio respiratory exercise training for at least 30 minutes per day for at least five days a week, which should take place in bouts of at least 10 minutes). Higher age, female gender, less physical fitness and greater motor problems were related to less daily physical activity (R²=0.69; p<0.001).

CHAPTER 6

**RESULTS OF THE PARKFIT STUDY**

The results of the ParkFit study showed that overall time spent in physical activities was comparable between the ParkFit group and the control intervention (adjusted group difference 7%; 95% confidence interval (CI), -3 to 17%; p=0.19). Analyses of three secondary outcomes indicated increased physical activity in ParkFit patients, as suggested by an activity diary (difference 30%; p<0.001), a tri-axial accelerometer (difference 12%; p<0.001), and the 6-minute walk test (difference 4.8 meters; p=0.05). Quality of life measured with the PDQ-39 did not differ between ParkFit and controls (difference -0.9 points; p=0.14). The number of fallers was comparable between both groups: ParkFit (62%) and controls (67%).

Compared with objective assessment of physical activity behavior in PD patients using a tri-axial accelerometer, the screening questionnaire used in the ParkFit study showed to be sensitive to include sedentary patients. Whether this screening questionnaire is also sensitive to exclude patients who meet the recommendations for healthy physical activity, should be further investigated.
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.

CHAPTER 7
EVALUATION OF THE PARKFIT PROGRAM

The findings of three secondary outcomes in the ParkFit study suggest increased activity (Chapter 6); therefore, further implementation of the program could now be considered. To facilitate this potential implementation process, we evaluated our trial experience with the ParkFit program 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.

Data of 255 patients (85%) and 116 physiotherapists (97%) were collected. The ParkFit program was well received. Seventy-three percent of patients indicated they would recommend the program to other patients, and 90% of physiotherapists indicated they wanted to use the ParkFit program in future patients. Less baseline physical activity and better mobility were associated with larger changes in physical activity over two years \(R^2 = 48\%\). The program was effective in almost all subgroups; the estimated effect size was largest in women, in patients who were most sedentary at baseline, and in patients with lower disease severity.

The ParkFit program was effective in almost all subgroups. Therapists and patients experienced no major hurdles. This knowledge can be used for further implementation into everyday clinical practice.
CHAPTER 09
GENERAL DISCUSSION & FUTURE PERSPECTIVES
PATIENTS WITH PD MOVE LESS
We showed that patients with PD are less active compared to controls (Chapter 2). We additionally observed that not all patients lead a sedentary lifestyle. Even some patients with advanced disease severity performed sport activities. This implies that a number of patients with PD in later stages of the disease are still able to perform (sport) activities. Since physical activity may improve specific symptoms of PD such as sleep impairment, depression, and constipation, and because rodent work suggests that physical activity may counter neurodegeneration in experimental parkinsonism, this is an important message for patients as well as for clinicians.

The finding that not all PD patients are sedentary was confirmed during the inclusion procedure of the ParkFit study (Chapter 3). Out of the 3453 finally invited participants, about one third was physically sufficiently active according to international recommendations for healthy physical activity. However, since more than fifty percent in the healthy older population meets these recommendations, this difference between healthy adults and PD patients corroborates our previous results that patients are less active.

THE CHALLENGE TO ASSESS PHYSICAL ACTIVITY
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. The complexity of physical activity was also confirmed by the fact that a lot of determinants are associated with this behavior, which were identified in different chapters of this thesis (Chapter 2, 4 and 5). The complex nature of physical activity behavior makes it also difficult to accurately measure all of its aspects. Various assessment methods have been used in research, both with advantages and disadvantages. The doubly labeled water method is the most accurate method to assess physical activity energy expenditure under free living conditions. However, this method is expensive and complex, and provides no information about which activities were performed.

An alternative for objective assessment of levels of physical activity are ambulatory accelerometers; these devices are feasible and increasingly recognized as valid and objective instruments for assessing free-living physical activity. However, their disadvantage is that they generally underestimate total energy expenditure of daily living: upper body movements, activities such as cycling, and static movements such as gardening or strength training are difficult to detect. Pedometers offer an inexpensive alternative for objective ambulatory assessments, however, they are specifically designed to assess walking only.
Self-report techniques are the most common measures of physical activity. Due to their subjective character, questionnaires as well as diaries might result in an under- or overestimation of physical activities.\(^{172,173}\) However, self-report techniques are feasible to assess habitual physical activity in large populations since they are practical and easy to administer, have relatively low costs and create low participant burden.\(^{154,171}\)

All methods described above have their shortcomings and advantages. In each situation, one has to choose the method(s) which is/are most appropriate given the specific circumstances, despite their shortcomings. Two examples are described below:

The ParkFit program was designed to change behavior in sedentary patients. For the purpose of trial inclusion, physical activity levels of 3453 individuals had to be screened, so that we could include only the sedentary ones. Since objective assessment (for example with activity monitors or doubly labeled water) was impossible (i.e. not feasible), inclusion was based on a physical activity screening questionnaire (Chapter 3). To examine whether indeed only sedentary patients were included, daily physical activity behavior was subsequently measured with a tri-axial accelerometer (Chapter 5). The results showed that none (except for one) of the included met the international guidelines of daily physical activity; therefore, we concluded that the screening questionnaire was an appropriate tool to include sedentary PD patients. Despite the well known difficulties of measuring daily physical activity using questionnaires, it is important to know that this questionnaire was able to include the right patients. Whether this questionnaire is additionally able to exclude patients who did meet the recommendations for healthy physical activity, can only be investigated by assessments of all patients who were excluded based on their activity levels.

When we designed the ParkFit study, we had to choose the most appropriate instrument to assess physical activity in daily life. We chose an interview-based physical activity questionnaire, the LAPAQ.\(^{26}\) The most important reason for this choice was the fact that the LAPAQ covers a wider range of activities compared to accelerometers. In addition, we chose two secondary measures to assess physical activity as well: a tri-axial accelerometer and a diary. As a consequence, we were able to corroborate changes in physical activity detected with the LAPAQ using both an objective instrument and a subjective instrument. After 24 months, the overall LAPAQ did not change. However, both the activity monitor (+12%) and the diary (+30%) showed increased physical activity. Stimulated by these positive findings, we re-examined the primary outcome using post hoc analyses. Specifically, the LAPAQ questionnaire reflects the net sum of ‘outdoor and sport activities’ plus ‘household activities’. These post hoc analyses showed that a significant and possibly relevant (+24%) increase in outdoor and sport activities for ParkFit patients was offset by a concurrent decrease in household activities (-16%).

Although each instrument measures physical activities in a different way, the conclusions of the diary, accelerometer and post hoc analyses of the LAPAQ were comparable: patients in the ParkFit program increased their activity levels based on these outcome measures. Since the overall LAPAQ did not show differences in physical activity, while accelerometers, diaries and the post hoc analyses of the primary outcome did, we regard our decision to select overall physical activity as primary outcome as a shortcoming in the study design. It seems that the total sum of outdoor and household activities obscure the changes in physical activity behavior. 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 since they generally perform (light and moderate) activities which are easy to overestimate when using questionnaires, and difficult to detect using accelerometers.

### THE TWOFOLD CHALLENGE TO CHANGE BEHAVIOR

In recent years, a number of physiotherapy programs have been tested in patients with PD.\(^{140-146}\) Overall, these programs were generic (i.e. for each patient the same) and were delivered for a short period (2-10 weeks). Before and after the intervention period, patients were tested and basic characteristics such as strength, gait speed or balance improved (Figure 9.1). Furthermore, some reviews and two meta analyses were conducted on the effectiveness of physiotherapy and exercise interventions (under the umbrella of physiotherapy) in PD.\(^{75,77,152-155}\) Generally, they found evidence to support ‘exercise’ as being beneficial with regards to physical functioning, strength, balance and gait speed. Although these conditions might be important to be able to arrange an active lifestyle anyway, a physiotherapy program as tested in those studies is not sufficient to achieve this lifestyle. In the knowledge that (1) patients with PD tend to lead a sedentary lifestyle; (2) the fact that some patients - even in more advanced stages - still perform activities; (3) the well known benefits of physical activity in general; and (4) the lack of a disease-specific physiotherapy program aiming to change sedentary behavior, we developed the ParkFit program (Chapter 3).

### PHYSIOTHERAPISTS

Before we could measure a behavioral change in patients, we first had to change the behavior of all participating physiotherapists (n=154). Physiotherapists had to be educated to ‘coach’ patients, rather than just treating them. Thus, the ParkFit study included a twofold challenge to change behavior. To change the behavior of physiotherapists, we took several steps. We first developed a specific handbook for physiotherapists, including information about the benefits and risks of physical activity, about the process of behavioral change, covering specific user information for the tools included in the ParkFit program, and a scheme to guide therapists through the coaching sessions. Second, we developed an educational workbook for patients...
which included all elements of the ParkFit program. This workbook not only intended to inform patients, but also aimed to guide therapists in dealing with all specific elements that are important for behavioral change. Third, physiotherapists were trained to treat patients in the ParkFit program during three educational sessions. Fourth, 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 any 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 (Chapter 7).

FIGURE 9.1
AIMS OF PHYSIOTHERAPY, (GROUP) EXERCISE AND PHYSICAL ACTIVITY PROMOTION IN PD

Although it was a post hoc analysis, it is interesting to speculate about the observation that patients increased outdoor activities and decreased household activities. First, patients allocated to the ParkFit program might have spent more time to sport activities instead of household activities. In other words, they could have shifted from indoor to outdoor activities. Second, since ParkFit patients performed more other outdoor activities, they might have underestimated the time spent on household activities. It is possible that they came to consider these activities as less important since they started to perform other, more strenuous activities. Both clarifications can be true, and might in fact co-exist. Since the aim of most behavioral change programs is to increase the time spent on outdoor and sport activities, and not to increase the time spent on household activities, we recommend future studies to use an instrument which is able to categorize activities or even ignores household activities, for example our activity diary. Another possibility would be to split up the total LAPAQ scores into ‘household’ and ‘outdoor activities’. Otherwise, one might falsely conclude that participants did not change their behavior, while they possibly did.

While statistically significant, the increase in physical activities per week was not much in an absolute sense. Expressed in time units (based on the activity diary), ParkFit patients spent almost one and a half hour per week extra on outdoor and sport activities, compared to baseline. Although not much, this increase was comparable with findings in elderly populations and patients with other chronic conditions. For example, behavioral counseling for elderly in primary care yielded a one-hour increase in moderate-intensity physical activity. In addition, pedometer-based counseling programs increased total physical activity of cardiac patients by almost 1.5 hour/week. However, the long term follow-up sets the ParkFit study apart from these other studies. Specifically, follow-up periods in these earlier studies were only six months, while we followed our patients for two years.

Our results concerning adherence are comparable with previous short-term programs (up to 6 months follow-up), but are remarkably higher compared with previous long-term programs (up to 14 months follow-up). In an exercise program of six months aiming to reduce fall risk in PD, 54% of patients completed at least 75% of the sessions. Another study of group exercise in PD found an attendance rate of 73% during 14 months. Several aspects of the ParkFit program could have contributed to its high adherence. First, the individually tailored character of the ParkFit program – with activities that participants enjoyed – makes participation more pleasant compared with exercise in general. Since patient and therapist jointly chose one or more (sport) activities, every patient was allowed to follow his or her 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. ParkinsonNet networks were specifically developed to improve the PD-specific expertise of health professionals, and to increase patient volumes per
HEALTH BENEFITS RELATED TO PHYSICAL ACTIVITY

The two other secondary outcomes (fitness and falls) aimed at finding possible health benefits related to the ParkFit program (Chapter 6). Physical fitness showed a small but significant difference in favour of ParkFit. Furthermore, we were concerned about possibly increased fall rates, because the amount of physical activity is associated with a greater risk of falling. However, the ParkFit program was not associated with more falls or injuries.

We can speculate that the observed increase in physical activity measured with the secondary outcomes may in turn lead to generic health benefits. For example, significant risk reductions of cardiovascular disease have been observed with 45 to 150 minutes per week of brisk walking.155 This suggests that the increase in physical activities observed in ParkFit patients based on the secondary outcomes might help to prevent development of cardiovascular disease in PD patients. This was not specifically studied in the present ParkFit trial, but should be a focus of future research.

No differences were found for quality of life (secondary outcome) between both study arms (Chapter 6). We performed post hoc analyses for the complete battery of tertiary outcome measures to investigate the relationship between physical activity and specific health benefits (for example mobility, sleep and depression; all outcome measures were described in Chapter 3). Small but 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. 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 other health benefits in the ParkFit study could possibly be explained by several reasons. First, it is possible that there is no relationship between (increased) physical activity and health. However, this seems unlikely, since many studies have shown beneficial effects of (increased) regular physical activity.14 15 165 Second, the intensity of the performed activities might have been too low. We showed that ParkFit patients were able to increase their time spent on outdoor and sport activities, but the increase in time may not have been enough to achieve tangible health effects (apart from the improved physical fitness, which did occur in the ParkFit group). This hypothesis is in accordance with an earlier study which concluded that intensity, and not duration, of physical activities is related to improvements in cognitive function.156 Since the ParkFit program was individually tailored and every patient was allowed to choose his or her own ‘activity’, patients selected mainly activities such as walking or fitness. We cannot exclude that greater health benefits might have been achieved when the one hour increase had been spent on more vigorous physical activity such as running. To determine whether a higher intensity of physical activity will translate into clinically relevant health improvements, more work remains necessary. The same applies to specific type and duration of activities. We are now performing a new exercise study where patients are instructed to participate in fairly intensive cycling activities for five times a week (the ParkCycle study). In addition, we participate in a large European multicenter study which studies the combined effects of treadmill walking plus a complex three-dimensional stimulation that necessitates gait adaptations (the V-time study).121 Third, our choice for the control intervention might have obscured larger differences between the ParkFit patients and controls. Specifically, we elected 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. Indeed, debriefing of patients confirmed that patients were unaware of treatment allocation, and patients in both arms felt they had received an ‘active’ intervention. A strong element of our study was the careful matching of treatment intensity between both study arms. An additional reason for having a physiotherapy program as control intervention was that we felt that abstaining control patients from physiotherapy for two years was unethical. Certainly, having a control group without any physiotherapy might have helped to create maximal contrast...
between both study arms. However, the ParkFit study took place in ‘the real world’ and physiotherapy in PD is ‘usual care’, certainly in the Netherlands where at least 60% of PD patients receives physiotherapy annually.7 We therefore considered a control group with physiotherapy as the most meaningful design.

Finally, new perspectives in the literature propose that ‘too much sitting’ is different from ‘too little exercise’.175-177 Chronic unbroken periods of muscular unloading associated with prolonged sedentary time may have deleterious biological consequences.178 In the ParkFit study, sitting time was not measured. As a consequence, we cannot conclude whether time spent on prolonged periods of sitting was changed during the intervention period. Whether this could be a clarification for the lack differences between both groups, should be investigated in further studies by measuring prolonged sitting periods as well.

**EXTRAPOLATION AND IMPLEMENTATION OF THE PARKFIT PROGRAM**

The ParkFit study showed 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.

Since our participants were on average less sedentary compared to patients who declined to participate, it remains unclear whether the effects can be generalized to more sedentary patients. The same applies to patients with severe apathy, severe cognitive impairment or depression since these were not included in the ParkFit study. As physiotherapists reported that patients with relatively mild cognitive impairments were more difficult to coach (Chapter 7), it is relevant to further investigate how these patients can best be stimulated to become more active.

The ParkFit program was now offered solely by physiotherapists with PD-specific expertise, which likely helped to overcome any barriers imposed by the physical and mental limitations of PD patients. The question is whether adding professionals from other disciplines might help to further improve the quality of the behavioral change program. One suggestion that was raised during the debriefing interviews was to add a psychologist, who could address the cognitive issues associated with PD, but who also adds specific expertise about behavioral change. One could also consider adding sport instructors, since they have specific knowledge about coaching, counseling, sports and exercise (Figure 9.1). It will be interesting to examine the possible role of such sport instructors within an upgraded version of 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 (Chapter 7).

Irrespective of which healthcare professional(s) deliver(s) the ParkFit program, education of these providers is an important prerequisite. Aspects such as self-efficacy and outcome expectations are key elements for behavior and thus for behavioral change.33 To be able to optimally offer such a behavioral change program, providers have to be educated in these principles and in the specific strategies which can be used to coach people towards a more active lifestyle.

In conclusion, patients with PD are less active compared to controls. Reversing this sedentary lifestyle could have various benefits. Therefore, we developed a multifaceted intervention program aiming to increase physical activity in patients with PD. The ParkFit behavioral change program did not increase overall physical activity, as measured with the LAPAQ. The analysis of the secondary endpoints suggest possible merits of behavioral change programs to increase physical activities in daily life in patients with PD. These findings implies the ParkFit intervention as a meaningful supplement in the care of PD, although more work remains needed to further optimize the intervention and to investigate the effects.
HOOFDSTUK 2
FYSIEKE INACTIVITEIT BIJ MENSEN MET DE ZIEKTE VAN PARKINSON

Van mensen met de Ziekte van Parkinson wordt verondersteld dat ze vanwege hun fysieke, cognitieve en emotionele beperkingen inactief zijn. Desondanks zijn er maar een paar studies die dit hebben onderzocht en de resultaten waren inconsistent. In Hoofdstuk 2 onderzoeken we deze veronderstelling door het niveau van fysieke activiteit van mensen met de Ziekte van Parkinson te vergelijken met controles. We hebben hiervoor een gevalideerde vragenlijst gebruikt (LASA Physical Activity Questionnaire, LAPAQ).

De studie laat zien dat patiënten inderdaad minder actief zijn dan mensen zonder de ziekte van Parkinson: we vonden een verschil van 29% in hun dagelijks activiteiten niveau (95% betrouwbaarheidsinterval 10 tot 44%). Dit verschil was het duidelijkst bij mensen met een hogere ziekte-ernst. Daarnaast hebben we gekeken naar ziektegerelateerde factoren die het niveau van fysieke activiteit bij mensen met de ziekte van Parkinson beïnvloeden. Multivariate regressie analyses lieten zien dat hogere ziekte-ernst, loopproblemen en meer beperkingen in het dagelijks leven een negatieve invloed hadden op het activiteiten niveau ($R^2=24\%$).

Mensen met de ziekte van Parkinson zijn bijna een derde minder actief dan mensen zonder de ziekte. De mate van ziekte ernst, loopproblemen en beperkingen in het dagelijks leven zijn factoren die een rol spelen bij deze inactieve leefstijl.

HOOFDSTUK 3
DESIGN VAN EEN GERANDOMISEERDE GECONTROLEERDE STUDIE OM MENSEN MET DE ZIEKTE VAN PARKINSON TE STIMULEREN TOT MEER FYSIEKE ACTIVITEIT

Regelmatige fysieke activiteit vermindert het risico op chronische ziekten zoals hart- en vaatziekten, diabetes mellitus type 2, osteoporose en obesitas. Tevens zou fysieke activiteit invloed kunnen hebben op de klinische symptomen van de ziekte van Parkinson en zelfs het verloop van de ziekte positief kunnen beïnvloeden. Echter, een inactieve levensstijl veranderen is moeilijk; het verhogen van fysieke activiteit bij ouderen of bij mensen met een chronische ziekte is mogelijk nog moeilijker. Wij hebben een interventie programma ontwikkeld om inactieve mensen met de ziekte van Parkinson te stimuleren tot meer fysieke activiteit (het ParkFit programma). Om het effect van het programma te onderzoeken, wordt in een gerandomiseerde gecontroleerde studie het ParkFit programma vergeleken met reguliere fysiotherapie conform de KNGF Richtlijn Ziekte van Parkinson.

Het ParkFit programma is enerzijds gebaseerd op theorieën en modellen over gedragsverandering,
en anderzijds bevat het frequent gebruikte gedragsveranderingstechnieken die effectief blijken te zijn. De belangrijke elementen van het programma zijn: (a) de fysiotherapeut fungeert als coach die gedurende maandelijkse coachsessies de patiënt begeleidt naar een actieve leefstijl; (b) een handboek met informatie over bewegen, de voordelen van sporten en bewegen, en geschikte activiteiten voor mensen met de ziekte van Parkinson; (c) het in kaart brengen en overwinnen van barrières ten aanzien van bewegen; (d) het systematisch stellen van doelen middels een gezondheidscontract tussen coach en patiënt, en een logboek; (e) het stimuleren om deel te nemen aan groepsessies om te ervaren hoe het is om te bewegen en om stimulans van andere patiënten te ervaren; en (f) een activiteitenmonitor die registreert en feedback geeft over het dagelijks activiteiteniveau. Hoofdstuk 3 beschrijft het ParkFit programma en het design van de ParkFit studie. De primaire uitkomst van het onderzoek is de verandering in fysieke activiteit gedurende twee jaar, gemeten met de LAPAQ, een gestructureerde vragenlijst die vraagt naar dagelijkse activiteiten over de afgelopen week. Daarnaast wordt onderzocht in hoeverre bewegen voordelen danwel nadelen heeft voor deze specifieke patiëntengroep.

De ParkFit studie toetst een nieuw interventie programma met als doel een gedragsverandering te bewerkstelligen bij inactieve mensen met de ziekte van Parkinson. Met deze studie worden gedragsveranderingsschommelen en -technieken voor het eerst toegepast bij mensen met de ziekte van Parkinson. Met deze studie worden gedragsveranderingsschommelen en -technieken voor het eerst toegepast bij mensen met de ziekte van Parkinson.

**HOOFDSTUK 4**

**MULTIVARIABELE ANALYSES HEBBEN VAAK MEERDERE OPLOSSINGEN: EEN VOORBEELD**

In Hoofdstuk 2 hebben we middels multivariale analyse gezocht naar determinanten van fysieke activiteit bij mensen met de ziekte van Parkinson. We vonden in eerste instantie een model met vier variabelen die het niveau van fysieke activiteit (mede) konden verklaren: geslacht, aanwezigheid van andere ziekten, de mobiliteit en beperkingen in het dagelijks leven. Dit model verklaarde 22% van de variatie in fysieke activiteit bij mensen met Parkinson. Ondanks dat de verklaarde variantie slechts 22% was, bleken andere variabelen geen toegevoegde waarde te hebben; alle variabelen samen verklaarden slechts 24% van de variatie in fysieke activiteit bij deze groep. In Hoofdstuk 4 laten we aan de hand van dezelfde data zien dat er meerdere opties zijn om die relatie te ‘beschrijven’ en concluderen we dat er geen sprake is van één juiste oplossing.

Meerdere modellen blijken geschikt om de relatie tussen de afhankelijke variabelen en het niveau van fysieke activiteit bij mensen met de ziekte van Parkinson te beschrijven. Als het doel van een studie is om determinanten te identificeren die zijn geassocieerd met een bepaalde uitkomst, is het dus aan te bevelen om zowel het uiteindelijke model als modellen met een vergelijkbare ‘fit’ te presenteren.

**HOOFDSTUK 5**

**KWANTIFICEREN VAN HET NIVEAU VAN INACTIVITEIT EN HET IDENTIFICEREN VAN DE MOGELIJKE DETERMINANTEN BIJ MENSEN MET DE ZIEKTE VAN PARKINSON**

Vragenlijsten worden in grote populaties veelvuldig gebruikt om fysieke activiteit te meten. Echter, resultaten kunnen een onder- of een overschatting zijn vanwege het subjectieve karakter van deze instrumenten. Binnen de ParkFit studie werden alleen inactieve patiënten geïncludeerd, gebaseerd op een screeningsvragenlijst over fysieke activiteit. De vraag is in hoeverre de patiënten die middels een objeceitementof instrument gemeten werden als zijnde inactief zijn. Om dit vast te stellen werd het niveau van fysieke activiteit van alle deelnemers aan de ParkFit studie objectief gemeten met behulp van een activiteitenmonitor. Fysieke activiteit werd gemeten met een drie-assen activiteitenmonitor die om de nek, in de broekzak of aan de riem gedragen kan worden. Aanvullend werden de determinanten van fysieke activiteit bepaald.

In totaal hadden 467 patiënten (80%) een valide meting over minimaal zeven opeenvolgende dagen. De mediaan van het totale energieverbruik was 464 kilocalorieën per dag en gemiddeld waren patiënten 12 minuten per dag matig tot intensief actief. Niemand van hen, behalve één, haalde de Nederlandse Norm voor Gezond Bewegen die stelt dat mensen op minimaal vijf dagen per week 30 minuten voor in blokken van tien aaneengesloten minuten matig tot intensief actief moeten zijn. Een hogere leeftijd, het vrouwelijk geslacht, een lagere fitheid en meer motorische problemen waren gerelateerd aan een lager niveau van fysieke activiteit ($R^2=0.69; p<0.001$).

Vergelijken met het objectief meten van beweeggedrag bij mensen met de ziekte van Parkinson middels een activiteitenmonitor, blijkt de screeningsvragenlijst uit de ParkFit studie geschikt om inactieve patiënten te identificeren. In hoeverre dit instrument ook geschikt is om mensen die volgen aan de Nederlandse Norm Gezond Bewegen te identificeren moet verder worden onderzocht.
HOOFDSTUK 6
RESULTATEN VAN DE PARKFIT STUDIE

De resultaten van de ParkFit studie laten zien dat de tijd die besteed werd aan fysieke activiteit niet verschilde tussen de ParkFit groep en controles (verschil: 7%; 95% betrouwbaarheidsinterval -3 tot 17%; p=0.19). Analyses van de secundaire uitkomsten lieten echter wel een toename zien van fysieke activiteit bij patiënten die het ParkFit programma hadden gevolgd. Zowel op basis van het beweegdagboek (verschil van 30%; p<0.001), als op de activiteitenmonitor (verschil van 12%; p<0.001), als op de 6 minuten wandeltest (verschil van 4.8 meter; p=0.05) waren patiënten in ParkFit significant verbeterd ten opzichte van controles. Kwaliteit van leven gemeten met de PDQ-39 verscheilde 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 ParkFit groep (62%) en de controlegroep (67%).

HOOFDSTUK 7
EVALUATIE VAN HET PARKFIT PROGRAMMA

Drie secundaire uitkomsten van de ParkFit studie laten een toename van fysieke activiteit zien (Chapter 6); derhalve zou verdere implementatie van het programma zinvol kunnen zijn. Om het implementatieproces te faciliteren, werd de ParkFit studie op verschillende wijzen ge-evalueerd: (a) ervaringen van patiënten en therapeuten middels interviews en vragenlijsten; (b) inventarisatie van factoren die geassocieerd waren met veranderd niveau van fysieke activiteit; en (c) 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; ziekteduur; en mobiliteit van de patiënt.

Data van 255 patiënten (85%) en 116 fysiotherapeuten (97%) liet zien dat zij over het algemeen heel tevreden waren over programma: 73% van de patiënten gaf aan dat zij het zouden aanbevelen aan andere patiënten, en 90% van de therapeuten zou het programma in de toekomst bij andere patiënten toepassen. Een lager niveau van fysieke activiteit op baseline en een hoger niveau van mobiliteit waren geassocieerd met een hogere toename van fysieke activiteit over een periode van twee jaar (R²=48%). Het ParkFit programma was effectief in nagenoeg alle subgroepen; patiënten die hun activiteiten niveau het meest verbeterden, waren vrouwen, patiënten met een lager niveau van fysieke activiteit op baseline, en patiënten met een lagere ziekte ernst.

Als gevolg van het ParkFit programma verhoogde het niveau van fysieke activiteit in bijna alle subgroepen van patiënten. Zowel therapeuten als patiënten hebben geen grote belemmeringen ervaren voor verdere implementatie.
CHAPTER

DANKWOORD
DANKWOORD

Bij het schrijven van een proefschrift is het eigenlijk als bij het rijden van de Tour de France, op de laatste dag in Parijs staat alleen de winnaar van de gele trui in de schijnwerpers, maar die renner had de gele trui niet behaald zonder de jarenlange en bovenmatige inspanningen van knechten, ploegleiders en verzorgers en zonder de steun van het enthousiaste publiek. Ik had vooraf nooit gedacht dat er zoveel bij een promotie onderzoek kwam kijken en misschien is dat maar goed ook…. Dank dus aan allen zonder wie ik hier vandaag niet had kunnen staan!

Een speciaal woord van dank aan:

DE PATIjTEN EN THERAPEUTEN
die deel hebben genomen aan het onderzoek. Logistiek was de ParkFit studie voor ons een enorme klus maar het échte werk moest gebeuren in de praktijk. De studie duurde lang en heeft veel gevraagd; ik hoop oprecht dat deelname aan de studie voor ieder van u op één of andere manier iets heeft opgeleverd.

Mijn ploegleiders, verzorgers en ploeggenoten:

BAS EN MARTEN
promotor en copromotor; dankzij jullie ligt dit boekje er. Jullie hebben mij jaren geleden overtuigd om te gaan promoveren. En jullie kregen gelijk; ik heb genoten van dit project, alle jaren. Ik ben trots op het resultaat maar ook heel trots dat ik bij jullie heb mogen bereiken. Dank voor jullie vertrouwen en inspiratie. Jullie bezitten de kracht en het vermogen om te blijven enthousiasmeren en keer op keer een mogelijkheid te zien in het (nagenoeg) onmogelijke.

GEORGE
wat een verademing is het om met jou samen te werken. Tijd, rust, eenvoud en betrokkenheid; sleutelwoorden kenmerkend voor jou. Jouw aanwezigheid bij de besprekingen leidde per definitie tot resultaat, vaak zelfs letterlijk én figuurlijk. Ik gun elke promovendus zo’n begeleider en ik vind het bijzonder dat jij mijn tweede promotor bent.

SEBASTIAAN
wat heb ik moeten wennen aan jouw manier van feedback geven; met lood in mijn schoenen ging ik aanvankelijk naar je toe. Het is uitgegroeid tot een leuke en constructieve samenwerking en mijn stukken zijn allemaal beter geworden door jouw kritische blik en trouwe begeleiding. Je hebt me meer dan eens laten zien als een echte copromotor naast me te staan, dank daarvoor!
FRANK BACKX
als mede-aanvrager en initiator van het project heb je vanaf het begin af aan meegedaacht. Dank voor je betrokkenheid gedurende al die jaren. Ook de andere leden van de Projectgroep en Adviesraad van de ParkFit studie dank voor alle adviezen en betrokkenheid bij de opzet van het interventieprogramma en de uitvoering van de trial.

LEden van de Manuscriptcommissie
Ria van der Sanden-Nijhuis, Bob van Hilten en Marijke Hopman-Rack; dank voor de tijd en energie die gestoken is in het lezen en beoordelen van mijn manuscript.

College’s van de Afdeling Neurologie en de onderzoekers van Parc
helaas gebeurde het veel te weinig maar de momenten die er waren buiten werktijd om, hebben me geleerd dat fijne collega’s van een niet te onderschatten waarde zijn voor een leuke baan.

Alle stagiaires en alle studenten
van de opleidingen Sport, Gezondheid en Management en Fysiotherapie van de HAN. Jullie hebben onvoorstellbaar veel werk verricht; dank voor al jullie tijd besteed aan het meten van patiënten, het invoeren van data, het bellen van therapeuten en aan alle andere klussen die jullie geklaard hebben.

De onderzoeksassistenten
Marloes, Karin, José, line, Anita, Mirte en Thijs; bedankt voor jullie bijdrage aan het project! Tia, Willeke en Marije; jullie zijn van begin tot (bijna) eind betrokken geweest. Zonder al jullie inspanningen hadden Arlène en ik de afgelopen jaren geen leven gehad …. Jullie aanwezigheid maakte het werk leuk en leuwer, dank daarvoor!

Katrijn
wat heerlijk rustig kan jij zijn en wat een enorme dosis vrolijkheid heb je in huis. Inhoudelijk ben je een kei en heb ik veel van je geleerd. Maar boven alles heb ik genoten van jouw gezellige, (naoit saai!) aanwezigheid bij ons op de kamer en dat had ik voor geen goud willen missen!

Arlène
“niet eenvoudig, zo’n duopromotie” is ons vaak gezegd. Inderdaad: het heeft een paar nadelen maar het heeft ons vooral veel opgeleverd. Het is ongelofelijk hoeveel tijd wij samen hebben doorgebracht de afgelopen jaren! We waren elkaars klankbord, steun en praatpaal op allerlei vlakken. We konden leren van en met elkaar, en ik hoop dat we daar allebei nog lang de vruchten van kunnen plukken. Maar het aller-allerbelangrijkste: het was vooral veel en veel leuwer om dit samen met jou te mogen doen! Het kan ook niet anders dan dat we op dezelfde dag promoveren en dat jij er dan óók bent als mijn paranimf.

En dan het ‘publiek’:

Mijn SCHOONFAMILIE
Voornamelijk vanwege het proefschrift dat nu voor jullie ligt, verhuisde Wouter een paar jaar geleden naar Nijmegen. Ik hoop dat de afstand naar ‘het oosten’ ooit ietsje minder ver zal voelen. Dank voor jullie gezelligheid en dank voor de lieve opa’s, oma’s, tantes, ooms, en nietjes (!) die jullie zijn voor Jolijn.

Mijn LIEVE, LEUK VRIENDINNEN
Anneke, Jeanine, Jorinde, Lianka, Lotte, Maaike, Maaikje en Marleen; in mindere mate betrokken bij dit proefschrift maar allemaal betrokken bij mij. Het waren voor ieder van jullie bewogen jaren met veel hoogtepunten maar ook verdrietige gebeurtenissen; ik ben heel dankbaar voor alle leuke, gezellige, mooie en indrukwekkende momenten die ik met jullie heb doorgebracht. En hopelijk nog mag delen!

Lieve papa
weer een mijlpaal zonder jouw aanwezigheid, de zoveelste…. Nog steeds als mensen zeggen dat ik een echte ‘van Nimwegen’ ben, ben ik trots. En zeker sinds ik in Nijmegen woon, is die verbinding met mijn achternaam nog sterker: mijn eigen, blijvende herinnering aan jou.

Mama & Lisette
mijn basis, mijn wortels, mijn leven deel ik met jullie. Eén ‘drie-eenheid’ noemden mensen ons wel eens. Ik zie het als een compliment. Dat we ondanks datgene wat ons is overkomen zo sterk en verbonden uit de strijd zijn gekomen, maakt me trots en ontroerd me nog steeds. Mam, bedankt voor jouw trouw, aandacht en voor mijn ‘onbezorgde’ jeugd; dankzij jou en mijn ‘tweede thuis’ denk ik vol warmte, liefde én met een glimlach terug aan vroeger. Lisette, hoe kan het ook anders, vandaag mijn paranimf; altijd aanwezig, als een rode draad in mijn leven. Norbert, ik had me geen betere ‘man van Lisette’ kunnen wensen; dank voor wie je bent en dát je er bent!

Lieve, kleine Jolijn
zo jong als je nu bent, heb je nog geen idee van wat je allemaal te wachten staat in deze wereld. We genieten enorm van jou en vinden het heerlijk om samen met jou de wereld opnieuw te ontdekken.

Lieve Wouter
vanaf de eerste dag dat wij samen zijn, geef je rust. Juist datgene wat ik het meeste nodig had, in alles! Dankjewel voor ‘ons’ en voor ons enorm fijne leven samen, mijn thuis is bij jou.
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Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients. BMC NEUROLOGY 2010; 10:70-79
Maria Louise (Marlies) van Nimwegen was born on January 29th 1982 in Apeldoorn (the Netherlands). After finishing secondary school (VWO) in 2000 at the Veluws College Walterbosch in Apeldoorn, she studied Physiotherapy at the Hogeschool Utrecht (HU). She gained her Bachelor of Science degree in 2004. Thereafter, she moved to Nijmegen to start studying Biomedical Sciences at the Radboud University Nijmegen and she chose Clinical Human Movement Sciences as her specialization. She completed her final internship at the Department of Neurology of the Radboud University Nijmegen Medical Centre. This internship was dedicated to measuring quality of gait in patients with Parkinson’s disease. She received her Master of Science Degree in 2007 and further to this, she started her PhD project, also at the department of Neurology. Funded by grants of ZonMw (The Netherlands Organization for Health Research and Development) and The Michael J Fox Foundation for Parkinson’s research, she studied the levels of physical activity in patients with Parkinson’s disease, under supervision of Dr Marten Munneke en Prof Dr Bas Bloem. Furthermore, she developed a multifaceted physiotherapy intervention program for patients with Parkinson’s disease aiming to increase their physical activity levels. The effectiveness of this program was tested in a large group of physiotherapists and patients. The results of this project are described in this thesis. Marlies lives in Nijmegen, together with her husband Wouter and their daughter Jolijn.
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