Fear of falling, falls and near falls in Parkinson's disease

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ABSTRACT

AIM: The overall aim of this longitudinal PhD project was to gain increased knowledge about factors associated with fear of falling (FOF) falls and near falls, as well as to contribute to improved clinical fall prediction for people with mild Parkinson's disease (PD).

METHODS: People diagnosed with PD and receiving care at the university hospital outpatient neurology clinic were assessed during the "on" phase using a broad range of rating scales and clinical tests targeting balance and gait problems as well as motor and non-motor symptoms. The participants then registered all prospective falls and near falls for six months by using a diary.

RESULTS: Paper I identified everyday walking difficulties as the strongest factor independently associated with FOF, followed by independence in daily activities, functional balance, and fatigue. Paper II identified FOF to be the strongest factor independently associated with prospective falls and/or near falls, followed by history of near falls, and retropulsion during an unexpected shoulder pull. Paper III showed that the discriminate ability of a recently suggested clinical 3-Step Falls Prediction Model (3-step model) is acceptable and better than that of single predictors. Extended analyses showed that a new model for prediction of falls and/or near falls (including history of near falls, tandem gait and retropulsion) had better discriminant ability than the 3-step model. Paper IV found that different standardizations of the 10-Meter Walk Test (10MWT) for measuring gait speed yielded very similar results, including cut-off scores for future falls, suggesting that the clinical conduct of 10MWT can be simplified.

CONCLUSIONS: Everyday walking difficulties should be a primary target when attempting to reduce FOF in mild PD, and balance training should focus on self-generated perturbations caused by everyday activities rather than external perturbations. Moreover, FOF and asking about prior near falls seem to be important issues for prediction of falls and near falls early in the disease course. The 3-step model can be recommended as a clinical prediction tool but a new model may be considered a promising alternative. Clinical gait speed measurement by the 10MWT can be simplified by not using acceleration distance or repeated trials in mild PD.

Key words: Parkinson's disease, Fear of falling, Self-Efficacy, Falls, Near falls, Walking, Balance, Prediction, Validation studies, Rehabilitation, Prevention.

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Till De drabbade och till ER som kan hjälpa till här och nu

“Do not wait – the time will never be just right. Start where you stand, and work whatever tools you may have at your command and better tools will be found as you go along.”

Napoleon Hill

[“Vänta inte – tidpunkten kommer ändå aldrig att bli den rätta. Om du börjar där du är och jobbar med de verktyg du har, kommer du att hitta bättre på vägen.”]

Okänd Översättare

[”Nie czekaj – właściwa chwila nigdy nie nadchodzi. Zacznij natychmiast – tu i teraz. Posługuj się narzędziami, jakie masz pod ręką, a lepsze znajdziesz w trakcie pracy.”]

Tłumacz Nieznany

Content

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List of publications

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IV. Lindholm B, Nilsson MH, Hansson O, Hagell P. The clinical significance of different standardizations of the 10-Meter Walk Test in mild Parkinson's disease (Submitted for publication).

Abbreviations

AUC	Area under the Receiver Operating Characteristic curve
BBS	Berg Balance Scale
CGS	Comfortable gait speed
CI	Confidence interval
ES	Effect size
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue scale
FES(S)	Swedish version of the Falls Efficacy Scale
FOF	Fear of falling
FOG	Freezing of Gait Questionnaire
FOGQsa	Self-administered version of the Freezing of Gait Questionnaire
H&Y	Hoehn and Yahr staging
ICC	Intra-class Correlation Coefficient
KC	Kappa Coefficient
LDE	Levodopa equivalent daily dose
MMSE	Mini Mental State Examination
NRT	Nutt Retropulsion Test
OR	Odds ratio
PADLS	Parkinson's disease Activities of Daily Living Scale
PD	Parkinson's disease
PROMs	Patient-related outcomes measures
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SEM	Standard Error of Measurement
TG	Tandem gait
10MWT	The 10-Meter Walk Test
UPDRS	Unified Parkinson's Disease Rating Scale
Walk-12G	The generic Walk-12

Definitions

Balance	A broad "umbrella" term [1] describing the dynamics of body posture to prevent falling [2]. Balance may also be generally defined as the ability to control one's centre of body mass in relation to the base of support [3].
Falls	An unexpected event in which the participants come to rest on the ground, floor, or lower level [4].
Fear of falling	Fear of falling can be considered an umbrella term and conceptualized in different ways. In this thesis, FOF is defined as a low self-efficacy in performing activities without falling, i.e. low fall-related self-efficacy [5, 6].
Walking	Walking is fundamental for a physically independent life-style and is a predictor of overall health status [7]. Walking results from the complex interaction of multiple systems e.g. balance and generation of stepping [3].
Near falls	A fall initiated but arrested by support from a wall, railing, other person etc. [8].
Postural instability	One of the four cardinal symptoms of PD due to a deficit in postural reflexes. Means a lack of postural control i.e. difficulties in maintaining balance in static and dynamic situations [9].

Introduction

Parkinson's disease

Parkinson's disease (PD) is an age-related, progressive, neurodegenerative disease that has no cure. The typical age of onset is around the age 60. The crude incidence (year 2004-2007) of PD in Sweden was about 22/100 000 individuals [10] and the prevalence is estimated at approximately 22 000 [11]. In general, there is higher incidence and greater prevalence of PD in men than in women (ratio 1.5:1) [11, 12]. Given the tendency for people to live longer and that the risk of PD increases with age, [12] the number of people with PD is expected to double by the year 2030 [13].

In PD, degeneration of the dopaminergic pathways from the substantia nigra results in striatal dopamine deficiency. This is considered the core neuropathology of PD, although several brain areas, circuits and transmitter substances are involved, as well as the brain stem and the peripheral autonomic nervous system [14, 15]. However, the aetiology remains unclear. Several mechanisms have been considered as contributing factors, including genetic and environmental factors [16] such as pesticides [17].

PD is characterized by four cardinal signs: resting tremor, bradykinesia, muscle rigidity, and postural instability. In addition to these classic motor symptoms, non-motor features (e.g. fatigue, cognitive impairments, depression, orthostatism) are also common [18]. According to the United Kingdom PD Society Brain Bank clinical diagnostic criteria, a diagnosis of idiopathic PD requires the presence of bradykinesia and at least one of the other cardinal signs [19]. In early stages of the disease, PD may be difficult to distinguish from other parkinsonian disorders that partly share the same clinical manifestations [20], but unilateral onset, a progressive course and a positive response to anti-PD medication (i.e. levodopa) are supportive criteria for a PD diagnosis [19].

The severity of disease is commonly classified according to the Hoehn and Yahr staging (H&Y) ranging from I (unilateral symptoms) to V (wheelchair-bound or bedridden) [21, 22]. Postural instability is a key component of H&Y and the hallmark of moving from stages I&II to stage III.

Treatments for Parkinson disease

Medical treatments include medication and surgical therapy (Deep Brain Stimulation) [23, 24]. The core and first-choice therapy is dopaminergic medication (levodopa) that targets the neurotransmitter imbalance within the basal ganglia circuits [23]. Other oral drugs that target dopaminergic pathways are also used and include dopamine agonist and enzyme inhibitors [25, 26]. Transdermal, subcutaneous and enteral drug administration routes are also available in addition to traditional oral administration [27]. While these compounds work through different routes, they all target the dopaminergic system and their dopaminergic potentials can be converted into levodopa equivalent (LDE) doses, where 1 LDE represents 1 mg of regular oral levodopa [28]. Treatment complications such as a fluctuating drug response and dyskinesia often develop over time [29]. Motor fluctuations manifest with periods of good antiparkinsonian drug response ("on" phase) interrupted by periods of poor drug response and increased disability ("off" phase). These occur in relation to fluctuating levodopa levels, but may also occur in a more random fashion. Dyskinesia are involuntary movements that typically occur during the "on" phase.

In addition to medical treatment, rehabilitation is needed, which can be provided by a multidisciplinary team including, e.g. physician, nurse, occupational therapist, physiotherapist, speech therapist, social worker, neuropsychologist, and dietician [30]. In recent guidelines regarding the care of persons with PD, the Swedish National Board of Health and Welfare (Socialstyrelsen) highlighted the importance of considering the person's individual needs as the starting point for the team-based rehabilitation [31].

Key issues for physiotherapists that work with people with PD include gait and balance problems as well as fall prevention [32]. Importantly, reducing both falls and balance problems have been identified as a top research priority by persons with PD, their carers and professionals [33].

Balance and gait in Parkinson's disease

People with PD are particularly unstable backwards [34-36]; an external perturbation induced by a push backwards challenges their reactive responses [37, 38]. Every day transfers and activities (e.g. walking, turning, and transferring to/from sitting) induce self-generated perturbations that challenge balance [39]. Walking is particularly challenging because the body is in a continuous state of imbalance, and

the only way to prevent falling is to take the next step [2]. PD-related walking difficulties are common and mainly characterized by decreased gait speed, reduced step length, shuffling [32, 40] and turning difficulties [41]. Stooped posture and reduced arm swing are also common [32]. Walking difficulties as well as turning difficulties have already been reported in the early stages of PD [42-44]. Walking may be affected by conducting an additional task (dual-tasking, e.g. carrying something while walking) because of wrong prioritization i.e. the "posture second" strategy [45, 46]. Moreover, approximately 50% of people who have had PD for five years or more experience freezing of gait (FOG), i.e. the feet are perceived as getting glued to the ground [47-49]. Freezing is particularly common when initiating gait (start hesitation) and when the person is passing through narrow/confined spaces (e.g. doorways), in crowded places or immediately before reaching a destination such as a chair (destination hesitation). FOG occurs also when turning and in stressful situations, with unsteadiness and falls as consequences [8, 50-53].

Falls and near falls

Falls

According to the Prevention of Falls Network Europe (ProFaNE) consensus [4], a fall is defined as "an unexpected event in which the participants come to rest on the ground, floor, or lower level". Having a PD diagnosis implies almost a three-fold increased risk for falls [54, 55]. This risk is higher than among healthy individuals of the same age [55, 56] but also in relation to people with other neurological disorders such as stroke [54, 57]. Falls and balance problems are common early in the course of PD [55, 58-61]. ProFaNE recommends that "falls should be recorded using prospective daily recording and a notification system with a minimum of monthly reporting. Telephone or face-to-face interviews should be used to rectify missing data" [4]. Studies based on prospective recording of falls in PD have reported that 31–90% of people with PD fall, of which 16–68% experience recurrent falls [62-64]. The time frame during which prospective falls have been recorded in these studies differs. Those that used a prospective six-month follow-up reported falls in 48%-78% of which 24-68% were recurrent fallers [56, 65, 66]. Corresponding values for studies with a 12-month follow-up were 31-90% and 16-50% for recurrent fallers [51, 63, 67-71].

To differentiate the conditions in which a fall occurs, patient-related or environmental risk factors have been proposed [72]. Commonly cited patient-related risk factors in PD are postural instability [9] and FOG [73]. Environmental risk factors

generally include tripping, slipping, walking on uneven surfaces and inadequate illumination [72].

Most people with PD fall while walking, but falls also occur while turning, moving to/from sitting, bending forwards or reaching [50, 74-76]. Performing attention-demanding tasks (dual-tasking, e.g. carrying something while walking) also relate to falls [50, 74]. Most falls occur in the medicated "on" phase (60-67%) [8, 56] within the home or in familiar environments (60-80%) [8, 50, 56, 64, 74]. Falls regardless of location occur mainly in daytime and in the morning [77]. Walking over a carpet or transitioning between tiled and wooden surfaces have been identified as the most common environmental factors indoors, while tripping and slipping were the most common environmental factors outdoors. Importantly, postural instability was the most common patient-related risk factor for both indoor and outdoor falls [77]. Falling forward has been reported to be more common than sideways and backwards falls in PD [74, 77].

Near falls

It is also common for people with PD to experience the so-called 'near fall' [65, 74, 78-82], which has been suggested to be an early precursor of an increased fall risk [8, 83-86]. Retrospective studies that used the time frame when asking about experience of near falls reported that 55% [79] and 75 % [74] of individuals with PD had experienced near falls in the past six and 12 months, respectively. Importantly, a higher number of individuals experience near falls than falls [74, 79, 82], and near falls occur in 37-62% of those who do not experience any falls [74, 78, 82]. Moreover, approximately 50% of those who experience near falls, but not falls, report fear of falling (FOF) [82].

Only two prospective studies included near falls when addressing risk factors for falls in PD [8, 87]. However, these studies used different definitions of a near fall. Ashburn et al. defined near falls "as an occasion on which an individual felt that he/she was going to fall but did not" [87] while Gray & Hildebrand described near falls as " a fall initiated but arrested by support from a wall, railing, other person etc." [8]. In this thesis, the definition by Gray & Hildebrand will be used because it is more specific than that of Ashburn et al.

There is limited knowledge about circumstances of near falls because the majority of studies only investigated falls. However, near falls seem to occur mainly at home, commonly while turning or while negotiating steps or doorways [74, 88].

Consequences of falls

Falls in PD represent continuing, disabling, costly problems [51, 68, 73, 89, 90] and lead to psychological consequences [91]. Compared with healthy individuals,

people with PD have a nine-fold increased risk of injurious fall [56]. In one study, 15 years after diagnosis 81% of people with PD reported falls, of which 23% sustained fractures [73], and it has been estimated that people with PD have a four-fold higher risk for hip fractures than age- and sex-matched healthy controls [92]. Consequently, fractures generate higher health care costs in PD than in other groups [93]. Fractures of the upper limbs (shoulder, radius, hand), as well as head contusions [77], and brain injuries also occur [94]. A greater proportion of fall-related brain injuries occur in patients with PD compared to patients without PD [94]. However, soft-tissue injuries are most commonly reported in relation to falls [64, 77].

Falls in PD often result in activity limitations, participation restrictions, social isolation, hospital admissions and in some cases premature or injury mortality [95], and are among the most common reasons for nursing home admittance [96]. Falling outside the home and the need for help from strangers may lead to psychological trauma and embarrassment [76].

Fear of falling

FOF is an umbrella term including different concepts i.e. fall-related self-efficacy [5, 6], balance confidence [97], concerns about falling [98] and fall-related activity avoidance [99]. In this thesis, FOF is defined as low self-efficacy in performing activities without falling, i.e. low fall-related self-efficacy [5, 6].

FOF is more common and pronounced in people with PD than in age-matched controls [56, 100-103]. When using a single-item dichotomous question (*"Are you afraid of falling"*), 35-59 % of people with PD responded that they were afraid of falling [80, 104-106]. Seventy percent of them with FOF reported avoidance of activities [82]. FOF is also more common and pronounced among those who have experienced falls [106]. However, the history of falls is not independently associated with FOF in people with PD [80, 107-109], and FOF is also reported among those without prior falls [82, 106].

In people with PD, FOF has been shown to be a predictor for recurrent falls [62]. It has been found to impact negatively on community walking i.e. walking outside the home [110], and to be a major barrier to physical exercise [111]. FOF can induce social isolation [112], and negatively affect self-reported health [113] as well as perceived participation [114]. FOF therefore appears to be important to acknowledge and address in PD care and rehabilitation.

In order to gain an increased understanding of factors that are independently associated with FOF, studies using multivariable analyses are needed. Factors that have been shown to be independently associated with FOF in such studies are presented in Table 1. One of these studies (Nilsson et al.) [80] used fall-related self-efficacy as the dependent variable and identified walking difficulties, need of help in daily activities, fatigue, turning hesitation and fluctuations as independent factors associated with FOF. Until the year 2013 few studies had comprehensively investigated factors associated with FOF in people with PD [80, 108, 109, 115].

Table 1.
Factors independently associated with FOF in PD

Factors	
Age [109, 116]	Motor symptoms [108, 116]
Anxiety [115]	**Need help from others in daily activities [80]**
Balance [107] *	Orthostatism [116] *
Cognition (global) [108]	PD duration [108]
Disability [115]	Postural instability and gait difficulty [109]
Depressive symptoms [107, 108, 115]	Severity of disease [108]
Fatigue [80, 116]	**Turning hesitations [80]**
Fluctuations [80]	Use of mobility devices [107] *
Knee muscle weakness [109]	**Walking difficulties [80, 116]**

*These factors have been identified after the publication of Paper I.
Those that are bolded have been shown to be independently associated with low-fall-related self-efficacy.

Prediction of future falls

Prospective studies that monitored falls according to European consensus [4] have identified several independent predictive factors (e.g. in Table 2). Despite this, fall prediction is still a clinical challenge. One of the reasons may be that predictive factors typically have been identified based on logistic regression models and associated odds ratios (ORs) (e.g. [51, 71]). However, ORs do not inform about the ability of predictive factors to discriminate between future fallers and non-fallers [117, 118] and therefore taking these factors into account is not easy in clinical practice [119]. It has therefore been recommended to estimate the accuracy of clinical prediction models measured in terms of the area under the Receiver Operating Characteristic curve (AUC). To this end the 3-Step Falls Prediction Model (3-step model) has been proposed for people with PD [120]. However, successful implementation of existing prediction models in clinical practice requires external validation in different study samples. Besides an external validation, it is also recommended to consider whether existing models can be improved, e.g. by additional predictors [121].

Table 2.
Predictive factors independently associated with future falls in PD

Factors	
Abnormal posture [51]	Hallucinations [122] *
Balance and gait [51, 56, 66]	History of falls [51, 56, 68, 71]
Bradykinesia/rigidity [122] *	Leg muscle weakness [51]
Dementia [71]	Levodopa daily equivalent dose [63, 122] *
Difficulties when arising from chair [122] *	Loss of arm swing [71]
Diuretics [122] *	Motor symptoms [64] *
Disability [63] *	Motor symptoms and disability [122] *
Dyskinesia [122] *	Orthostatism [66, 122]
Education [122] *	PD duration [71]
Fall frequency [68]	Power of attention [68]
Female gender [122] *	Reaction time variability [68]
Freezing of gait [51, 66, 122]	Severity of disease [56]
Frontal impairment [51]	

*These factors have been identified after the publication of Paper II.

Assessment

Several commonly used clinical balance and gait tests that are administered by physiotherapists have good measurement properties when applied to individuals with PD [32, 123]. Coverage of all these is beyond the scope of this thesis. However, a common conclusion is that multiple approaches are needed to cover the complexity of balance and gait problems in PD [123-126]. Below follows a brief summary of some of the main tests and assessment scales relevant to this work.

The Berg Balance Scale (BBS) [127] is widely used as a functional test of balance performance. The validity of the BBS in PD has been supported by correlations with comfortable gait speed and severity of disease [32]. The total score has been shown to significantly differentiate between fallers and non-fallers [124, 126, 128]. Test-retest reliability (Intra-class Correlation Coefficient, ICC) ranged between 0.80-0.94 [32]. The 10-Meter Walk Test (10MWT) is widely used and recommended as a measure of gait speed in PD. Comfortable gait speed according to the 10MWT correlates with the Unified Parkinson's Disease Rating Scale (UPDRS) total, motor and activity of daily life (ADL) scores [32]. The test-retest reliability (ICC) has ranged between 0.75-0.98 [123]. Gait speed according to the 10MWT has been found to predict fall risk in PD [129, 130]. Different standardizations of the 10MWT exist, such as measuring over different distances (10 or 6 m) and the inclusion or exclusion of acceleration distance, i.e. dynamic vs. static start [123, 129, 130]. It is also generally recommended to perform multiple trials and use the mean of these as

the test result [32, 131]. Postural reflexes are typically assessed by means of pull tests, of which there are several variations [38]. The most commonly used is item 30 of the UPDRS, which involves an expected shoulder pull [132]. The sensitivity and specificity for detecting those with retrospective falls has been reported to be 0.66 and 0.82, respectively, and test-retest reliability (Kappa coefficient, KC) was 0.63 [32, 38]. Others advocate using an unexpected shoulder pull, i.e., the Nutt Retro-pulsion Test (NRT) [37, 38]. Sensitivity and specificity for detecting retrospective falls have been reported to be 0.63 and 0.88, respectively, and test-retest reliability (KC) was 0.93 [32, 38]. Tandem gait (TG) is a routine clinical test incorporated in the standard neurological examination as a measure of dynamic balance [133, 134]. Sensitivity and specificity for detecting those with prospective falls has been reported to be 0.63 and 0.80, respectively [56]. The feasibility of these different clinical tests varies in terms of cost, time, space, and effort [32, 123].

To cover the individuals' perceptions of their functions and/or how activities and participation are affected, patient-reported outcome measures (PROMs) may be used. There is growing evidence that PROMs may be useful in clinical practice. Research has shown that integration of PROMs in clinical practice improves patient-clinician communication and can also enhance patient care and outcomes [135]. A large number of PROMs related to various PD-related problems are available. However, the main PROMs related to the focus of this thesis are the Swedish Falls Efficacy Scale [136], the generic Walk-12 [137] and the self-administered Freezing of Gait Questionnaire (FOGQsa) [138, 139]. These assess self-efficacy in performing activities without falling, walking difficulties in daily life, and gait difficulties related to FOG, respectively.

The generic Walk-12 (Walk-12G) was developed from the 12-item Multiple Sclerosis Walking Scale (MSWS-12) that assesses walking difficulties in daily life among people with multiple sclerosis [140]. That scale was modified twice; first in order to be applicable also for people with other neurological disorders [141], and second, when it was changed into a completely generic version, Walk-12G [137]. The latter version has demonstrated supported scoring assumptions, reliabilities (>0.91) and construct validity among people with PD as well as MS [137].

Similarly, the FES(S) has demonstrated supported scoring assumptions, reliabilities (>0.81) and construct validity in PD [79, 136]. The FES(S) has also been linked to the International Classification of Functioning, Disability and Health [142]. The linking process showed that it mainly focuses on FOF in relation to mobility but also in relation to a more diverse set of activities, such as self-care.

The (FOGQsa) [138, 139] was developed from the clinician-administered Freezing of Gait Questionnaire (FOGQ) [143, 144]. Scores from the two versions have shown

excellent correlation and the FOGQsa has demonstrated supported scoring assumptions, reliabilities (>0.91) and concurrent validity in PD [138].

Aim

Overarching aims of the thesis

The overall aim of this longitudinal PhD project was to gain increased knowledge about factors associated with FOF, falls and near falls, as well as to contribute to improved clinical fall prediction for people with mild PD.

Specific aims

Paper I To determine factors associated with FOF (conceptualized as low fall-related self-efficacy) among people with PD. More specifically, the aim was to determine whether previous postal survey based findings could be replicated in an independent clinical sample and, secondly to investigate whether additional and previously unexplored motor aspects as well as cognitive features independently may contribute to FOF.

Paper II To determine factors associated with future falls and/or near falls in mild PD.

Paper III To externally validate the 3-step model in an independent sample of people with mild PD. In addition, it was sought to explore the ability of additional historical information and clinical tests to predict falls as well as near falls, and compared those with the proposed 3-step model.

Paper IV To examine the clinical significance of two aspects of the standardization of conducting the 10MWT in mild PD: (i) using static vs. dynamic start and (ii) using data from a single vs. two repeated trials. In addition, the implications of these standardizations in terms of prediction of future falls were explored.

Methods

Design

This project includes a baseline examination and a prospective six-month follow-up regarding falls and near falls. Paper I (cross-sectional design) included the data from the baseline examination. Papers II-IV included both data from the baseline examination and the six months follow-up of prospective falls and near falls.

Participants

All people diagnosed with PD and receiving care at a south Swedish university hospital neurology outpatient clinic during 2007–2013 were considered eligible for inclusion. The overall exclusion criteria were age above 80 years old, inability to stand without support (i.e., from a person or other aids), inability to understand instructions, or having severe comorbidity. Selection was conducted based primarily on medical records. In cases of uncertainty, the PD specialized nurse and /or neurologist at the clinic was consulted. Potential participants were invited to participate between October 2008 and May 2013. Participants were invited by post and after telephone contact. The overall recruitment process is presented in Figure 1.

The total cohort consists of 151 individuals, of whom 68 (45%) were women. The mean (SD, min-max) age was 68 (9.6, 35-80) years. The median (q1-q3, min-max) PD duration, UPDRS (motor part) and H&Y were 2 (1-6, 0.1-17) years, 12 (8-18, 1-46), and II (II-III, I-IV), respectively. Although all individuals in the thesis were from the same cohort, the numbers of included individuals vary in Papers I-IV due to different recruitment periods, the specific aims, and additional exclusion criteria. The details are presented in Table 3.

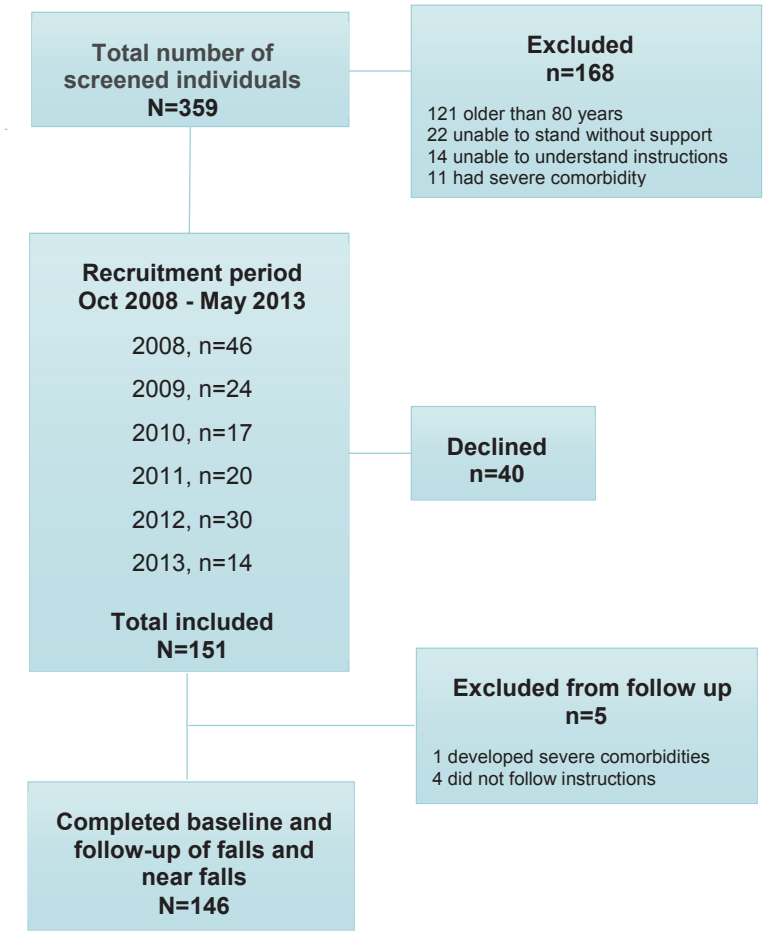

Figure 1.
Overall recruitment process of all individuals included in this thesis.

Table 3.
Demographic characteristics of the participants in Papers I-IV [1]

	Paper I N=104	Paper II N=141	Paper III [2] N=138	Paper IV N=151
Female gender, n (%)	49 (47)	65 (46)	64 (46)	68 (45)
Age (years)				
Median (q1-q3)	69 (62-76)	69 (63-75)	69 (62-75)	69 (63-75)
Mean (SD; min–max)	68 (9.4; 35-80)	68 (9.7; 35-80)	67 (9.8; 35-80)	68 (9.6; 35-80)
PD duration (years)				
Median (q1-q3)	4 (1-7)	2 (1-6)	2 (1-6)	2 (1-6)
Mean (SD; min–max)	5 (4.2; 0.4-17)	4 (3.9; 0.1-17)	4 (4.0; 0.1-17)	4 (4.0; 0.1-17)
Cognition (MMSE)				
Median (q1-q3)	28 (26-29)	28 (26–29)	28 (26-29)	28 (26-29)
Mean (SD; min–max)	27 (2.3; 18-30)	27 (2.1; 19-30)	28 (1.7; 24-30)	27 (2.2; 18-30)
Motor symptoms (UPDRS III)				
Median (q1-q3)	13 (8-20)	13 (8-18)	12 (8-18)	12 (8-18)
Mean (SD; min–max)	14 (8.1; 2-46)	14 (7.8; 1-46)	14 (7.5; 1-34)	14 (7.9; 1-46)
Severity of disease (H&Y)				
Stage I, n (%)	10 (9.5)	12 (8.5)	12 (9)	12 (8)
Stage II, n (%)	54 (52)	79 (56)	76 (55)	87 (57.5)
Stage III, n (%)	34 (32.5)	43 (30.5)	43 (31)	45 (30)
Stage IV, n (%)	6 (6)	7 (5)	7 (5)	7 (4.5)
Stage V	-	-	-	-
L-dopa equivalents (LDE) mg/day [3]				
Median (q1-q3)	450 (300-622)	400 (286-600)	400 (300-600)	400 (300-600)
Mean (SD; min–max)	489 (305; 0-1477)	444 (297; 0-1477)	449 (297; 0-1477)	441 (292; 0-1477)

[1]All participants were from the same cohort and were consecutively included during the recruitment period 2008-2013.
[2]Those with MMSE<24 (n=8) were excluded due to specific issues and additional exclusion criteria.
[3]Derived according to Tomlinson et al. (2010) [28].
H&Y, Hoehn and Yahr stage (possible stages, I-V; higher=worse); LDE, daily total levodopa equivalent dose (mg); MMSE, Mini Mental State Examination (possible scores, 0–30; higher=better); PD, Parkinson's disease; UPDRS III, motor part of the Unified PD Rating Scale (possible scores, 0–108; higher=worse).

Ethical considerations

The project was conducted in accordance with the Helsinki Declaration and was approved by the Regional Ethical Review Board in Lund, Sweden (Dnr 2011/768). The main ethical principle for all scientific work should always be that a project/study must not cause the participants any unnecessary harm or discomfort. However, most studies involve some level of discomfort for their participants; if nothing else, there is usually the aspect of time consumption. The foreseeable benefits of the project included were considered to outweigh any foreseeable discomfort experienced by the participants.

Potential participants were contacted by post with information explaining the project, an invitation to participate, and an offer to receive additional verbal information. Participation was voluntary. All participants were informed of the aim of the project and gave their written informed consent. They were also informed about the right to withdraw from the study at any time and that withdrawal would not affect their care.

Those who reported falls or near falls during the prospective investigation were encouraged to contact a physiotherapist in their own municipality for further assessment.

Data collection

Procedure and Instruments

All participants were assessed during an outpatient visit, which was scheduled at a time of day when the participant usually reported feeling at his/her best.

During the study visits, the participants first completed a battery of PROMs:

- The Swedish version of the Falls Efficacy Scale (FES(S)) targets fall-related self-efficacy, and was used to assess FOF. The FES(S) includes 13 items (activities) scored from 0 (not confident at all) to 10 (completely confident) [5, 136]. The maximum total score is 130 and higher scores denote “higher” fall-related self-efficacy.
- The self-administered Freezing of Gait Questionnaire (FOGQsa) consists of six items scored 0-4 (higher scores=more FOG) [139, 144]. In this thesis, we only used items three (freezing) and six (turning hesitations). Those

scoring ≥1 on item three were categorized as “freezers” and those scoring ≥1 on item six were considered to have turning hesitations [80].

- The generic Walk-12 (Walk-12G) assesses walking difficulties in everyday life, and includes 12 items. Items one to three are scored 0-2 and items four to 12 are scored 0-4. The total score ranges from 0 to 42 (higher scores=more walking difficulties) [137].
- The Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F) consists of 13 items scored 0-4, with a total score ranging from 0 to 52 (higher scores=less fatigue) [145, 146].
- The Parkinson's disease Activities of Daily Living Scale (PADLS) is a five-grade (higher scores=more ADL-difficulties) single-item scale regarding ADL-difficulties/dependence [147, 148]. Those scoring >2 were categorized as” needing help from others in daily activities”.

Swedish versions of the above PROMs were used. The validity and reliability of all included instruments have previously been found to be acceptable in people with PD [136-139, 145, 147, 148].

Clinical assessments were then administered and targeted different aspects of balance and disease-specific symptoms. All participants self-rated their motor status at the time of examination as “good/on”, “on with dyskinesia”, or ”bad/off” immediately before testing. All clinical assessments and tests were conducted by the same physiotherapist (BL) in the following order:

- The Berg Balance Scale (BBS) assesses functional balance performance of importance in daily life. It includes 14 items (tasks) scored 0-4, and the maximum score is 56 (higher scores=better functional balance) [127].
- The Nutt Retropulsion Test (NRT) assesses retropulsion [37, 38]. The participant stands with feet slightly apart and eyes open, with the examiner giving a sudden, firm backwards pull to the shoulders from behind. Only one trial was performed. The NRT is scored 0-3: 0 (normal, ≤2 steps to recover); 1 (≥3 or more steps; recovers unaided); 2 (would fall if not caught); 3 (spontaneous tendency to fall or unable to stand unaided). Those scoring ≥1 were categorized as having retropulsion [38].
- Tandem gait (TG) assesses dynamic balance [133, 149]. Participants were instructed to take 10 consecutive heel-to-toe steps along a straight line without walking aids or support, with eyes open. Performance is scored 0-3; 0 (no side steps), 1 (a single side step), 2 (multiple side steps), 3 (unable to take 4 consecutive steps) [149]. Those scoring ≥1 were categorized as having an abnormal TG performance [56, 150].

- The 10-Meter Walk Test (10MWT) was conducted in comfortable gait speed at 10-meter distance with two different standardizations; with and without an additional 2 m for acceleration, i.e. with a dynamic or static start, respectively. Two trials of each standardization were conducted [151].
- The Unified PD Rating Scale (UPDRS) part III (motor examination) assesses parkinsonian motor symptoms. It consists of 14 items (scored 0-4) with a total score ranging from 0 to 108 (higher scores=more motor symptoms) [132].
- Item 30 of UPDRS assesses retropulsion; the participant was first told that s/he was to be pulled and instructed to prevent falling [132]. The person was prepared by one practice trial [152]. Performance was scored 0-4: 0 (normal), 1 (retropulsion, but recovers unaided), 2 (absence of postural response, would fall if not caught by examiner) and 3 (very unstable, tends to lose balance spontaneously), and 4 (unable to stand without assistance). Those scoring ≥1 were categorized as having retropulsion [38].
- Hoehn and Yahr staging (H&Y) [21, 22] assesses the severity of disease and consists of five stages: I (unilateral involvement only, usually with minimal or no functional disability), II (bilateral or midline involvement without impairment of balance), III (bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent), IV (severely disabling disease; still able to walk or stand unassisted), and V (confinement to bed or wheelchair unless aided).
- The Mini Mental State Examination (MMSE) was used for coarse global cognitive screening. It yields a total score ranging between 0-30 (higher scores=better cognition) [153].

All included clinical tests have previously been found to have acceptable validity and reliability in people with PD [21, 37, 38, 127, 132, 151, 153]. The exception is TG, which does not seem to have been fully assessed regarding test-retest reliability.

Additional PROMs and self-reported single-items were then administered:

- Self-rated dyskinesia according to part IV of the UPDRS, scored 0-4 (higher scores=more dyskinesia). Those scoring ≥1 on item 32 (dyskinesia present during ≥1-25% of the day) were categorized as having dyskinesia [132].
- History of falls (Yes/No): *In the last six/twelve months, have you fallen in such a way that your body hit the ground?*
- History of near falls (Yes/No): *Are you ever close to falling, but you manage to grab on to something/someone at the last minute so that your body does not hit the ground?*

- Balance problems while dual-tasking (Yes/No): *Do you experience balance problems while standing or walking when doing more than one thing at a time, e.g. carrying a tray while walking?*
- Pain (Yes/No): *Do you presently suffer from pain?*
- Fear of falling (Yes/No): *Are you afraid of falling?*

Demographic data and anti-parkinsonian medications were recorded. Daily levodopa equivalent (LDE) doses (mg/day) were calculated according to recommended conversion factors [28].

As the last step during the outpatient visit, the participants were instructed to register all consecutive falls and near falls during the following six months [4]. They were provided with a diary-folder consisting of pre-printed pages for recording the date and time of every event and questions (Yes/No) clarifying whether the incident was a fall or a near fall. The question in relation to a fall was phrased as follows: *Did you fall in such a way that your body hit the ground?* The corresponding question about a near fall incident was phrased: *Were you close to falling, but managed to brace yourself at the last moment (e.g. grabbed on to someone, to an object or the wall?* Falls were defined as "an unexpected event in which the participants come to rest on the ground, floor, or lower level" [4]. Near falls were defined as" a fall initiated but arrested by support from the wall, railing, other person etc." [8]. The definitions of a fall and a near fall were thoroughly described during the outpatient visit. All the participants were telephoned monthly to ensure that registrations had been completed according to instructions. During the last telephone call, they were requested to return the diary-folder in a pre-stamped envelope.

Overview of Papers I-IV

Paper I (n=104)

The first step of this study was to replicate a postal survey study [80] that included 11 independent variables (potential factors associated with FOF). The dependent variable was FOF, conceptualized as fall-related self-efficacy (FES(S) scores).

In the second step, previously untested clinically assessed variables targeting balance, gait, motor symptoms and cognition were also included. In total, 18 variables were considered as potential associated factors with FOF. An overview of the study design, specific aim, statistical methods and included variables is presented in Table 4.

Paper II (n= 141)

In Paper II, the 18 potential associated factors that were included in Paper I as well as FES(S) were considered as potential factors associated with future falls and/or near falls. Based on the prospective six-month follow-up with fall diaries, participants were defined as experiencing falls and/or near falls if they had prospectively reported at least one fall or one near fall. An overview of the study design, specific aim, statistical methods and included variables is presented in Table 4.

Table 4.
Study design, specific aims, statistical methods, and variables included in Papers I-II

	Paper I **N=104**	**Paper II** **N=141**
Design	Cross-sectional.	Cross-sectional with prospective investigation of falls and /or near falls for 6 months.
Specific aim	To determine factors associated with FOF.	To determine factors associated with future falls and/or near falls.
Statistical methods	Bivariate analyses. Multiple linear regression analysis.	Simple and multiple logistic regression analysis.
Dependent variable	Low fall-related self-efficacy (FES[S]).	Prospective falls and/or near falls (no/yes).
Variables		
Age (years)	X	X
Balance problems while dual-tasking *	X	X
Cognition (MMSE)	X	X
Comfortable gait speed (10MWT)	X	X
Dyskinesia (item 32, UPDRS IV) *	X	X
Fatigue (FACIT-F)	X	X
Fear of falling (FES[S])	-	X
Freezing of gait (item 3, FOGQsa) *	X	X
Functional balance (BBS)	X	X
Female Gender	X	X
History of falls in past 6 months *	X	X
History of near falls *	X	X
Motor symptoms (UPDRS III)	X	X
Need help from others in daily activities (PADLS) *	X	X
Pain *	X	X
PD duration (years)	X	X
Retropulsion (NRT) *	X	X
Turning hesitations (item 6, FOGQsa) *	X	X
Walking difficulties (Walk 12 G)	X	X

*Dichotomized
BBS, Berg Balance Scale; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue scale; FES(S), Falls Efficacy Scale (Swedish version); FOGQsa, Freezing of Gait Questionnaire, self-administered version; MMSE, Mini Mental State Examination; NRT, Nutt Retropulsion Test; PADLS, Parkinson's disease Activities of Daily Living Scale; UPDRS III, motor part of the Unified Parkinson's Disease Rating Scale; UPDRS IV, part IV of UPDRS (complications of therapy); 10MWT, 10-Meter Walk Test; Walk-12 G, the generic Walk-12.

Paper III (n=138)

The study was based on previous reports regarding the 3-step model as a clinical prediction tool for falls in PD [120]. The model includes the following predictors: history of falls, history of FOG and comfortable gait speed (CGS) <1.1m/s. In order to replicate the original methodology as closely as possible, individuals with significant cognitive impairment (MMSE score <24; n=8) were excluded, and the mean value (m/s) of two trials of 10MWT (with static start) was used to dichotomize gait speed.

In order to further investigate the 3-step model, we also explored the value of additional historical information (history of near falls) and brief clinical tests (TG, NRT, and item 30 of the UPDRS) to predict falls as well as falls and/or near falls. Data from the six-month prospective fall diaries were used as described above (se Paper II). An overview of the study design, specific aims, statistical methods and included variables is presented in Table 5.

Paper IV (n=151)

Data according to two trials of different standardizations of the 10MWT, i.e. with static and dynamic starts were used to explore the clinical significance of these various test conditions (static vs. dynamic start, and single vs. mean m/s gait speed). A twelve-meter distance was used; the following distances were marked with red markers on the wall/floor: 0m, 2m, 10m, and 12m. Walking time (s) was measured with a digital stopwatch (Origo, model 365510) using a split time function. A verbal start command was given. Timing at 2m, 10m and 12m began when the lead foot passed the marker. Each trial generated walking time (s) at the first 10 m (static start) and at the second 10 m distance (dynamic start). Two trials were conducted. Walking aids were permitted. Time was recorded to the nearest 0.001 s. Gait speed was calculated as m/s. The mean values of the two trials were calculated. To explore the implications of the various test conditions in terms of fall prediction, data from the six-month prospective fall diaries were also used as described above. An overview of the study design, specific aims, statistical methods and included variables is presented in Table 5.

Table 5.
Study design, specific aims, statistical methods, and variables included in Papers III-IV

	Design	Specific aim	Statistical methods	Variables
Paper III **N=138**	Cross-sectional with prospective investigation of falls and /or near fall for 6 months.	To externally validate the 3-step model in an independent sample of people with mild PD. In addition, it was sought to explore the ability of additional historical information and clinical tests to predict falls as well as near falls, and compared those with the proposed 3-step model.	Simple and multiple logistic regression analysis. Receiver Operating Characteristics.	**Dependent variable** Prospective falls * Prospective falls and/ or near falls * **3-step model** History of falls in past 12 months * Freezing of gait (item 3, FOGQsa) * Comfortable gait speed <1.1m/s * **Additional variables** History of near falls * Retropulsion (NRT) * Retropulsion (Item 30 of UPDRS III) * Abnormal tandem gait *
Paper IV **N=151**	Cross-sectional with prospective investigation of falls and /or near fall for 6 months.	To examine the clinical significance of two aspects of the standardization of conducting the 10MWT in mild PD: (i) using static vs. dynamic start and (ii) using data from a single vs. two repeated trials. In addition, the implications of these standardizations in terms of prediction of future falls were explored.	Paired sample t-test. Cohen's effect size. Intra-class Correlation. Standard Error of Measurement. Simple and multiple logistic regression analysis. Receiver Operating Characteristics. Sensitivity/specificity. Youden index.	**Dependent variable** Prospective falls * **Comfortable gait speed (10MWT)** Static start test 1 Static start test 2 Static start mean value of test 1 and 2 Dynamic start test 1 Dynamic start test 2

*Dichotomized
FOGQsa, Freezing of Gait Questionnaire, self-administered version; NRT, Nutt Retropulsion Test; UPDRS part III, motor part of the Unified PD Rating Scale; 10MWT, 10-Meter Walk Test.

Statistical methods

Unless otherwise stated, data were checked regarding underlying assumptions, then analysed with IBM SPSS (IBM Corp., Armonk, NY) and p-values <0.05 were considered statistically significant.

Continuous and ordinal (or non-normal distributed) data are expressed as mean ± standard deviation, and median value (25th-75th percentile), respectively. Categorical variables were described by n (%).

Paper I

Between-groups comparisons and correlations of non-normally distributed data were analysed by using the Mann-Whitney U-test and Spearman's correlations. Multiple linear regression analysis (forward method) was used to identify factors associated with FOF. The inclusion of factors (independent variables) was initially based on a previously published model [80] and then extended with clinically assessed variables.

Paper II

Logistic regression analysis was used for identifying factors associated with prospective falls and/or near falls. Initially, simple logistic regression analyses were used for factors (independent variables) that were considered potentially important for falls and/or near falls. Variables that were significant at the alpha level of 0.2 were subsequently included as independent variables in a multiple logistic regression analysis in order to identify those independently associated with prospective falls and/or near falls. Both forward and backwards methods were used. In order to facilitate comparisons with prior studies, we also explored factors associated with prospective falls only (i.e. non-fallers and near falls only vs. fallers). The statistical procedure was otherwise identical to the main analysis (see above).

Paper III

Multiple logistic regression analysis (enter method) was used to externally validate the 3-step model [120] with its three suggested predictors (history of falls, history of FOG and CGS <1.1m/s) as independent variables and the occurrence of falls during the six-month follow-up as the dependent variable. Secondly, simple logistic regression analyses were used to evaluate how well each single predictor included in the 3-step model and four additional independent variables (history of near falls, TG, NRT, and item 30 of the UPDRS) predicted future falls. Thirdly, all potential predictors were entered into a multiple logistic regression analysis (backwards

method) to explore if this could improve prediction of future falls as compared to the 3-step model. We also calculated the sensitivity and specificity of relevant prediction models. In order to account for near falls, we also explored factors associated with the combination of prospective falls and/or near falls according to the same procedures as described above. Receiver Operating Characteristic (ROC) curve analyses were used to assess the overall accuracy of each model by estimating the AUC [154, 155]. In constructing the ROC curve, sensitivity (true positives; y-axis) is plotted against 1 – specificity (false positives; x-axis), and the optimal point is the cut-off with the highest true positive and lowest false positive values. AUCs can range between 0 and 1; an AUC <0.5 indicates that the model performs worse than chance, whereas an AUC of 1 indicates perfect discrimination. AUCs ≥0.7 and >0.9 are considered acceptable and high, respectively [156].

Paper IV

Paired sample t-tests were used for head to head comparison between different standardizations and different trials of the 10MWT. In order to explore sizes of differences derived from comparisons, the effect size (ES) was computed using Cohen's d calculation [157]. To determine the agreement between different standardizations and trials of the 10MWT, Intra-class Correlation (ICC, 2-way mixed effects model, absolute agreement, single measure) coefficients were calculated. In addition, the measurement error was determined by calculating the Standard Error of Measurement (SEM) using the formula SD (t1) $\times\sqrt{}$(1–ICC).

ROC curve analysis was used to identify the optimal cut-off scores of gait speed for distinguishing those with and without future falls. In addition, AUCs were calculated. To select the optimal cut-off scores, the Youden index was calculated as sensitivity + specificity – 1. The cut-off score associated with the highest Youden index indicates the optimal cut-off point to discriminate those with and without future falls [154].

Results

Paper I

According to the dichotomous question *"Are you afraid of falling?"* 38 out of 104 (37%) participants reported having FOF. FES(S) scores demonstrated significant bivariate associations with all variables but gender. The median FES(S) score for our study population was 117 (q1-q3, 69.5-129; min-max, 11–130). The first multiple linear regression, a replication based on a previous postal survey study [80], resulted in three significant independent variables explaining 66% of the variance in FES(S) scores. The strongest independent variable (as assessed by the standardized regression coefficients, β) was walking difficulties (Walk-12G scores), which could account for 59.5% of the variance in FES(S) scores. This was followed by need help from others in daily activities (4.2%) and fatigue (2.1%).

After including clinical assessments in multiple linear regression analysis, four significant independent variables were identified explaining 73% of the variance in FOF scores. The strongest factor associated with FOF was still walking difficulties, which explained 64% of the variance, followed by need help from others in daily activities (4.5%), functional balance (2.7%) and fatigue (1.4%). The details are presented in Table 6.

Table 6.
Multiple linear regression with FES(S) scores as the dependent variable in people with Parkinson's disease, n=104 [1]

Significant independent variables [2]		B	β	Adjusted R^2	
				Stepwise change	Cumulative
Walking difficulties (Walk-12G), median (q1-q3)	8 (4.5-21)	-1.543	-0.446	0.642	0.642
Need help from others in daily activities (PADLS), n (%)	11 (10)	-21.823	-0.189	0.045	0.687
Functional balance (BBS), median (q1-q3)	52.5 (46-55)	0.877	0.221	0.027	0.714
Fatigue (FACIT-F) median (q1-q3), median (q1-q3)	38 (29-44)	0.547	0.179	0.014	0.728

[1]Independent variables in the analysis were: need help from others in daily activities (PADLS), walking difficulties (Walk-12G), fatigue (FACIT-F), age (years), PD duration (years), history of falls, history of near falls, dyskinesia (item 32 UPDRS), freezing (FOGQsa item 3), turning hesitations (FOGQsa item 6), pain, cognition (MMSE), motor symptoms (UPDRS III), functional balance (BBS), comfortable gait speed (10-MWT), retropulsion (NRT), balance problems while dual-tasking.
[2]Listed by order of entry into the model (forward method).
BBS, Berg Balance Scale; FACIT-F, Functional Assessment of Chronic Illness Therapy; FES(S), Falls Efficacy Scale, Swedish version; FOGQsa, Freezing of Gait Questionnaire, self-administered version; MMSE, Mini Mental State Examination; NRT, Nutt Retropulsion Test; PADLS, Parkinson's disease Activities of Daily Living Scale; PD, Parkinson's disease; UPDRS III, motor part of the Unified PD Rating Scale; 10MWT, 10-Meter Walk Test; Walk-12G, the generic Walk-12.

Paper II

During the six-month follow-up, 63 out of 141 (45%) participants experienced at least one fall and/or near fall. Forty-five out of 141 participants (32%) reported falls, of whom 26 (58%) reported more than one fall (i.e. recurrent falls). On average, they reported 5.3 falls (min-max, 2-12). In total, 44 participants (31%) reported near falls. Eighteen of those reported only near falls whereas 26 also reported falls. Twenty-six out of the 44 (59%) reported more than one near fall; they reported on average 10.6 near falls (min-max, 2-45). The total number of all reported incidences was 452 (n=63); 158 (35%) of those were falls, whereas 294 (65%) were near falls.

The multiple logistic regression analysis resulted in three significant independent predictors of falls and/or near falls. The strongest factor was FOF conceptualized as fall-related self-efficacy (OR=1.03, $p<0.001$) followed by history of near falls (OR=3.48, p=0.009) and retropulsion/NRT (OR=2.81, p=0.035). Additional analyses (not included in Paper II) conducted in order to test the model's ability to distinguish between individuals with and without future falls and/or near falls yielded an AUC of 0.84. The details are presented in Table 7.

Rerunning the above analysis with future falls as the dependent variable resulted in four independent predictors (OR, 95% CI): pain (OR=4.89, p=0.002), history of near falls (OR=3.28, p=0.011), retropulsion/NRT (OR=3.49, p=0.012) and PD duration (OR=1.15, p=0.021). Additional analyses (not included in Paper II) conducted in order to test the model's ability to distinguish between individuals with and without future falls yielded an AUC of 0.79. The details are presented in Table 7.

Table 7
Multiple logistic regression models for prediction of falls and near falls, n=141

Independent variables		Wald	OR (95% CI)	AUC [1] (95 % CI)	Sens [2]/Spec [3]
Prediction of future falls and/or near falls [4, 5]					
Age (years), mean (SD)	*68 (9.7)*	*0.49*	*1.02 (0.97-1.07)*		
Female gender, n (%)	*65 (46)*	*1.74*	*1.79 (0.75-4.27)*		
Fear of falling (FES[S]), median (q1–q3) [6]	118 (84-129)	14.25	1.03 (1.02-1.05)	**0.84 (0.78-0.91)**	**0.77/0.84**
History of near falls, n (%)	50 (35)	6.75	3.48 (1.36-8.89)		
Retropulsion (NRT), n (%)	35 (25)	4.28	2.81 (1.07-7.37)		
***Prediction of future falls [4,5]**					
Age (years), mean (SD)	*68 (9.7)*	*4.93*	*1.07 (1.01-1.13)*		
Female gender, n (%)	*65 (46)*	*0.19*	*1.23 (0.49-3.06)*		
Pain, n (%) [7]	40 (28)	9.71	4.89 (1.80-13.49)	**0.79 (0.72-0.87)**	**0.58/0.87**
History of near falls, n (%)	50 (35)	6.43	3.28 (1.31-8.29)		
Retropulsion (NRT), n (%)	35 (25)	6.32	3.49 (1.32-9.39)		
PD duration, median, (q1–q3)	2 (1-6)	5.32	1.15 (1.02-1.29)		

*Details from this analysis were available on request (Paper II).
[1]Area under the Receiver Operating Characteristic curves.
[2]The proportion of people with prospective falls who had a positive result (scored above given cut-off point).
[3] The proportion of people without prospective falls who had a negative result (scored below given cut-off point).
[4]Forward/backwards method (Wald); the model was controlled for age and gender (italics in the table).
[5]Independent variables initially entered in the analysis were: age (years), gender, PD duration (years), cognition (MMSE), motor symptoms (UPDRS III), functional balance (BBS), comfortable gait speed (10MWT), fatigue (FACIT-F), pain, walking difficulties (Walk-12G), fear of falling (FES[S]), history of falls, history of near falls, balance problems while dual-tasking, need help from others in daily activities (PADLS), freezing (FOGQsa, item 3), turning hesitations (FOGQsa, item 6), retropulsion (NRT).
[6]Possible score range, 0-130; for the regression analysis, scores were adjusted so that higher scores = more problems.
[7]The dichotomous questions (Yes/No) *Do you presently suffer from pain?*
BBS, Berg Balance Scale; FACIT-F, Functional Assessment of Chronic Illness Therapy; FES(S), Falls Efficacy Scale, Swedish version; FOGQsa, Freezing of Gait Questionnaire, self-administered version; MMSE, Mini Mental State Examination; NRT, Nutt Retropulsion Test ; PADLS, Parkinson's disease Activities of Daily Living Scale; PD, Parkinson's disease; UPDRS III, motor part of the Unified PD Rating Scale; 10MWT, 10-Meter Walk Test; Walk-12G, the generic Walk-12.

Paper III

External validation

We found the discriminative ability of the 3-step model (i.e. history of falls, FOG and CGS <1.1m/s) to be acceptable (AUC, 0.74). The AUC for single predictors varied between 0.61 and 0.69.

Extended analyses with additional predictors

Extended analyses generated two new models. The best discriminant ability (AUC, 0.82) was shown by the model for prediction of falls and/or near falls. That model included a history of near falls, abnormal TG and retropulsion/NRT.

All models are presented in Table 8.

Table 8.
External validation of the 3-step model and extension with additional predictors, n=138

Predictors		Wald	OR (95% CI)	AUC [1] (95 % CI)	Sens [2]/Spec [3]
External validation of the 3-step model for prediction of future falls [4]					
History of falls, n (%) [5]	38 (28)	7.26	3.34 (1.39-8.02)		
History of FOG, n (%) [6]	57 (41)	0.79	1.48 (0.62-3.49)	**0.74 (0.65-0.84)**	**0.37/0.92**
CGS <1.1 m/s (10MWT), n (%)	54 (39)	6.02	2.88 (1.24-6.72)		
Extended model for prediction of future falls [7, 8]					
History of near falls, n (%) [9]	48 (35)	6.33	3.03 (1.28-7.17)		
Retropulsion (NRT), n (%) [10]	36 (26)	7.43	3.53 (1.43-8.72)	**0.78 (0.70-0.86)**	**0.58/0.87**
CGS <1.1 m/s (10MWT), n (%)	54 (39)	4.64	2.55 (1.09-5.98)		
*** Extended model for prediction of future falls and/or near falls** [7, 8]					
History of near falls, n (%)	48 (35)	12.24	5.08 (2.04-12.66)		
Abnormal TG, n (%) [11]	78 (57)	12.07	4.41 (1.91-10.19)	**0.82 (0.75-0.89)**	**0.57/0.86**
Retropulsion (NRT), n (%)	36 (26)	5.87	3.40 (1.26-9.14)		

*Details from this analysis were available on request (Paper III).
[1]Area under the Receiver Operating Characteristic curves.
[2]The proportion of people with prospective falls who had a positive result (scored above given cut-off point).
[3]The proportion of people without prospective falls who had a negative result (scored below given cut-off point).
[4]Multiple logistic regression analysis (enter method).
[5]Dichotomous question (Yes/No): In the last 12 months, have you fallen in such a way that your body hit the ground?
[6]Scores ≥1 on the FOGQsa, item 3 (Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?) were categorized as having FOG.
[7]Multiple logistic regression analysis (backwards method).
[8]Included independent variables in the analysis were: history of falls, history of near falls, history of FOG (FOGQsa item 3), CGS<1.1 m/s (10MWT), retropulsion (NRT), retropulsion (UPDRS item 30), tandem gait (TG).
[9]Dichotomous question (Yes/No): Are you ever close to falling, but you manage to grab on to something/someone at the last minute so that your body does not hit the ground?
[10]Scores ≥1 on the NRT (unexpected shoulder pull) were categorized as having retropulsion.
[11]Scores ≥1 on the TG were categorized as abnormal.
CGS, comfortable gait speed; FOG, Freezing of Gait; FOGQsa, Freezing of Gait Questionnaire, self-administered version; NRT, Nutt Retropulsion Test; 10MWT, 10-Meter Walk Test; m/s, meter per second; TG, tandem gait.

Paper IV

All 151 participants (mean age and median PD duration, 68 and two years, respectively) completed the 10MWT testing. Of these, 146 (97%) participants completed the prospective six-month follow-up of falls.

Mean absolute differences (n=151) between outcomes from the various 10MWT conditions were generally small, ranging between 0.01-0.04 m/s (ESs, 0.03-0.014) with high levels of agreement (ICC, 0.93-0.99) and small errors of measurement (SEM, 0.03-0.08 m/s).

ROC curve analyses (n=146) showed similar discriminate abilities for future falls across the various 10MWT conditions (AUC, 0.70-0.73). The Youden index ranged between 0.37-0.39, with corresponding cut-off points estimated at 1.1-1.2 m/s. The details are presented in Table 9.

Table 9.
Discriminant ability of 10-Meter Walk Test (10MWT) for identification of individuals with prospective falls [1], n=146

	AUC [2] (95 % CI)	Cut-off point (m/s)	Sens [3] /Spec [4]	Youden index [5]
Static start				
t1	0.72 (0.64, 0.81)	1.1	0.70/0.69	0.39
t2 [n=145]	0.72 (0.63, 0.81)	1.2	0.70/0.69	0.39
$M_{t1,t2}$ [n=144]	0.73 (0.64, 0.81)	1.1	0.67/0.70	0.37
Dynamic start				
t1 [n=144]	0.71 (0.62, 0.80)	1.1	0.72/0.66	0.38
t2 [n=144]	0.70 (0.60, 0.79)	1.1	0.70/0.67	0.37
$M_{t1,t2}$ [n=144]	0.70 (0.61, 0.80)	1.1	0.70/0.68	0.38

[1] As determined using a prospective falls diary during a six-months follow-up.

[2] Area under the Receiver Operating Characteristic curves of t1, t2 and $M_{t1,t2}$ during 10MWT with static and dynamic start.

[3]The proportion of people with prospective falls who had a positive result (scored above given cut-off point).

[4] The proportion of people without prospective falls who had a negative result (scored below given cut-off point).

[5]Sensitivity + specificity – 1

m/s, meters per second; t1, trial 1; t 2, trial 2; $M_{t1,t2,}$ mean value of t1 and t2.

Discussion

This project was intended to contribute to increasing knowledge about factors associated with FOF, falls and near falls, as well as to improving clinical fall prediction in people with PD.

The participants were recruited from the same cohort composed of 151 individuals. Although the number of included individuals varies in Papers I-IV, several demographic characteristics are identical or very similar in the different studies. Most participants (>60%) were scored as H&Y stage I or II, which indicates early stages of PD [21]. The remaining individuals were mostly (about 30%) scored as H&Y stage III while stage IV was represented to a lesser extent (about 5%). Moreover, the short PD duration as well as the low motor scores support mild PD severity in our sample. Despite the fact that the sample represents relatively mild PD, 42% experienced FOG, 25% exhibited retropulsion during an unexpected shoulder pull and at least 57% had impaired dynamic balance (i.e. failed in tandem gait performance). This illustrates that postural and gait-related impairments are common early in the disease [42-44, 58-61, 158].

Data regarding prospective falls and near falls was comprehensively reported in Paper II for 141 individuals, of whom about a third reported at least one fall. The proportion of fallers in Paper II was lower as compared to other studies of falls in people with PD that used a six-month prospective follow-up, where the proportion of fallers was reported to range from 48 to 78% [56, 65, 66]. This discrepancy may have been because our sample represented relatively mild PD or methodological aspects of monitoring falls. For example, Kerr et al. [66] reported 48% of fallers in a similar, relatively mild sample of PD. Participants in that study were given a set of monthly falls calendars to complete and return every month over a six-month period. In this project, we made monthly telephone calls to ensure that registrations were completed according to instructions but the participants returned the diaries after the six-month period. Ashburn et al. [65] also used a monthly return system and reported that 78% of the participants were fallers; their sample was slightly more affected by PD as compared to that of Kerr et al. This suggests that differences in the data collection procedure may influence the proportion of individuals who report falls.

In Paper II, 58% of fallers reported two or more falls, which is in accordance with the findings reported in other studies using the same prospective time period that

24-68% of participants were recurrent fallers [56, 65, 66]. Importantly, there is some evidence suggesting that the risk factors for single falls may differ from the risk factors for recurrent falls [103]. Mak et al. reported that single fallers fell mostly outdoors due to tripping, while recurrent fallers mostly fell at home due to ‘‘muscle giving way’’. Recurrent fallers also had significantly worse walking endurance and functional muscle strength in the lower extremities as well as more FOF. The authors suggested that recurrent fallers require different intervention strategies to prevent future falls than non-fallers or single fallers [103]. However, near falls were not taken into account in the study by Mak et al., which may explain the lack of differences between non-fallers and single fallers on clinical measurements.

Near falls in PD are poorly investigated in prospective studies. Gray & Hildebrand [8] reported that 36% of all fall events were near falls while we found almost a double rate (65%) in our sample of people with similar PD severities. These differences may be due to different follow-up periods. Gray & Hildebrand [8] used a three-month prospective follow-up while we used six months. These observations imply that the length of the follow-up period may influence the proportion of individuals who experienced and reported near falls.

Associations between fear of falling, falls and near falls

Fear of falling: low fall-related self-efficacy

In Paper I, we comprehensively investigated factors associated with FOF conceptualized as fall-related self-efficacy. By using FES(S) scores as the dependent variable and by replicating the Nilsson et al. postal survey study [80] we confirmed that walking difficulties in daily life is the strongest factor associated with FOF in PD. As a second step of analysis, we also included clinical assessments such as gait speed (10MWT) as independent variables. However, walking difficulties in daily life were still the strongest independent associated factor with FOF, while gait speed did not independently contribute. The importance of walking difficulties also corroborates recent results by Jonasson et al. where walking difficulties in daily life were found to be the strongest independent factor when investigating FOF conceptualized as concerns about falling [116]. It needs to be noted that a history of falls has not been identified as an independent risk factor for FOF in people with PD [80, 107-109].

In Paper I (as well as in the two previous described studies [80, 116]) perceived walking difficulties in daily life were assessed according to the Walk-12G, which includes 12 questions targeting important mobility aspects of daily life such as balancing while walking, stair climbing, smoothness of walking and walking distance [137]. Importantly, most people with PD fall while walking [50, 76]. The

strong association between FOF and walking difficulties (Paper I) [80, 116] may indirectly mirror associations between falls and walking difficulties, since FOF was identified as the strongest factor associated with future falls and/or near falls (Paper II). This suggests that minimizing walking difficulties in daily life should not only be a primary target when aiming at reducing FOF, but also when aiming for the prevention of near falls and falls. Interventions should focus on training in daily life situations such as walking in various environments and on various surfaces that induce self-generated perturbation and challenge balance [39]. Learning to slow down and concentrate on a single task (without unnecessary distraction) during everyday activities has been suggested as an effective strategy to reduce falls [76]. The knowledge about the circumstances of falls and near falls (e.g. walking over carpets, transition between tile and wooden surfaces or negotiating steps and doorways) [64, 74, 77] is important to consider when working proactively. Stair climbing may need some specific attention since studies have revealed that it was associated with FOF [79, 80, 159], walking on slippery and uneven surfaces and walking in crowds were among activities that were scored as difficult in several studies [40, 79, 136, 160-162].

Walking difficulties among people with PD have furthermore been described in terms of decreased gait speed, reduced step length, shuffling [32, 40], turning difficulties [32, 41] and FOG [8, 32, 47-53]. Thus, minimizing disease-specific walking difficulties needs to be considered in the care and rehabilitation of individuals with PD. Importantly, a history of FOG and CGS <1.1 m/s have been independently associated with future falls (Paper III) [120, 129]. Thus, interventions that promote gait speed and focus on strategies to handle FOG seem to be of special importance.

However, in addition to walking and mobility per se, interventions should also consider related emotional and psychological aspects based on each person's unique situation [163]; the feeling of being able to walk without help has been suggested to be intimately linked to an individual's social identity, emotional well-being, integrity and, presumably quality of life. Indeed, walking difficulties in daily life have been identified as an independent factor associated with life satisfaction in PD [164].

In Paper I, fatigue, needing help from others in daily activities, and functional balance were also independently associated with FOF but to a lesser extent than walking difficulties. That fatigue and independence in daily activities are of importance for FOF is in line with the results by Nilsson et al. [80]. A recent study also showed that fatigue was independently associated with FOF, conceptualized as concerns about falling [116]. Moreover, in a recent qualitative study, participants expressed that their FOF increased due to tiredness/fatigue [159]. Interestingly, there are data suggesting a relationship between poor walking economy (increased

energy expenditure) and fatigue in people with PD [165]. Walking economy was determined by measuring the rate of oxygen consumption at rest and while walking at different walking speeds. Significant differences were found as compared to healthy controls suggesting the occurrence of physiological stress (e.g. heart rate and minute ventilation) in relatively early stages of PD. This stress was hypothesized to be linked to PD symptoms involved during movement/walking and may affect key aspects of walking economy, such as gait spatiotemporal parameters [166]; altered regulation of step length is the fundamental deficit in gait hypokinesia [167]. Tremor contributes to increased resting energy expenditure [168, 169]. Postural instability in PD requires a greater magnitude of muscle activity during challenging tasks than in healthy controls, while rigidity and hypokinesia, besides aspects of gait, also affect pulmonary function [170]. Consequently, increased work of breathing may affect the total energy cost of walking [165]. Thus, physiological stress during moving/walking might potentially explain the association between fatigue and FOF, because of the close relation between walking difficulties and FOF.

A novel finding in Paper I was that functional balance (which is of importance in daily activities) was identified as an additional significant independent factor associated with FOF, whereas reactive postural responses after an external perturbation were not. This suggests that interventions should target functional balance performance and not reactive postural responses if aiming to reduce FOF among people with PD. Functional balance includes turning, moving to/from sitting, bending forward, or reaching [127] – activities closely related to falls in PD [50, 74-76]. Thus, interventions targeting functional balance performance may potentially have effects on both FOF and falls. Indeed, a recently published study on the effects of a corrective exercises program showed improvements of functional balance (BBS), FOF (concerns about falling) and a decreased frequency of falls [171].

Falls and near falls

In Paper II we comprehensively investigated factors associated with future falls and/or near falls. Three independent associated factors were identified; the strongest was FOF (fall-related self-efficacy), followed by a history of near falls, and retropulsion during an unexpected shoulder pull. To the best of our knowledge, this is the first study presenting FOF as an independent factor associated with experiencing future falls and/or near falls in people with mild PD. Previous studies have however identified FOF as an independent risk factor for recurrent falls in people with PD [62]. FOF is also of importance since it is a major barrier to physical exercise for an ambulatory person with PD [111]. FOF has also been associated with physical inactivity [172], activity limitations/avoidance [82, 172], participation restrictions [114] and social isolation [112]. Moreover, FOF is negatively associated with health-related quality of life [115] and is a more important factor of health-

related quality of life than balance impairment and actual falling [113]. Importantly, fall-related avoidance has been reported among people that do not fall and already in mild PD stages (H&Y I-II) [82]. Taken together, FOF should probably be considered as an integral part of PD assessments, irrespective of disease severity.

A Cochrane review concluded that physiotherapy can yield short-term improvements in walking, mobility and balance as compared with no intervention in people with PD [173]. However, the review did not support reduction of FOF by physiotherapy. This may be explained by several factors. For example, few of the reviewed studies included FOF as an outcome; the compromised methodological quality of the included studies; or that the key ingredients of the interventions did not address walking difficulties in daily life. Future trials targeting walking ability that includes FOF as an outcome are thus needed. Furthermore, FOF may be such a complex construct that it best benefits from using an interdisciplinary approach. The latter may be supported by the fact that dependence in daily activities as well as fatigue was independently associated with FOF. However, a recent randomized controlled intervention study with the primary aim to reduce FOF in persons with PD [174] showed that a twelve-week intervention with balance and gait training with augmented feedback led to significantly reduced FOF (conceptualized as concerns about falling) in persons with PD, up to 12 months after the intervention [174]. Other intervention studies have included the reduction of FOF as a secondary aim, e.g., by exposing persons with PD to supervised challenging balance exercises [174, 175]. Moreover, it has been suggested that teaching people how to get up from the floor can be successful in preventing or reducing FOF [114]. It has been argued that a considerable proportion of persons with PD require help to stand up [76]. Those unable to stand up after a fall must be carefully instructed to summon help, e.g, by using electronic systems [176].

Interestingly, the strongest factor associated with prospective falls (only) was pain followed by history of near falls, retropulsion/NRT and PD duration (Paper II). To the best of our knowledge, this is the first prospective study to identify pain to be independently associated with future falls in PD. Pain is an underappreciated and under diagnosed symptom in PD [177] and probably needs more attention. Moreover, pain has been reported to be one of the most troublesome non-motor symptoms in early stages of PD [178]. Interestingly, pain together with depression and anxiety, compromised motivation, and axial/postural/gait impairment was independently associated with fatigue [179] that (in turn) was shown to be an independent factor associated with FOF (Paper I) [80, 116].

The second strongest independent factor for future falls and/or near falls was a history of near falls. Although it has been suggested that one should ask people with PD about prior near falls [32, 74], a study by Ashburn et al. did not confirm that near falls during the past year predicted future falls [87]. Near falls were defined as

"occasions on which individuals felt that they were going to fall but did not actually do so". Besides using a different definition, future falls were collected based on retrospective recall covering a shorter period (three months) than the prospective six-month follow-up used in this thesis. Our finding indicates that asking about prior near falls as defined by Gray et al. [8] may be helpful in identifying persons with mild PD that are at risk for future falls and/or near falls. In contrast to near falls, a history of falls was not identified as a risk factor for future falls and/or near falls (Paper II). This finding differs from those of several previous studies (e.g. [51, 56, 68, 71, 180]. The differences might be because our dependent variable included both near falls and/or falls, and because a history of near falls was included as an independent variable. The latter has not been the case in previous studies. Another explanation might be that our sample represented relatively mild PD. However, when excluding near falls from the dependent variable, a history of near falls but not falls was still identified as a risk factor. This may indicate that a history of near falls is a precursor of experiencing future falls. Moreover, this finding suggests that it may be more effective to ask about prior near falls than actual falls if the aim is to work proactively in mild PD. We suggest that near falls deserve more attention in PD research in order to gain increased knowledge about associated factors, consequences, and whether the occurrence of near falls is a precursor of falls. Importantly, the occurrence of near falls has been suggested as a clinically relevant marker of falls in older people [181, 182]. However, current knowledge of near falls, based on self-reports, may underestimate the true occurrence of such events [85, 86]. There is ongoing research that aims to develop accelerometers for improvement of investigation of near falls and evaluation of fall risk [75, 83, 183].

The third independent associated factor was retropulsion according to the NRT, which was positive in 25% of our participants. In relatively mild PD, this might be a surprising finding. However, postural instability has been shown to be already present at diagnosis [158] although it worsens with disease progression. For example, the Sydney multicenter longitudinal study reported that 34% of participants demonstrated postural instability two years after diagnosis [184], which increased to 71% after ten years [185]. In the present study (Paper II), the reasoning for choosing the NRT as a pull test is that it incorporates an unexpected shoulder pull and only one trial is performed; this version of the pull test has been suggested to provide a more valid evaluation of fall risk that better reflects unpredictable situations in everyday life than an expected pull test does (Paper III) [38].

Several studies have shown that many different modes of physiotherapy e.g. training in responding to external perturbations [186-189] have some effect on balance and balance-related activities performance. However, there is currently no evidence of different treatment effects with different types of physiotherapy intervention or effects on falls [173]. Therefore, while physiotherapy can improve the postural stability of people with PD, the optimal design and delivery of training programs

remains unclear. Clearly, physiotherapy may teach patients how to cope with a given degree of balance impairment. Perhaps most importantly, physiotherapists may help patients to reduce FOF, allowing them to participate more in social activities. Also, interventions by a multidisciplinary team can help patients to cope with postural instability in different ways. Occupational therapists can help reduce the incidence of home accidents caused by domestic hazards such as loose rugs, slippery floors or insufficiently light rooms. High chairs and beds as well as handrails (e.g. in the bathroom) and shoes with leather soles and raised heels may reduce fall risk during transfers. Many patients benefit from use of walking aids [176]. Importantly, several studies have suggested that it is advisable to teach persons with PD and FOF how to use their walking aids [107, 114, 176, 190].

An overview of all the factors that were independently associated with fear of falling, falls and near falls based on Papers I and II is presented in Figure 2.

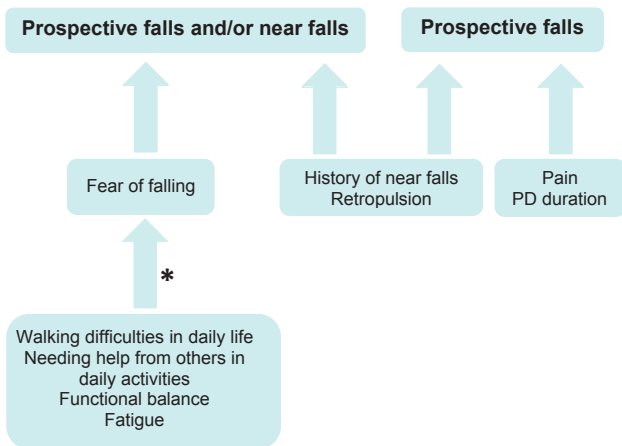

Figure 2.
Overview of factors that were independently associated with fear of falling, falls, and near falls based on Papers I and II.
* The direction of associations is not firmly established due to the cross-sectional design.

Prediction of falls and near falls

This thesis concerns five prediction models for falls and near falls. A brief overview of the included predictors, discriminant ability, sensitivity and specificity is presented in Figure 3.

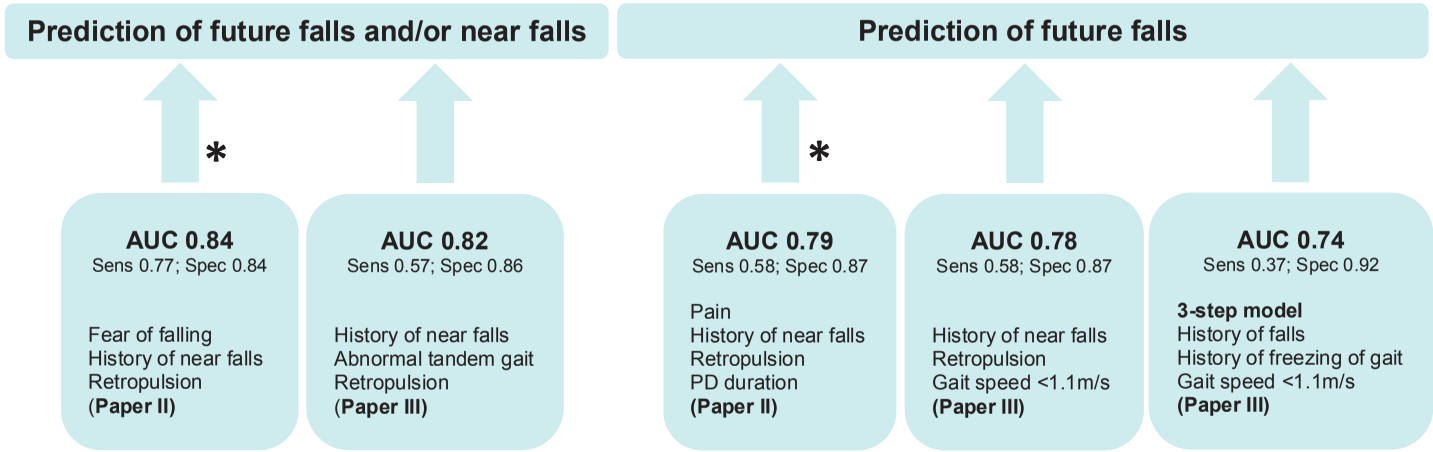

Figure 3.
Overview of predictive models based on Papers II and III.
* Controlled for age and gender.

The 3-step model

Successful implementation of prediction models in clinical practice generally requires three main phases: model development, external validation, and investigations of the model's clinical impact. It is also recommended to consider whether existing models can be improved, e.g. by additional predictors [121]. Furthermore, in order to be applicable, useful, and practical for routine clinical use, prediction models must not only have sufficient ability to discriminate between future fallers and non-fallers, but also be easy and quick to implement. To this end, Paul et al. proposed the 3-step model consisting of three variables: history of falls during the past 12 months, history of FOG, and CGS <1.1 m/s based on the mean of two trials of walking a standardized distance. According to the recommendations regarding implementations of prediction models [121], we aimed (Paper III) to externally validate the 3-step model [120] in our mild PD sample.

We found the discriminant ability of this model to be lower (AUC, 0.74) but acceptable and overlapping (given the 95% CIs of AUCs) compared to the results of two previous studies [120, 129]. Importantly, we found that the discriminant ability of each single predictor was lower and below acceptable values as compared to the full 3-step model. The results from this comparison support the value of the 3-step model over reliance on single predictors. However, in our sample, the 3-step model had low sensitivity (0.37) and high specificity (0.92). This implies a high risk of under diagnosing the risk of future falls. This finding is in contrast to the results of Duncan et al. who reported a sensitivity and specificity of 0.91 and of 0.66, respectively [129]. It is notable that a history of falls in the study by Duncan et al. had an OR of 16.9 while the corresponding value in our sample was 3.34 and in the sample of Paul et al. it was 5.8. However, ORs for history of FOG (1.06-2.39) and gait speed (1.86-2.88) were similar in all three samples. Differences in observed ORs for history of falls may relate to the different mode of data collection used by Duncan et al. [129]. We asked about falls during the past 12 months once, at baseline (a similar procedure seems to have been used by Paul et al.), while Duncan et al. combined data from two time points, six months apart using a question with five response categories. However, although possibly more reliable, the procedure employed by Duncan et al. appears less common and practical from a clinical perspective. Nevertheless, it appears reasonable to hypothesize that this difference in procedure may account for the difference in ORs across the three studies, and the procedure used by Duncan et al. may have boosted the sensitivity. It should be noted that Paul et al. did not report the sensitivity and specificity in their study.

Comfortable gait speed

In order to explore the possibility of simplifying the investigation of gait speed we aimed in Paper IV to examine the clinical significance of two aspects of the conduct of the 10MWT: the use of a single vs. two repeated trials, and dynamic vs. static

start (i.e., with or without an acceleration distance). The results suggested that there are no meaningful differences between either, which in turn suggests that the 10MWT can be simplified by using a single trial with static start in mild PD. Moreover, the optimal cut-off scores for prediction of future falls were around 1.1 m/s for all test conditions. Supporting this finding, a previous prospective study of falls in people with newly diagnosed PD identified a threshold for CGS of 1.13 m/s as the strongest predictor for a first fall during a 36-month follow-up period [58]. This suggests that gait speed reaches a threshold early on but does not attenuate as the disease advances. However, replications in people with more advanced PD stages are needed for this finding to be more generalizable. Nevertheless, that gait speed is a predictor of falls in PD is not surprising. Reduced gait speed is a classic feature of parkinsonian gait, driven by hypokinesia and reduced step length because of basal ganglia dysfunction [167, 191]. Thus, including CGS <1.1 m/s as a predictor appears clinically feasible.

Improvement of the 3- step model

Following current recommendations regarding improvement of prediction models [121, 129], we explored the addition of history of near falls, retropulsion/NRT and TG to the 3-step model. This generated a new model that included history of near falls, retropulsion/NRT and CGS <1.1 m/s. The discriminate ability of this new model as well as its sensitivity were somewhat better compared to the originally proposed 3-step model, although the AUC 95% CIs overlapped. Similarly, using falls and/or near falls as the dependent variable generated a model that included history of near falls, retropulsion/NRT and TG. These observations have important clinical implications. Near falls are more frequent than falls in PD [74, 79] and may occur also among those who do not experience falls [74, 78]. We previously found that history of near falls but not falls was a risk factor for future falls (Paper II). This is further supported by the findings in Paper III and suggests that information about near falls may be a useful predictor of future falls. Furthermore, since a history of near falls may be seen as an early precursor of increased fall risk [8, 83-86], it is argued that prediction of falls and/or near falls may be of greater clinical value than prediction of falls alone. This is also in line with previous studies highlighting the importance of fall risk identification before the first fall has occurred, in order to optimize the planning of interventions [66, 180]. From this perspective, our new model (history of near falls, TG and retropulsion according to the NRT) may be considered a promising alternative to the suggested 3-step model, at least among people with milder PD. Indeed, the use of TG and NRT has been recommended in the prediction of falls before [38, 56, 192]. Importantly, this new model had the best discriminant ability (AUC, 0.82) among the models presented in Paper III, and it had a higher sensitivity (0.57) than the original 3-step model while specificity (0.86) was still relatively high.

Pull tests

NRT (unexpected shoulder pull), but not UPDRS item 30 (expected shoulder pull) was identified as a predictor in both of the new models (Paper III). UPDRS item 30 involves prior instructions, which does not mimic daily life circumstances where perturbations per definition are unexpected [192]. Accordingly, the unexpected pull test according to the NRT has been considered more relevant in the context of fall prediction [38], which is supported by our findings.

Additional considerations

When calculating the discriminate ability of the models presented in Paper II it was found that the model for prediction of falls and/or near falls had the highest AUC (0.84) among all models in this thesis. Also, sensitivity was highest (0.77) with relatively high specificity (0.84). The strongest predictor in this model was FOF conceptualized as fall-related self-efficacy (FES(S)) followed by history of near falls and retropulsion/NRT. The strength of FOF as a predictor is not surprising because FES(S) captures a broad spectrum of different aspects such as mobility, domestic life, self-care and communication [142]. Importantly, recently published guidelines for building clinically useful prediction models have highlighted the need for discriminant ability (AUC) >0.80. Moreover, included predictors should be strongly associated with the outcome variable and prevalent in the population, e.g., one predictor with prevalence ≥20% and OR ≥8, or three predictors with prevalence ≥10% and OR ≥4 [193]. Thus, the models including a continuous predictor such as FOF are not easy to interpret in terms of clinical usefulness according to current guidelines [193]. However, the model for prediction of falls and/or near falls with an AUC of 0.82 including history of near falls (OR, 5.08), abnormal tandem gait (OR, 4.41), and retropulsion/NRT (OR, 3.4) is very close to meeting the above-mentioned criteria. Notably, the 3-step model does not fulfil the criteria mentioned above in our mild PD sample. The same is also true for the earlier studies of the 3-step model [120, 129], where the discriminate ability was appropriative (AUC >0.80) but only history of falls had an OR ≥4. That gives an additional reason to explore our new model in different study samples.

To sum up, five different prediction models was presented in this thesis (Figure 3); two were developed from a larger set of potential predictors (Paper II), two were developed as potential improvements of the 3-step model (Paper III) and the 3-step model was externally validated and confirmed for the third time (Paper III) [120, 129]. The next step for successful implementation of the 3-step model requires studies to investigate the influence of this model on decision making, patient outcomes and costs [121]. Successful examples of such clinically well used prediction models have been tested in many, often large, validation studies [194]. For example, the Örebro Musculoskeletal Pain Screening Questionnaire [195] has

been validated in several independent samples by multiple research groups, with 11 external validation studies up to 2009 [121].

Limitations

The participants in this study had relatively mild PD, and people above the age of 80 years were not included. Our findings may thus not apply to older people with PD or those with more severe PD. However, the sample appears representative for its target population. Furthermore, focusing on individuals with relatively mild PD has been recommended in order for professionals to work proactively [66, 180].

Furthermore, in Paper III, individuals with severe cognitive impairment (MMSE < 24) were excluded. This was done in order to conform with previous studies on the 3-step model [120, 129].

Several of the independent variables were assessed by relatively coarse indicators, e.g. dual-task difficulties, and cognition (MMSE). By using a coarse indicator, one may not capture those having mild problems. For instance, it has been suggested that the Montreal Cognitive Assessment is preferable to MMSE when screening for early cognitive impairments in PD [196]. Furthermore, retrospective recall of near falls may be more problematic than that for falls, and no retrospective time frame was used in relation to near falls. The extent to which this may have influenced the results is unclear. In addition, several variables (e.g. dyskinesia, freezing of gait and turning hesitations) were dichotomized, which may have led to loss of information. This was done for reasons related to the distributional properties of item responses. However, dichotomizing may also imply simplification and may thereby improve the efficiency of clinical assessment of individuals with PD.

Furthermore, there may well be other variables, not included in this study, that also are of relevance in relation to the objectives of this thesis. However, this is a general limitation with essentially any observational study of this kind, and the included variables were selected based on clinical experience and what was known from previous studies at the time.

Main conclusions and clinical implications

- Previous observations [80] suggesting that walking difficulties in daily life represent the strongest factor associated with fear of falling were replicated in mild PD (Paper I). Other, less strong associations were found with need for help in daily activities, functional balance, and fatigue. These observations suggest that everyday walking difficulties should be a primary target when attempting to reduce fear of falling in mild PD and that an interdisciplinary approach should be used.
- The strongest contributing factors for experiencing future falls and/or near falls in mild PD was fear of falling, followed by a history of near falls and retropulsion during an unexpected shoulder pull (Paper II). This suggests that fear of falling is an important issue to consider, and that it may be more effective to ask about prior near falls than actual falls when attempting to prevent future falls in early PD.
- The usefulness of the 3-step model [66, 180] as a clinical fall prediction tool was confirmed. However, sensitivity was low and an alternative model for prediction of falls and/or near falls, including history of near falls, tandem gait and retropulsion during an unexpected shoulder pull may be considered a promising alternative in mild PD (Paper III).
- Different 10-Meter Walk Test standardizations yielded very similar results, suggesting that there is no practical need for an acceleration distance or repeated trials when conducting this test in mild PD (Paper IV).

Future perspective

- Longitudinal studies are warranted in order to gain an increased understanding of risk factors concerning fear of falling in PD.
- Near falls deserve more attention in PD research to gain increased knowledge about associated factors, consequences and whether prior experience of near falls is a precursor of falls. The latter requires longitudinal studies. There might also be a need for studies of how to best monitor and register incidences and circumstance of near falls, retrospectively as well as prospectively.
- Future studies are needed to address the potential impact of using a retrospective time frame (e.g. six or 12 months) in relation to a history of near falls in people with PD.
- A new model for prediction of falls and near falls, including history of near falls, tandem gait and retropulsion during an unexpected shoulder pull needs to be tested in additional samples.
- Further studies are warranted to explore if one trial with a static start can be used as a predictor in the 3-step model, as well as to explore the generalizability of these findings in different PD samples and across other standardizations of the 10-Meter Walk.

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Paper I

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RESEARCH ARTICLE Open Access

Factors associated with fear of falling in people with Parkinson's disease

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Abstract

Background: This study aimed to comprehensibly investigate potential contributing factors to fear of falling (FOF) among people with idiopathic Parkinson's disease (PD).

Methods: The study included 104 people with PD. Mean (SD) age and PD-duration were 68 (9.4) and 5 (4.2) years, respectively, and the participants' PD-symptoms were relatively mild. FOF (the dependent variable) was investigated with the Swedish version of the Falls Efficacy Scale, i.e. FES(S). The first multiple linear regression model replicated a previous study and independent variables targeted: walking difficulties in daily life; freezing of gait; dyskinesia; fatigue; need of help in daily activities; age; PD-duration; history of falls/near falls and pain. Model II included also the following clinically assessed variables: motor symptoms, cognitive functions, gait speed, dual-task difficulties and functional balance performance as well as reactive postural responses.

Results: Both regression models showed that the strongest contributing factor to FOF was walking difficulties, i.e. explaining 60% and 64% of the variance in FOF-scores, respectively. Other significant independent variables in both models were needing help from others in daily activities and fatigue. Functional balance was the only clinical variable contributing additional significant information to model I, increasing the explained variance from 66% to 73%.

Conclusions: The results imply that one should primarily target walking difficulties in daily life in order to reduce FOF in people mildly affected by PD. This finding applies even when considering a broad variety of aspects not previously considered in PD-studies targeting FOF. Functional balance performance, dependence in daily activities, and fatigue were also independently associated with FOF, but to a lesser extent. Longitudinal studies are warranted to gain an increased understanding of predictors of FOF in PD and who is at risk of developing a FOF.

Keywords: Fear of falling, Physical therapy, Parkinson's disease, Postural Balance, Rehabilitation

Background

Approximately 75% of people with Parkinson's disease (PD) have an impaired balance [1], which constitutes one of the most distressing symptoms [2]. People with PD are particularly unstable when perturbed backwards due to impaired postural reflexes [3-5], which is suggested to be evaluated clinically by using an unexpected shoulder pull [6]. Already early during the disease, turning difficulties are common [7] and an unsteadiness while turning is also associated with having more severe freezing of gait (FOG) [8]. Walking difficulties are also common and mainly characterized by a decreased gait speed and shuffling gait. Gait and balance problems are also related to non-motor features (e.g. cognitive dysfunction) of PD and are exacerbated by dual tasking [9].

People with PD have an increased risk of falling as compared to healthy individuals at the same age, but also in relation to people with other neurological disorders [10-12]. They usually fall while performing activities such as walking, turning, transferring to/from sitting, bending forwards or while reaching [13]. It is also common for people with PD to experience near falls, which can be defined as "a fall initiated but arrested by support from a wall, railing, other person, etc." [14]. A recent review scrutinized specific factors associated with recurrent falls among people with PD, and fear of falling (FOF) was then highlighted as one of the risk factors [15]. In addition, FOF has been shown to be a predictor for community walking [16] and a major barrier to

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engaging in exercise [17]. FOF can be defined as a lack of confidence (low self-efficacy [18]) to be able to perform activities without falling, i.e. low fall-related self-efficacy.

Among people with PD, FOF is common and about 70% report activity limitations due to FOF, which also may cause social isolation [10,19]. Although FOF influences activity and participation negatively among people with PD, there is yet limited knowledge regarding contributing factors. Such knowledge is highly warranted in order to develop means that efficiently tap causal factors. At present, there are four published studies that used multivariate analysis to investigate contributing factors to FOF in PD [1,20-22]. Two out of these four studies were postal surveys and lacked clinical data [1,21], and none of them have been replicated [1,20-22]. More importantly, no study has included independent variables targeting functional balance performance, dual tasking, and gait speed or used an unexpected shoulder pull when assessing postural instability. Since gait speed and functional balance performance have been shown to correlate to FOF in bivariate analyses [23,24], these aspects may tentatively be of importance when investigating contributing factors to FOF. Dual-tasking might also be of interest since it worsens gait impairments in PD and may lead to wrong prioritization, i.e. the "posture second" strategy [9,25]. There is thus a need for a more thorough understanding of contributing factors to FOF in PD in order to address this efficiently in clinical practice and research.

This study aimed at determining factors associated with FOF (conceptualized as low fall-related self-efficacy) among people with PD. More specifically, the aim was to determine whether previous postal survey based findings could be replicated in an independent clinical sample and, secondly to investigate whether additional and previously unexplored motor aspects (e.g. gait speed, functional balance performance) as well as cognitive features independently may contribute to FOF.

Methods

All people diagnosed with PD receiving care at a south Swedish university hospital during 2007–2011 were considered eligible for inclusion (n = 273). Exclusion criteria were age above 80 years old (n = 106), inability to stand without support (n = 17), inability to understand instructions (n = 8) or being mentally or medically unstable (n = 7). The remaining 135 patients were invited to participate. Twenty-eight (12 women) participants declined to participate, and they did not differ significantly ($p \geq 0.07$, the Mann–Whitney U test) from the included ones with respect to age and PD-duration. Three additional participants (2 women) were excluded due to missing data on the dependent variable: the Swedish version of the Falls Efficacy Scale, i.e. FES(S). The final study sample consisted of 104 participants.

Ethics statement

The Regional Ethical Review Board in Lund (Sweden) approved the study (Dnr 2011/768). All participants gave written informed consent.

Instruments

Demographic questions included, e.g., age, sex and disease duration. Additional questions (no/yes responses) included experience of falls during the past six months [26], near falls [14], dual-task difficulties (*"Do you experience balance problems when doing more than one thing at a time, e.g. carrying a tray while walking?"*) and pain (*"Do you presently suffer from pain?"*). For descriptive purposes, an additional dichotomous question (no/yes) specifically targeted FOF.

A battery of self-reported questionnaires was included. FES(S) targets fall-related self-efficacy, and includes 13 items (activities) rated from 0 (not confident at all) to 10 (completely confident) [23,27]. The maximum total score is 130 and higher scores denote "better" balance confidence. The self-administered version [8] of the freezing of gait questionnaire (FOGQsa) [28] consists of six items scored 0–4 (higher scores = more difficulties). In this study, we only used items 3 (freezing) and 6 (turning hesitations). Those scoring ≥1 on item 3 were categorized as "freezers" and those scoring ≥1 on item 6 were considered as having turning hesitations [1]. The generic Walk-12 (Walk-12G) assesses walking difficulties in everyday life, and the total score ranges from 0 to 42 (higher scores = more walking difficulties) [29]. The Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F) consists of 13 items with a total score ranging from 0 to 52 (higher scores = less fatigue) [30,31]. The Parkinson's disease Activities of Daily Living Scale (PADLS) is a five-grade (5 = worse) single-item scale regarding ADL-difficulties [32,33]. Those scoring >2 were categorized as "needing help from others in daily activities".

Before clinical assessments, all participants self-rated their motor status at the time of examination as "good/on", "on with dyskinesias", or "bad/off". Clinical assessments targeted functional balance, retropulsion due to abnormal reactive postural responses, gait speed, parkinsonian motor status and cognition. The Berg balance scale (BBS) was used to assess functional balance performance of importance in daily life [34]. It includes 14 items (tasks) scored 0–4, and the maximum score is 56 (56 = better) [34,35]. The Nutt retropulsion test (NRT) assesses reactive postural responses [6,36]. The patient then stands with eyes open and feet slightly apart; the examiner stands behind the patient and gives (without

prior warning) a sudden, firm and quick backward pull to the shoulders. Only one trial was performed (scored 0–3, 3 = worse) [6], and those scoring ≥1 were categorized as having abnormal reactive postural responses. The 10-meter walk test (10MWT) was used to measure gait speed [35]. It was performed in both comfortable and fast walking speed (randomized order, two trials each). In this study, we only used comfortable gait speed and a total distance of 14 meters, from which gait speed (m/s) was calculated for the mid 10 meters. The trial with the highest comfortable gait speed was used in the analyses. Parkinsonian motor symptoms were assessed with the Unified PD Rating Scale (UPDRS) part III (motor examination) [35,37]. It consists of 14 items (graded 0–4) with a total score ranging from 0 to 108 (108 = worse). In addition, dyskinesia was self-rated using part IV (complications of therapy) of the UPDRS; those scoring ≥1 on item 32 (dyskinesia duration) were categorized as having dyskinesias [37]. The Mini-Mental State Examination (MMSE) was used as a coarse cognitive test [38], and yields a total score ranging between 0–30 (30 = better).

Procedure

All participants were assessed during an outpatient visit, which was scheduled at a time of day when the participant usually reported to feel at best. First, the participants completed the self-administered questionnaire booklet. Thereafter, all participants were evaluated by the same physical therapist (BL). Clinical assessments were performed in the following order: BBS; NRT; 10 MWT; UPDRS part III; and the MMSE. These were followed by additional self-administered questions targeting dyskinesia and demographic information.

Statistical analyses

Data were checked regarding underlying assumptions and described and analyzed accordingly using IBM SPSS version 19. The alpha level of significance was set at 0.05 (2-tailed, exact *P*-values were used). Spearman correlations (r_s) and Mann–Whitney *U*-tests were used for bivariate analyses of associations with the dependent variable FES(S). Forward multiple linear regression models were used based on the results from a recently published study [1]. In our first model, we replicated the model identified by Nilsson et al. [1] by using age, disease duration, walking difficulties, fatigue, need help from others in daily activities, turning hesitations, freezing of gait, dyskinesia, experiencing falls or near falls, and pain as independent variables. In our second model, we explored the effects of taking dual-task difficulties and variables based on clinical examination, i.e., parkinsonian motor symptoms (UPDRS III), cognition (MMSE), balance (NRT, BBS) and gait speed (10MWT) into account as additional independent variables. Models were checked regarding underpinning assumptions.

Results

Sample characteristics and results from bivariate analyses are presented in Table 1. According to the dichotomous FOF-question, 38 out of 104 (37%) participants reported having FOF. FES(S) scores demonstrated significant bivariate associations with all variables but gender. The median FES(S) score was 117 (q1-q3, 69.5-129; min-max, 11–130). At the time of assessments, 91 out of the 104 participants (87.5%) rated their motor status as "on", whereas 9 (8.7%) rated it as "on with dyskinesias", and four (3.8%) rated it as "off".

The first multiple linear regression based on the results from Nilsson et al. [1] resulted in three significant independent variables explaining 66% of variance in FES(S) scores (Table 2). The strongest independent variable (as assessed by the standardized regression coefficients, β) was walking difficulties (Walk-12G scores), which could account for 59.5% of the variance in FES(S) scores. This was followed by fatigue and needing help from others in daily activities (Table 2).

Adding information about the occurrence of dual-task difficulties and clinical assessments as independent variables resulted in a model with four independent variables explaining 73% of variance in FES(S) scores (Table 3). The three variables identified in the first model remained significant also in the second model, and the only variable that contributed additional explanatory power was functional balance (BBS). The strongest independent variable was still walking difficulties, followed by functional balance, needing help from others in daily activities and fatigue (Table 3).

Discussion

By comprehensibly investigating contributing factors to FOF among people with PD and by using multivariate analyses, this study confirms previous observations suggesting that walking difficulties in daily life is the strongest contributing factor in addition to independence in daily activities and fatigue. Although some previous PD-studies have shown similar results [1,20], none included independent variables that targeted functional balance performance, dual-task difficulties, and gait speed. A novel finding in this study is that functional balance (that is of importance in daily activities) was identified as an additional significant independent contributor to FOF, whereas a reactive postural response after an external perturbation (and other motor or cognitive aspects) was not. Including functional balance performance in the model increased the explanatory power from 66% to 73%, whereas other motor and cognition aspects do not appear to provide any improvements beyond the first model. The

Table 1 Sample characteristics and bivariate associations with FES(S) scores

	Total sample (n = 104)	Spearman correlations with FES(S) scores	P-value
Age (years), mean (SD)	68 (9.4)	−0.270	0.006
PD-duration (years), mean (SD)	5 (4.2)	−0.350	<0.001
Cognition (MMSE), median (q1-q3)	28 (26–29)	0.220	0.027
Motor symptoms (UPDRS III), median (q1-q3)	13 (8–20)	−0.510	<0.001
Balance (BBS), median (q1-q3)	52.5 (46–55)	0.650	<0.001
Gait speed (10MWT) (m/s), median (q1-q3)	1.18 (0.95–1.35)	0.480	<0.001
Walking difficulties (Walk-12G), median (q1-q3)	8 (4.5–21)	−0.760	<0.001
Fatigue (FACIT-F), median (q1-q3)	38 (29–44)	0.710	<0.001

	n (%)[a]		Median (q1-q3) FES(S) scores[a]		P-value Mann Whitney U-test
	No	Yes	No	Yes	
Freezing of gait (item 3, FOGQsa)[b]	60 (58)	44 (42)	128 (112–130)	87 (44–117)	<0.001
Turning hesitations (item 6, FOGQsa)[c]	68 (65)	36 (35)	126 (105–130)	81 (39–113)	<0.001
Dyskinesias (item 32, UPDRS IV)[d]	66 (63)	38 (37)	124 (95–129)	101 (48–125)	0.009
Need help from others in daily activities (PADLS)[e]	93 (90)	11 (10)	122 (94–129)	33 (18–50)	<0.001
Experienced falls	76 (73)	28 (27)	124 (96–130)	89 (41–114)	<0.001
Experienced near falls	64 (62)	39 (38)	127 (106–130)	91 (43–116)	<0.001
Experienced balance problems while dual-tasking	52 (50)	52 (50)	128 (111–130)	94 (51–118)	<0.001
Pain	78 (75)	26 (25)	123 (94–130)	91 (43–124)	0.005
Retropulsion (NRT)[f]	78 (75)	26 (25)	124 (83–130)	104 (59–120)	0.011
Female gender	55 (53)	49 (47)	118 (87–129)	113 (61–129)	0.258

[a]Refers to the dichotomous (No/Yes) variables, and n (%) clarifies the number (percentage) of participants that either have or do not have the specified characteristic.
[b]Item 3 ("freezing") of the FOGQsa. Those scoring ≥1 were categorized as freezers.
[c]Item 6 ("turning hesitations") of the FOGQsa. Those scoring ≥1 were categorized as having turning hesitations.
[d]Item 32 of the UPDRS part IV. Those scoring ≥1 were categorized as having dyskinesias.
[e]Those scoring >2 on the PADLS were categorized as needing help from others in daily activities.
[f]Scores ≥1 on the NRT were categorized as having retropulsion.
BBS, Berg Balance Scale (possible scores, 0–56; higher = better); FACIT-F, the Functional Assessment of Chronic Illness Therapy - Fatigue scale (possible score, 0–52; higher = better); FES(S), Falls Efficacy Scale, Swedish version (possible scores, 0–130; higher = better); FOGQsa, Freezing of Gait Questionnaire, self-administered version; MMSE, Mini Mental State Examination (possible scores, 0–30; higher = better); NRT, Nutt Retropulsion Test (possible scores, 0–3; higher = worse); PADLS, the Parkinson's disease Activities of Daily Living Scale (possible scores 1–5; higher = worse); PD, Parkinson's disease; q1-q3, 1st-3rd quartile; SD, standard deviation; UPDRS III, part III (motor score) of the Unified PD Rating Scale (possible scores, 0–108; higher = worse); UPDRS part IV (complications of therapy), item 32 (possible scores 0–4; higher = worse); 10MWT, 10-meter walking test; m/s, meters per second; Walk-12G, 12-item generic walking scale (possible scores, 0–42; higher = worse).
One participant had a missing value for the MMSE, and another participant had a missing value in relation to near falls.

Table 2 Model I (replication [1]): multiple linear regression with fear of falling (FES(S) scores) as the dependent variable in people with Parkinson's disease, n = 104[a]

					Adjusted R^2	
Significant independent variables[b]	B (95% CI)		β	P-value	Stepwise change	Cumulative
Walking difficulties (Walk-12G)	−1.844	(−2.423, −1.266)	−0.524	0.000	0.595	0.595
Need help from others in daily activities (PADLS)	−24.960	(−40.672, −9.247)	−0.213	0.002	0.042	0.637
Fatigue (FACIT-F)	0.667	(0.165, 1.169)	0.214	0.010	0.021	0.658

[a]Independent variables in the analysis were: need help from others in daily activities (PADLS: dichotomized, 1 = yes), walking difficulties (Walk-12G), fatigue (FACIT-F), age (years), PD-duration (years), falls (1 = yes), near falls (1 = yes), dyskinesia (dichotomized, 1 = yes), freezing (FOGQsa item 3: dichotomized, 1 = freezing), turning hesitations (FOGQsa item 6: dichotomized, 1 = turning hesitations), pain (dichotomized, 1 = yes).
[b]Listed by order of entry into the model (forward method).
FACIT-F, the Functional Assessment of Chronic Illness Therapy-Fatigue scale (0–52; higher = better); FES(S), Falls Efficacy Scale (0–130; higher = better); FOGQsa, Freezing of Gait Questionnaire, self-administered version (items are scored 0–4; higher = worse); PADLS, The Parkinson's disease Activities of Daily Living Scale (1–5; higher = worse; those scoring >2 were categorized as needing help from others in daily activities) Walk-12G, 12-item generic walking scale (0–42; higher = worse).
B: regression coefficient; CI: confidence interval; β: standardized regression coefficient.

Table 3 Model II (extended): multiple linear regression with FES(S) scores as the dependent variable in people with Parkinson's disease, n = 104[a]

Significant independent variables[b]	B (95% CI)		β	P-value	Adjusted R^2	
					Stepwise change	Cumulative
Walking difficulties (Walk-12G)	−1.543	(−2.118, −0.968)	−0.446	0.000	0.642	0.642
Need help from others in daily activities (PADLS)	−21.823	(−35.841, −7.806)	−0.189	0.003	0.045	0.687
Functional balance (BBS)	0.877	(0.333, 1.422)	0.221	0.002	0.027	0.714
Fatigue (FACIT-F)	0.547	(0.103, 0.991)	0.179	0.016	0.014	0.728

[a]Independent variables in the analysis were: need help from others in daily activities (PADLS: dichotomized, 1 = yes), walking difficulties (Walk-12G), fatigue (FACIT-F), age (years), PD-duration (years), falls (1 = yes), near falls (1 = yes), dyskinesia (item 32 UPDRS part IV: dichotomized, 1 = yes), freezing (FOGQsa item 3: dichotomized, 1 = freezing), turning hesitations (FOGQsa item 6: dichotomized, 1 = turning hesitations), pain (dichotomized, 1 = yes), cognition (MMSE), motor symptoms (UPDRS III), Balance (BBS), 10-meters walk test (comfortable gait speed), Nutt Retropulsion test (dichotomized, 1 = abnormal reactive postural response), self-reported dual-task difficulties (dichotomized, 1 = yes).
[b]Listed by order of entry into the model (forward method).
BBS, Berg balance scale, 0–56 (higher = better); FACIT-F, the Functional Assessment of Chronic Illness Therapy-Fatigue scale (0–52; higher = better); FES(S), Falls Efficacy Scale (0–130; higher = better); FOGQsa, Freezing of Gait Questionnaire, self-administered version (items are scored 0–4; higher = worse); MMSE, the Mini-Mental State Examination (possible scores, 0–30; higher = better); PADLS, the Parkinson's disease Activities of Daily Living Scale (1–5; higher = worse; those scoring >2 were categorized as needing help from others in daily activities); PD, Parkinson's disease; Walk-12G, 12-item generic walking scale (0–42; higher = worse); UPDRS III: motor part of the Unified PD Rating Scale; UPDRS IV: motor complications.
B: regression coefficient; CI: confidence interval; *β*: standardized regression coefficient.

present findings may have important implications for physical therapy and rehabilitation targeting PD.

Several variables that showed highly significant bivariate relationships with FOF (e.g. cognition and falls) were not independently associated with FOF when controlling for other independent variables. This illustrates a major pitfall in relying on bivariate analyses and highlights the importance of using multivariate analyses in this type of studies. Although it may appear surprising that falls did not contribute to FOF, this finding is in line with other PD-studies using multivariate analyses [1,20,22].

Our first regression model represents an independent replication of a prior study based on self-reported postal survey data [1]. The replication corroborates walking difficulties as a major contributing factor to low fall-related self-efficacy. This implies that walking difficulties should be a primary target when attempting to reduce FOF.

Although generally confirming previous findings, the present study did not identify turning hesitations as an independent contributor to FOF as shown in the study by Nilsson et al. [1]. This discrepancy is probably not related to differences in the dependent variable (i.e. FOF, operationalized as low fall-related self-efficacy), since the present median FES(S) score was similar to the one obtained in the study by Nilsson et al. (117 and 114, respectively) [1]. However, sample differences may still have contributed, as the present sample seemed to be less affected by their PD than the previous sample, e.g. proportions of fallers (33% versus 45% in the study by Nilsson et al. [1]) and of people needing help in daily activities (10% here versus 27%). An alternative explanation for the discrepancy may be that all independent variables were not identically assessed in the two studies.

Walking difficulties in daily life was identified as a major explanatory variable in both models, accounting for almost two thirds of the variance in FES(S) scores. This suggests that walking ability may be a primary therapeutic target for alleviating FOF. Functional balance performance (BBS scores) was significantly associated with FOF, whereas the NRT was not. The clinical implication of this finding is that balance training probably should focus on challenges induced by self-generated perturbations rather than external perturbations, if aiming at reducing FOF. In other words, it seems like interventions should target functional balance performance and not reactive postural responses if aiming at reducing FOF among people with mild PD.

FOF among people with PD needs specific attention since it has been identified as a risk factor for recurrent falls [15], a barrier for exercise [17], and a predictor for community walking [16]. Furthermore, FOF causes activity restrictions and avoidance as well as social isolation [10,19,23]. A recent Cochrane review concluded that physical therapy can yield short-term improvements in walking, mobility and balance as compared with no intervention in people with PD [39]. However, the review did not support reduction of FOF by physical therapy. This may be explained by several factors. For example, few of the reviewed studies included FOF as an outcome; compromised methodological quality of the included studies; or that the key ingredients of the interventions did not address walking difficulties in daily life. Future trials targeting walking ability and including FOF as an outcome are thus needed. Importantly, FOF may be such a complex construct that it best benefits from using an interdisciplinary approach. The latter may be supported by the fact that dependence in daily activities as well as fatigue was independently associated with FOF. Interestingly, it has been suggested that poor walking economy among people with PD may contribute to fatigue [40]. However, the exact role

of this enigmatic complaint remains speculative [41-43] and cannot be addressed based on the current study.

Limitations and future perspectives

This sample consisted of people with PD that were relatively mildly affected by their disease, which is mirrored by several of the descriptive variables, e.g. motor symptoms (UPDRS III), PD duration, gait speed, and the number of participants that had experienced falls. In addition, people being above the age of 80 years were not included. Our findings may thus not apply to very old people with PD or those with more severe PD. It should also be acknowledged that although several independent variables were included, there may be additional variables of importance for FOF such as general self-efficacy, environmental factors, anxiety and depression. In fact, a previous study that used multivariate analyses showed that greater depression contributed to perceived consequences of falling while anxiety contributed to activity avoidance due to the risk of falling [21]. However, ADL-difficulties showed a stronger independent association with activity avoidance than anxiety did. It should be noted that the study included few independent variables (disease severity, ADL, depression and anxiety), and the influence of anxiety and depression on FOF remains unclear due to the cross-sectional design of the study.

In the present study, some of the variables that did not show independent associations with FOF were assessed by relatively coarse indicators, e.g. dual-task difficulties and cognition (MMSE). By using a coarse indicator one may not capture those having mild problems. For instance, it has been suggested that the Montreal Cognitive Assessment (MoCA) is preferably to MMSE when screening for early cognitive impairments in PD [44,45]. Finally, due to the cross-sectional design of this study, it cannot be establish whether the identified associated factors actually are predictive of FOF. Longitudinal studies are needed to gain an increased understanding of risk factors for developing FOF, but also for determining factors that may aggravate existing FOF over time. Such knowledge is imperative to maximize the potential of interventions aiming at reducing FOF.

Conclusions

This study was able to replicate previous main findings in an independent sample of people with PD by identifying everyday walking difficulties as a primary FOF associated factor, and additional independent contributions by fatigue and the need for help in daily activities. Furthermore, functional balance performance was found to be the only factor among a range of additional clinical motor and cognitive variables that was able to account for additional significant proportions of the variance in FOF. These observations imply that walking difficulties and balance performance in daily life are candidate therapeutic targets in order to reduce FOF in PD. However, longitudinal studies are warranted in order to gain an increased understanding of predictors of FOF in PD and who is at risk of developing a FOF.

Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

BL, PH, OH and MHN conceived and designed the study. BL performed data collection. BL, MHN and PH analyzed the data. BL and MHN drafted the initial manuscript. All authors participated in writing (and approved) the final version of the manuscript.

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Paper II

PLOS ONE

RESEARCH ARTICLE

Prediction of Falls and/or Near Falls in People with Mild Parkinson's Disease

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Abstract

Objective

To determine factors associated with future falls and/or near falls in people with mild PD.

Methods

The study included 141 participants with PD. Mean (SD) age and PD-duration were 68 (9.7) and 4 years (3.9), respectively. Their median (q1–q3) UPDRS III score was 13 (8-18). Those >80 years of age, requiring support in standing or unable to understand instructions were excluded. Self-administered questionnaires targeted freezing of gait, turning hesitations, walking difficulties in daily life, fatigue, fear of falling, independence in activities of daily living, dyskinesia, demographics, falls/near falls history, balance problems while dual tasking and pain. Clinical assessments addressed functional balance performance, retropulsion, comfortable gait speed, motor symptoms and cognition. All falls and near falls were subsequently registered in a diary during a six-month period. Risk factors for prospective falls and/or near falls were determined using logistic regression.

Results

Sixty-three participants (45%) experienced ≥1 fall and/or near fall. Three factors were independent predictors of falls and/or near falls: fear of falling (OR = 1.032, $p<0.001$) history of near falls (OR = 3.475, p = 0.009) and retropulsion (OR = 2.813, p = 0.035). The strongest contributing factor was fear of falling, followed by a history of near falls and retropulsion.

Conclusions

Fear of falling seems to be an important issue to address already in mild PD as well as asking about prior near falls.

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Introduction

Postural instability is one of the cardinal signs of Parkinson's disease (PD). People with PD are particularly unstable backwards [1–3] which commonly is assessed by using the pull test. Several versions of the pull test exist, of which the Nutt Retropulsion Test (NRT) with an unexpected shoulder pull (1 trial) has been preferred [4]. Besides being able to counteract an externally applied perturbation, it is imperative to maintain balance while performing voluntary and self-generated movements in daily life [5]. That is, functional balance performance is also of importance.

In the postural instability and gait difficulty (PIGD) subtype of PD, walking difficulties and balance demanding activities may be affected already early on [6,7]. Gait and balance problems in PD relate to both motor and non-motor features such as cognitive dysfunction [8]. These problems are often aggravated while performing dual tasks [8], and walking difficulties have been shown to be the strongest associated factor to fear of falling (FOF) in people with PD [9,10].

Falls are one of the most disabling features of PD and occur in 35–90% of patients, among whom 18–65% experience recurrent falls [11]. It is also common for people with PD to experience so called near falls [9,10,12–16], which occur also among those who do not fall (60–62%) [12,13]. Previous studies have identified several risk factors for future falls in PD, such as freezing of gait, balance and mobility problems as well as cognitive impairments and a history of falls (e.g.[17–19]). To the best of our knowledge only one previous PD study included a history of near falls (during the past 12 months) as an independent variable when investigating risk factors for future falls [20]. Falls were however not registered prospectively as recommended [21] but registered based on recall at a three-month follow-up. Although the study by Ashburn et al. did not identify prior near falls as a risk factor [20], it has been suggested that near falls may in fact be a precursor of an increased risk for future falls [22,23]. Near falls may therefore be of specific importance in mild PD. Early detection of those at risk may facilitate preventive means. The objective of this study was therefore to determine factors associated with future falls and/or near falls in mild PD.

Methods

Ethics statement

The Regional Ethical Review Board in Lund, Sweden approved the study (Dnr 2011/768). All participants gave written informed consent.

Participants

All people diagnosed with PD receiving care at a south Swedish university hospital during 2007–2012 were considered eligible for inclusion (n = 349). Exclusion criteria were age above 80 years old (n = 116), inability to stand without support (n = 22), unable to understand instructions (n = 14) or having severe comorbidity (n = 11). Of the remaining 186 potential participants, 40 (16 women) declined participation. Those who declined did not differ significantly ($P \geq 0.061$, Mann—Whitney U test) from the 146 participants with respect to age and PD duration.

Procedure and Instruments

Anti-parkinsonian medications were recorded from medical records. All participants were assessed during an outpatient visit, which was scheduled at a time of day when the participant usually reported to feel at best.

Table 1. Descriptions of included self-administered questionnaires and clinical assessments.[1]

	Score range	Dichotomized	References
Cognition (MMSE)	0–30 [2]		37
Comfortable gait speed m/s (10MWT)	≥ 0 m/s		34
Dyskinesia (item 32, UPDRS IV)	0 (none)–4 (76%–100% a day)	No (0), yes (1–4)	36
Fatigue (FACIT-F)	0–52 [2]		28, 29
Fear of falling (FES [26])	0–130 [2]		30, 31
Freezing of gait (item 3, FOGQsa)	0 (never)–4 (always—whenever walking)	No (0), yes (1–4)	24–26
Functional balance (BBS)	0–56 [2]		5, 34
Motor symptoms (UPDRS III)	0–108 [3]		36
Need help from others in daily activities (PADLS)	1 (no difficulties with day-to-day activities)—5 (extremedifficulties with day-to-day activities)	No (1–2), yes (3–5)	32, 33
Retropulsion (NRT)	0 (normal, may take 2 steps to recover)—3 (spontaneoustendency to fall or unable to stand unaided, test not executable)	No (0), yes (1–3)	35
Severity of disease (H&Y)	I-V [3]		38
Turning hesitations (item 6, FOGQsa)	0 (never)—4 (more than 30 seconds)	No (0), yes (1–4)	24–26
Walking difficulties (Walk-12G)	0–42 [3]		27

[1] Additional dichotomous questions that were included targeted: history of falls, history of near falls, balance problems while dual tasking and pain.

[2]higher = better

[3]higher = worse

BBS, Berg Balance Scale; FACIT-F, the Functional Assessment of Chronic Illness Therapy—Fatigue; FES(S), Falls Efficacy Scale (Swedish version); FOGQsa, Freezing of Gait Questionnaire, self-administered version; H&Y, Hoehn & Yahr stage; MMSE, Mini Mental State Examination; NRT, Nutt Retropulsion Test; PADLS, the Parkinson's disease Activities of Daily Living Scale; UPDRS III, part III (motor score) of the Unified Parkinson's Disease Rating Scale; UPDRS IV, part IV (complications of therapy) UPDRS IV, part IV (complications of therapy) was self-administered; 10MWT, 10-Meter Walk Test; m/s, meters per second; Walk-12G, 12-item generic walking scale.

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First, the participants completed self-administered questionnaires targeting freezing of gait, turning hesitations [24–26], walking difficulties in daily life [27], fatigue [28,29], FOF (conceptualized as fall-related self-efficacy) [30,31], and independence in activities of daily living [32,33]. Further details are provided in Table 1.

All participants then self-rated their present motor status as "good/on", "on with dyskinesias", or "bad/off". This was followed by clinical assessments (Table 1) administered by the same physical therapist (BL). These were performed in the following order and targeted: functional balance performance (Berg balance scale, BBS) [5,34]; retropulsion (Nutt retropulsion test, NRT) [4,35]; comfortable gait speed (10-Meter Walk-test, 10MWT) [34]; motor symptoms (Unified Parkinson's Disease Rating Scale, UPDRS part III) [34,36] and cognition (Mini-Mental State Examination, MMSE) [37]. For descriptive purposes, severity of disease was assessed according to Hoehn & Yahr stage (H&Y) [38].

Additional self-administered questions were then administered. These targeted demographic data (age, sex, disease duration) and the presence or absence of dyskinesia [36] (Table 1). In addition, dichotomous questions (Yes/No) targeted history of falls during the past six months (*In the last six months, have you fallen in such a way that your body hit the ground?*), history of near falls (*Are you ever close to falling, but you manage to grab on to something/someone at the last minute so that your body does not hit the ground?*), balance problems while dual-tasking (*Do you experience balance problems while standing or walking when doing more than one*

thing at a time, *e.g. carrying a tray while walking?*) and pain (*Do you presently suffer from pain?*).

Prospective assessment of falls and near falls

By using a diary, participants were instructed to register all consecutive falls and near falls for six months. At the outpatient visit, the definitions of a fall and a near fall were thoroughly described to all participants. Falls were described and defined as "*an unexpected event in which the participants come to rest on the ground*, *floor*, *or lower level*" [21]. Near falls were described and defined as"*a fall initiated but arrested by support from the wall*, *railing*, *other person etc.*" [39].

In the diary, questions (Yes/No) clarified whether the incident was a fall or a near fall. The question in relation to a fall was phrased as follows: "*Did you fall in such a way that your body hit the ground?*" The corresponding question about a near fall incident was phrased: "*Were you close to falling*, *but managed to brace yourself at the last moment (e.g. grabbed on to someone*, *to an object or the wall?*"

All participants were telephoned monthly to ensure that registrations were completed according to instructions. During the last telephone call, they were requested to return the diary in a pre-stamped envelope.

Statistical analysis

Data were checked regarding underlying assumptions and described accordingly using IBM SPSS version 21. Normally distributed interval/ratio level variables were described using means and SDs. In other cases, medians (q1–q3) were used. Categorical variables were described using n (%). The alpha level of significance was set at 0.05 (2-tailed). Anti-parkinsonian medications were expressed as daily levodopa equivalent (LDE) doses (mg/day) [40].

Logistic regression analysis was performed in order to establish risk factors for prospective falls and/or near falls (dependent variable). Initially, simple logistic regression analysis was used for factors (independent variables) that were considered potentially important for falls and/or near falls. Variables that were significant at the alpha level of 0.2 were subsequently included as independent variables in a multiple logistic regression analysis in order to identify those independently associated with prospective falls and/or near falls. The <0.2 P-value threshold was chosen in order to avoid leaving a confounding variable out. Both forward and backward methods were used (Wald test). The final model was controlled for age and gender.

In order to facilitate comparisons with prior studies, we also explored factors associated with prospective falls only (i.e. non-fallers and near falls only vs. fallers). The statistical procedure was otherwise identical to the main analysis (see above).

Results

Five participants did not complete the prospective 6-month follow-up of falls and/or near falls due to e.g. developing severe comorbidities. The final sample (n = 141; 97%) had a mean (SD; min-max) age and PD duration of 68 (9.7; 35–80) and 4 (3.9; 0.1–17) years, respectively. Their median (q1–q3) UPDRS III score was 13 (8–18). Further details are provided in Table 2.

At the time of assessments, 123 out of the 141 participants (87%) rated their motor status as"on", whereas 12 (9%) rated it as "on with dyskinesias", and 6 (4%) rated it as"off".

Prospective falls and/or near falls

During the 6-month follow-up, 63 out of 141 (45%) participants experienced at least one fall and/or near fall. Forty-five out of 141 participants (32%) reported falls, of whom 26 (58%)

Table 2. Sample characteristics (n = 141).

Age (years), mean (SD)	68 (9.7)
Female gender, n (%)	65 (46)
PD-duration (years), median (q1–q3)	2 (1–6)
Cognition (MMSE), median (q1–q3) [1]	28 (26–29)
Motor symptoms (UPDRS III), median (q1–q3)	13 (8–18)
Dyskinesia (UPDRS IV, item 32), n (%) [2, a]	46 (33)
Severity of disease (H&Y), median (q1–q3)	2 (2–3)
Daily total levodopa equivalent (LDE) dose (mg), median (q1–q3) [b]	400 (286–600)
Dopamine agonist use, n (%)	55 (39)
Functional balance performance (BBS), median (q1–q3)	53 (48–55)
Comfortable gait speed (10MWT, m/s), mean (SD)	1.14 (0.28)
Fatigue (FACIT-F), median (q1–q3)	39 (29.5–44)
Pain, n (%)	40 (28)
Walking difficulties (Walk-12G), median (q1–q3)	8 (4–19.5)
Fear of falling (FES[S]), median (q1–q3) [3]	118 (84–129)
History of falls past 6 months, n (%)	34 (24)
History of near falls, n (%)	50 (35)
Balance problems while dual-tasking, n (%) [c]	68 (48)
Need help from others in daily activities (PADLS), n (%) [1, d]	13 (9)
Freezing of gait (item 3, FOGQsa), n (%) [1, e]	58 (41)
Turning hesitations (item 6, FOGQsa) n (%) [1, f]	49 (35)
Retropulsion (NRT), n (%) [g]	35 (25)

[1]One missing value

[2]Two missing values

[3]Four missing values

[a]Item 32 of the UPDRS part IV. Those scoring ≥1 were categorized as having dyskinesias.

[b]Derived according to Tomlinson et al. (2010).

[c]Investigated with dichotomous question (Yes/No) "*Do you experience balance problems while standing or walking when doing more than one thing at a time, e.g. carrying a tray while walking?*"

[d]Those scoring >2 on the PADLS were categorized as needing help from others in daily activities.

[e]Item 3 ("freezing") of the FOGQsa. Those scoring ≥1 were categorized as freezers.

[f]Item 6 ("turning hesitations") of the FOGQsa. Those scoring ≥1 were categorized as having turning hesitations.

[g]Scores ≥1 on the NRT were categorized as having retropulsion

BBS, Berg Balance Scale; FACIT-F, the Functional Assessment of Chronic Illness Therapy—Fatigue; FES (S), Falls Efficacy Scale, (Swedish version); FOGQsa, Freezing of Gait Questionnaire, self-administered version; H&Y, Hoehn & Yahr stage; MMSE, Mini Mental State Examination; NRT, Nutt Retropulsion Test; PADLS, the Parkinson's disease Activities of Daily Living Scale; PD, Parkinson's disease; q1–q3, 1st-3rd quartile; SD, standard deviation; UPDRS III, part III (motor score) of the Unified Parkinson's Disease Rating Scale; UPDRS IV, part IV (complications of therapy), item 32; 10MWT, 10-Meter Walk Test; m/s, meters per second; Walk-12G, 12-item generic walking scale.

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reported more than one fall (i.e. recurrent falls); on average they reported 5 falls (min-max, 2–12). In total, 44 participants (31%) reported near falls. Eighteen of those reported only near falls whereas 26 also reported falls. Twenty-six out of the 44 (59%) reported more than one near fall; they reported on average 11 near fall incidences (min-max, 2–45). The total number

of all reported incidences was 452 (n = 63); 158 (35%) of those were falls whereas 294 (65%) were near falls.

Predictors of prospective falls and near falls

Simple logistic regression analyses identified 16 independent variables associated with prospective falls/near falls at P<0.2 (Table 3). Table 4 summarizes the results when entering these independent variables into forward and backward logistic regression analyses controlling for age and gender. Three significant independent predictors for prospective falls/near falls were

Table 3. Descriptive statistics and results from simple logistic regression analyses for potential predictors of future falls and/or near falls.

Independent variables[1]	No falls or near fallsn = 78	Falls and/or near fallsn = 63	Simple logistic regression analyses	
			OR (95% CI)	P value
Age (years) mean (SD)	66 (10.4)	70 (8.3)	–	–
Female gender, n (%)	30 (38)	35 (56)	–	–
PD-duration (years), median (q1–q3)	2 (5–5)	4 (1–8)	1.12 (1.03–1.22)	0.011
Cognition (MMSE), median (q1–q3)	28 (26–29) [2]	27 (26–29)	1.20 (1.01–1.42)	0.034
Motor symptoms (UPDRS III), median (q1–q3)	11.5 (7–15)	18 (10–23)	1.13 (1.07–1.2)	<0.001
Dyskinesia (UPDRS IV item 32), n (%) [a]	22 (29) [3]	24 (38)	1.51 (0.74–3.07)	0.255
Balance (BBS), median (q1–q3)	55 (52–56)	50 (42–54)	1.20 (1.11–1.30)	<0.001
Comfortable gait speed (10MWT) (m/s), mean (SD)	1.24 (0.22)	1.02 (0.31)	21.92 (5.3–90.44)	<0.001
Fatigue (FACIT-F), median (q1–q3)	41.5 (36–47)	31.5 (23–41)	1.11(1.06–1.16)	<0.001
Pain, n (%)	15 (19)	25 (40)	2.76 (1.30–5.89)	0.008
Walking difficulties (Walk-12G), median (q1–q3)	6 (2–10)	17 (9–25)	1.12 (1.07–1,17)	<0.001
Fear of falling (FES[S]), median (q1–q3)	127 (117–130) [3]	88 (60–122) [3]	1.03 (1.02–1.05)	<0.001
History of falls past 6 months, n (%)	9 (11.5)	25 (40)	5.04 (2.14–11.90)	<0.001
History of near falls, n (%)	13 (17)	37 (59)	7.12 (3.27–15.50)	<0.001
Balance problems while dual-tasking, n (%)	26 (33)	42 (67)	4.00 (1.92–8.09)	<0.001
Need help from others in daily activities (PADLS), n (%) [b]	1 (1.3) [2]	12 (19)	17.88 (2.55–141.80)	0.006
Freezing of gait (item 3, FOGQsa), n (%) [c]	19 (25) [2]	39 (62)	4.96 (2.40–10.25)	<0.001
Turning hesitations (item 6, FOGQsa), n (%) [d]	16 (21) [2]	33 (52)	4.19 (2.00–8.79)	<0.001
Retropulsion (NRT), n (%) [e]	11 (14)	24 (38)	3.75 (1.66–8.47)	0.001

[1] For the regression analysis, scores were adjusted to be in the same direction: higher scores = more problems.

[2] One missing value

[3] Two missing values

[a] Item 32 of the UPDRS part IV. Those scoring ≥1 were categorized as having dyskinesias.

[b] Those scoring >2 on the PADLS were categorized as needing help from others in daily activities.

[c] Item 3 ("freezing") of the FOGQsa. Those scoring ≥1 were categorized as freezers.

[d] Item 6 ("turning hesitations") of the FOGQsa. Those scoring ≥1 were categorized as having turning hesitations.

[e] Scores ≥1 on the NRT were categorized as having retropulsion

Wald test

BBS, Berg Balance Scale; FACIT-F, the Functional Assessment of Chronic Illness Therapy—Fatigue; FES(S), Falls Efficacy Scale, (Swedish version); FOGQsa, Freezing of Gait Questionnaire, self-administered version; MMSE, Mini Mental State Examination; NRT, Nutt Retropulsion Test; PADLS, the Parkinson's disease Activities of Daily Living Scale; q1–q3, 1st-3rd quartile; SD, standard deviation; UPDRS III, part III (motor score) of the Unified Parkinson's disease Rating Scale; UPDRS IV, part IV (complications of therapy), item 32; 10MWT, 10-Meter Walk Test; m/s, meters per second; Walk-12G, 12-item generic walking scale.

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Table 4. Multiple logistic regression model: prediction of future falls and/or near falls (n = 135)[1].

Independent variables[2]	Wald	P-value	OR (95% CI)
Age (years)	0.485	0.486	1.017 (0.969–1.067)
Female gender	1.735	0.188	1.792 (0.752–4.267)
Fear of falling (FES[S])[3]	14.254	<0.001	1.032 (1.015–1.049)
History of near falls	6.750	0.009	3.475 (1.358–8.893)
Retropulsion (NRT)	4.428	0.035	2.813 (1.073–7.373)

[1]Forward/backward method (Wald); Nagelkerke pseudo R-square: 0.450; Hosmer and Lemeshow test: P = 0.438. The model was controlled for age and gender (italics in the table).

[2]Independent variables initially entered in the analysis were: age (years), gender, PD duration (years), cognition (MMSE), motor symptoms (UPDRS part III), functional balance (BBS), 10MWT, (comfortable gait speed), fatigue (FACIT-F), pain, walking difficulties Walk-12G, fear of falling (FES[S]), history of falls, history of near falls, balance problems while dual tasking, need help from others in daily activities (PADLS), freezing (FOGQsa, item 3), turning hesitations (FOGQsa, item 6), retropulsion (NRT).

[3] Possible score range, 0–130; for the regression analysis, scores were adjusted so that higher scores = more problems.

BBS, Berg Balance Scale; FACIT-F, the Functional Assessment of Chronic Illness Therapy; FES(S), Falls Efficacy Scale, Swedish version; FOGQsa, Freezing of Gait Questionnaire, self-administered version; MMSE, Mini Mental State Examination; NRT, Nutt Retropulsion Test; PADLS, the Parkinson's disease Activities of Daily Living Scale; PD, Parkinson's disease; UPDRS III, part III (motor score) of the Unified PD Rating Scale; 10MWT, 10-Meter Walk Test, m/s, meters per second; Walk-12G, 12-item generic walking scale.

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identified: FOF (FES(S)), history of near falls, and retropulsion (NRT). Results were identical for both forward and backward procedures.

Predictors of prospective falls

Simple logistic regression analyses identified 15 independent variables associated with prospective falls at P<0.2; the identified variables were the same as in Table 3 except for MMSE (P = 0.73). Four independent predictors for prospective falls were identified (OR, 95% CI): pain (4.9, 1.8–13.5), history of near falls (3.3, 1.3–8.3), retropulsion (3.5, 1.3–9.4) and disease duration (1.2, 1.0–1.3). Details from these analyses are available on request.

Discussion

This study comprehensively investigated contributing factors for experiencing future falls and/or near falls in people mildly affected by PD. When using multivariate analyses, three contributing factors were identified. The strongest factor was FOF, followed by a history of near falls and having retropulsion. That is, FOF seems to be an important issue to address already in mild PD as well as asking about prior near falls. Our findings may thus have important clinical implications since these aspects may not be addressed in those having mild PD. Although several prospective studies have investigated contributing factors for experiencing future falls (e.g, [17–20,41–44]) few included near falls as an independent or dependent variable [20]. This study thus contributes to the body of knowledge since it is imperative to early on detect those at risk in order to work proactively.

To the best of our knowledge, this is the first study presenting FOF as an independent associated factor for experiencing future falls and/or near falls in people with mild PD, although it has been identified as an independent risk factor for recurrent falls [11]. FOF in people with

PD is also of importance since it is a major barrier to physical exercise [45]; it may cause activity avoidance, participation restrictions and social isolation [44,46,47] and is negatively associated with health-related quality of life [48]. Taken together, FOF should probably be considered an integrate part of PD-assessments irrespective of disease severity.

The second strongest independent factor was a history of near falls. Although it has been suggested that one should ask people with PD about prior near falls [12] a study by Ashburn et al. did not support that near falls during the past year predicted future falls [20]. In that study, near falls was defined as "occasions on which individuals felt that they were going to fall but did not actually do so" [12]. Besides using a different definition, future falls were collected based on retrospective recall covering a shorter period (3 months) than the prospective 6-month follow-up used here. Our finding indicates that asking about prior near falls as defined by Gray et al. [39] may be helpful in identifying persons with mild PD that are at risk for future falls and/or near falls. Furthermore, it needs to be noted that during the 6-month follow-up, the proportion of near falls incidences far outweighed that for falls (65% versus 35%).

We suggest that near falls deserve more attention in PD research to gain an increased knowledge about associated factors, consequences and whether near falls is a precursor of falls. The latter requires longitudinal studies. There might also be a need for studies of how to best monitor and register near falls incidences.

In contrast to near falls, a history of falls was not identified as a risk factor for future falls and/or near falls. This finding is in contrast to several previous studies (e.g. [18–20,42,44]. The discrepancy might be due to that our dependent variable included both near falls and/or falls, and that a history of near falls was included as an independent variable, which has not been the case in previous studies. Another explanation might be that our sample represented relatively mild PD. For example, the proportion of participants that prospectively reported falls (32%) is lower compared to other prospective studies of falls in PD (range, 35–90%) [11]. However, in another study that investigated falls prospectively in people with mild PD about 68% reported fall [19]. Methodological aspects may also play a part in the number of falls reported. In the study by Wood et al., each subject was given a set of weekly prepaid postcards to return for one year. A fall report was followed up by telephone to outline the exact circumstances of the fall event. If cards were not returned one week after their expected return date, this would also prompt telephone contact [19].

Still, a history of near falls but not falls was identified as a risk factor when excluding near falls from the dependent variable. This may indicate that near falls is a precursor of experiencing future falls [22,23], suggesting that it may be more effective to ask about prior near falls than actual falls if you aim at working pro-actively. Additional studies are needed to support or refute the present findings and to understand the relationships between near falls and falls.

The third independent associated factor identified was retropulsion according to the NRT, which was positive in 25% of our participants. In relatively mild PD, this might be seen as a surprising finding. However, postural instability has been shown to be present already at diagnosis [6] although it worsens with disease progression. The Sydney multicenter longitudinal study reported that 34% demonstrated postural instability two years after diagnosis [7] which increased to 71% after ten years [49]. In the present study, the reasoning for choosing the NRT as a pull test is that it incorporates an unexpected shoulder pull and only one trial is performed; this version of the pull test has been suggested to provide a more valid evaluation that reflects everyday life situations [4].

Some methodological limitations and considerations need to be acknowledged. This study involves people with mild PD but people being above the age of 80 years were not included. Our findings may therefore not be applicable to very old people with mild PD. Although several independent variables were included, several other variables may contribute to the

occurrence of falls and near falls. Furthermore, some of the included variables that were not shown to be independently associated with prospective falls/near falls were assessed by using relative rough indicators. For instance, to capture those having mild cognitive impairments in PD, the Montreal Cognitive Assessment (MoCA) has been suggested to be preferably to MMSE [50,51]. In addition, several variables (e.g. dyskinesia, freezing of gait and turning hesitations) were dichotomized, which may lead to loss of information. However, this was done for reasons related to the distributional properties of item responses. We also acknowledge that retrospective recall of near falls may be more problematic than for falls. In this study, no retrospective time frame was used and whether this influenced the results is unclear. Future studies are needed to address the potential impact of using a retrospective time frame (e.g. six or twelve months) in relation to history of near falls in people with PD.

Conclusions

This study identified three contributing factors for experiencing future falls and/or near falls in people mildly affected by their PD. The strongest factor was FOF, followed by a history of near falls and having retropulsion. That is, FOF seems to be an important issue to address already in mild PD as well as asking about prior near falls. A history of near falls appears to be a stronger predictor for future falls than a history of falls. This highlights the need for addressing near falls in more depth in larger longitudinal studies including a broader range of PD severities.

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Author Contributions

Conceived and designed the experiments: BL PH OH MHN. Performed the experiments: BL. Analyzed the data: BL MHN PH. Wrote the paper: BL MHN. Performed data collection: BL. Drafted the initial manuscript: BL MHN. Participated in data interpretation and writing (and approving) the final version of the manuscript: BL PH OH MHN.

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Paper III

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ORIGINAL COMMUNICATION

External validation of a 3-step falls prediction model in mild Parkinson's disease

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Abstract The 3-step falls prediction model (3-step model) that include history of falls, history of freezing of gait and comfortable gait speed <1.1 m/s was suggested as a clinical fall prediction tool in Parkinson's disease (PD). We aimed to externally validate this model as well as to explore the value of additional predictors in 138 individuals with relatively mild PD. We found the discriminative ability of the 3-step model in identifying fallers to be comparable to previously studies [area under curve (AUC), 0.74; 95 % CI 0.65–0.84] and to be better than that of single predictors (AUC, 0.61–0.69). Extended analyses generated a new model for prediction of falls and near falls (AUC, 0.82; 95 % CI 0.75–0.89) including history of near falls, retropulsion according to the Nutt Retropulsion test (NRT) and tandem gait (TG). This study confirms the value of the 3-step model as a clinical falls prediction tool in relatively mild PD and illustrates that it outperforms the use of single predictors. However, to improve future outcomes, further studies are needed to firmly establish a scoring system and risk categories based on this model. The influence of methodological aspects of data collection also needs to be scrutinized. A new model for prediction of falls and near falls, including history of near falls, TG and retropulsion (NRT) may be considered as an alternative to the 3-step model, but needs to be tested in additional samples before being recommended. Taken together, our observations provide important additions to the evidence base for clinical fall prediction in PD.

Keywords Parkinon disease · Falls · Near falls · Gait · Balance · Prediction

Introduction

Falls and balance problems are common already early in Parkinson's disease (PD) [1–4] and progress over time [5–7]. Avoiding falls and its consequences is a major goal and challenge in the management of PD [8]. Several predictive factors for future falls and near falls have been identified, e.g. history of falls and near falls, impaired balance, retropulsion, reduced comfortable gait speed, freezing of gait (FOG), cognitive impairments, pain, and fear of falling (FOF) (e.g. [9–12]). However, prediction of falls is still a clinical challenge. For example, most available studies have identified predictive factors based on logistic regression models and associated odds ratios (ORs) (e.g. [10–12]). However, ORs do not inform about the ability of predictors to discriminate between future fallers and non-fallers [13, 14] and are therefore not easily implemented in clinical practice [15]. It is therefore unclear exactly what components to consider. For example, history of falls was proposed as the strongest predictor in several prospective studies [16], whereas other observations suggest that history of near falls is a stronger predictor and may be seen as a precursor of falls [12].

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Successful implementation of prediction models in clinical practice generally requires three main phases: model development, external validation, and investigations of their clinical impact; it is also recommended to consider whether existing models can be improved by, e.g. additional predictors [17]. Furthermore, in order to be applicable, useful and practical for routine clinical use, prediction models need not only to have sufficient ability to discriminate between future fallers and non-fallers, but also be easy and quick to implement. To this end, Paul et al. [18] proposed a 3-step falls prediction model (3-step model) consisting of three variables: history of falls during the past 12 months, history of FOG, and comfortable gait speed <1.1 m/s based on the mean of two trials of walking a standardized distance. Receiver operating characteristics (ROC) curve analyses found the 3-step model to discriminate between fallers and non-fallers over a prospective 6-month period with an area-under-the-curve (AUC) of 0.80 (95 % CI 0.73–0.86) [18]. These results were later replicated in a different PD sample (AUC, 0.83; 95 % CI 0.76–0.89) [19].

In contrast to other suggested fall prediction models, the 3-step model avoids reliance on relatively lengthy and time consuming clinical tests and assessments. For example, the model proposed by Kerr et al. [9] involves total scores of the Unified PD Rating Scale (UPDRS), the Tinetti scale and the FOG Questionnaire (FOGQ). The 3-step model therefore appears clinically promising and has been recommended in the European Physiotherapy Guidelines for PD [20]. However, it may be argued that measurement of gait speed according to the 3-step model may be considered cumbersome or difficult to achieve in clinical practice since it requires a standardized distance free of narrow passages, timing of two walking trials, and the calculation of the corresponding mean velocity as m/s. Meanwhile, common and easily conducted clinical PD tests such as pull-tests [21–24] and Tandem Gait (TG) [23, 25] were not considered in the development of the 3-step model [18], although previously recommended for the prediction of falls [23, 24].

This study aimed to externally validate the 3-step model in an independent sample of people with relatively mild PD. In addition, we explored the ability of additional historical information and clinical tests to predict falls as well as near falls, and compared those with the proposed 3-step model.

Method

Participants

The Regional Ethical Review Board approved the study (Dnr 2011/768). All participants gave written informed consent.

Participants were enrolled in a cohort study designed for evaluation of a broad spectrum of factors associated with falls and near falls in PD. All people diagnosed with PD receiving care at a south Swedish university hospital during 2007–2013 were considered eligible for inclusion ($n = 359$). Exclusion criteria were: age above 80 years old ($n = 121$), inability to understand instructions ($n = 14$), significant cognitive impairment (Mini-Mental State Examination (MMSE) score <24; $n = 8$), inability to stand without support ($n = 22$) and severe comorbidity ($n = 11$). Of the remaining 183 potential participants, 40 (16 women) declined participation and 5 did not complete the follow-up period, leaving 138 participants in the final study sample.

Assessments and procedure

Detailed description of the procedures are available elsewhere [12]. All participants were assessed during an outpatient visit, scheduled at a time of day when the participant usually reported to feel at best.

Data for the proposed 3-step model [18] were taken from the following sources: (1) history of falls was determined by yes/no responses to the question: *In the last 12 months, have you fallen in such a way that your body hit the ground?* In addition, history of near falls was considered (but not as part of the proposed 3-step model; see below) by responses to a similar yes/no question: *Are you ever close to falling, but you manage to grab on to something/someone at the last minute so that your body does not hit the ground?*; (2) responses to item 3 [*Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?*] of the FOGQ (self-administered version) [26], which is scored 0–4 (higher = worse); those scoring ≥1 were categorized as having history of FOG [27]; (3) gait speed measurement according to the 10-Meter Walk test (10MWT), conducted in comfortable gait speed without acceleration, using a digital timer (Origo, model 365510). To ensure the relevance of the suggested 1.1 m/s cut-off [18] we tested the optimal cut-point in the current sample [28], which was found to be 1.06. We therefore calculated each person's mean m/s from two trials and dichotomized the resulting mean m/s according to the proposed 1.1 m/s cut-off.

Retropulsion was assessed using an unexpected shoulder pull according to the Nutt Retropulsion test (NRT) [22] as well as an expected shoulder pull according to item 30 of the UPDRS [21]. The participant was standing with feet slightly apart and eyes open, with the examiner giving a sudden, firm backward pull to the shoulders from behind. The NRT was executed first and scored 0-3: 0 (normal, ≤2 steps to recover), 1 (≥3 or more steps; recovers unaided), 2 (would fall if not caught), 3 (spontaneous tendency to fall or unable to stand unaided) [22, 24]. Those scoring ≥1

were categorized as having retropulsion [24]. During assessments according to UPDRS item 30, the participant was first told that s/he was to be pulled and instructed to prevent falling [21, 29]. Performance was scored 0–4: 0 (normal), 1 (retropulsion, but recovers unaided), 2 (absence of postural response, would fall if not caught by examiner) and 3 (very unstable, tends to lose balance spontaneously), 4 (unable to stand without assistance). Those scoring ≥1 were categorized as having retropulsion [24].

To assess the ability to walk in tandem (TG) participants were instructed to take ten consecutive heal-to-toe steps along a straight line without walking aids or support, with eyes open. Performance was scored 0–3; 0 (no side steps), 1 (a single side step), 2 (multiple side steps), 3 (unable to take 4 consecutive steps) [30]. Those scoring ≥1 were categorized as having an abnormal TG performance [23, 25].

Additionally, demographic data (age, gender, PD duration and severity according to Hoehn and Yahr [HY]) [31] were recorded and parkinsonian motor symptoms were assessed using the UPDRS part III (motor examination), which yields a total score ranging from 0 to 108 (108 = worse) [21]. Antiparkinsonian medications were recorded from medical records and expressed as daily levodopa equivalent (LDE) doses (mg/day) [32].

Finally, participants were provided with a diary for recording prospective falls and near falls during a six-month follow-up, where falls were defined as "*an unexpected event in which the participants come to rest on the ground, floor, or lower level*" [33], and near falls were defined as "*a fall initiated but arrested by support from the wall, railing, other person* etc." [34]. In the diary, two yes/no questions were used to define whether an incidence was a fall (*Did you fall in such a way that your body hit the ground?*) or a near fall (*Were you close to falling, but managed to brace yourself at the last moment (e.g. grabbed on to someone, to an object or the wall?*) [12]. Those reporting at least one fall or near fall were considered fallers and near-fallers, respectively. To facilitate correct registration during the 6-month follow-up the definitions of a fall and a near fall were thoroughly described to all participants at the outpatient visit. All participants were also telephoned monthly to ensure that registrations were completed according to instructions. During the last telephone call, they were requested to return the diary in a pre-stamped envelope.

Statistical analyses

Data were checked regarding underlying assumptions and analysed accordingly using IBM SPSS version 22 (IBM Corp., Armonk, NY). The alpha level of significance was set at 0.05 (two-tailed).

To externally validate the 3-step model [18, 19] multiple logistic regression analysis (enter method) was used with the three suggested predictors (history of falls in 12 months, history of FOG, and comfortable gait speed <1.1 m/s) as independent variables and occurrence of falls during the 6-month follow-up as the dependent variable. In developing the 3-step model, Paul et al. [18] suggested weights for each predictor variable based on the ORs from their logistic regression model (history of falls, weight 6; history of FOG, weight 3; gait speed <1.1 m/s, weight 2), yielding a summed total score between 0 and 11. Based on these, three risk categories and associated 6-month prospective fall probabilities were suggested: low risk (score 0; 17 % fall probability), moderate risk (score 2–6; 51 % fall probability), and high risk (score 8–11; 85 % fall probability) [18]. In order to facilitate comparisons with prior studies [18, 19], risk categories for our sample were derived by the sum of the suggested predictor weights.

Secondly, simple logistic regression analyses were used to evaluate how well each single predictor (history of falls in 12 months, history of near falls, history of FOG, gait speed, NRT, UPDRS item 30, and TG) predicted falls during the 6-month follow-up. Thirdly, all potential predictors were entered into a multiple logistic regression analysis (backward method) to explore if this could improve prediction of future falls as compared to the 3-step model. We also calculated the sensitivity and specificity of relevant prediction models. In order to account for near falls, we also explored factors associated with the combination of prospective falls and/or near falls according to the same procedures as described above.

ROC curve analyses were used to assess overall accuracy of each model by estimating the AUC [35, 36]. AUCs can range between 0 and 1; an AUC <0.5 indicates that the model performs worse than chance, whereas an AUC of 1 indicates perfect discrimination. AUCs ≥0.7 and >0.9 are considered acceptable and high, respectively [37].

Results

The final sample ($n = 138$) is summarized in Table 1. During the 6 months of follow-up, 33 % (45/138) reported ≥1 fall and 14 % (19/138) reported only near falls (Table 2).

Testing the ability of the 3-step model to distinguish between individuals with and without future falls yielded an AUC (95 % CI) of 0.74 (0.65–0.84). Further details are presented in Table 3. Considering the suggested risk categories [18], 55, 48 and 32 people scored in the low, moderate and high risk categories, respectively. Of these,

Table 1 Sample characteristics, $n = 138$

Age (years), mean (SD; min–max)	67 (9.8; 35–80)
Female gender, *n* (%)	64 (46)
History of falls, *n* (%)[a]	38 (28)
History of near falls, *n* (%)[b]	48 (35)
History of FOG, *n* (%)[c,d]	57 (41)
Severity of disease (H&Y), median (q1–q3; min–max)	2 (2–3; 1–4)
PD-duration (years), mean (SD; min–max)	4 (4.0; 0.1–17)
Motor symptoms (UPDRS part III), median (q1–q3; min–max)	12 (8–18; 1–34)
Comfortable gait speed <1.1 m/s (10MWT), *n* (%)[e]	54 (39)
Retropulsion (NRT), *n* (%)[f]	36 (26)
Retropulsion (UPDRS, item 30), *n* (%)[g]	53 (38)
Abnormal tandem gait (TG), *n* (%)[h]	78 (57)
Daily total levodopa equivalent (LDE) dose (mg), median (q1–q3; min–max)[i]	400 (300–600; 0–1477)

At the time of assessments, 132 participants (96 %) rated their motor status as "on" or "on with dyskinesias" and 6 (4 %) rated it as "off"

FOGQsa, Freezing of Gait Questionnaire, self-administered version; H&Y, Hoehn and Yahr; NRT, Nutt Retropulsion test; PD, Parkinson's disease; q1–q3, 1st–3rd quartile; SD, standard deviation; TG, Tandem gait; 10MWT, 10-Meter Walk test; m/s, meter per second; UPDRS item 30, Item 30 of Unified PD Rating Scale; UPDRS part III, motor score of the Unified PD Rating Scale

[a] Dichotomous question (Yes/No): *In the last 12 months, have you fallen in such a way that your body hit the ground?*

[b] Dichotomous question (Yes/No): *Are you ever close to falling, but you manage to grab on to something/someone at the last minute so that your body does not hit the ground?*

[c] Scores ≥1 on the FOGQsa, item 3 (*Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?*) were categorized as having FOG

[d] One missing value

[e] Two missing values

[f] Scores ≥1 on the NRT (unexpected shoulder pull) were categorized as having retropulsion

[g] Scores ≥1 on the UPDRS, item 30 (expected shoulder pull) were categorized as having retropulsion

[h] Scores ≥1 on the TG were categorized as abnormal

[i] Derived according to Tomlinson et al. [34]

Table 2 Proportion of individuals with/without falls/near falls based on 6-month follow-up, $n = 138$

Falls, *n* (%)	Near falls, but no falls, *n* (%)	Falls and/or near falls, *n* (%)	No falls or near falls, *n* (%)
45 (33)	19 (14)	64 (46)	74 (54)

there were 7 (13 %), 18 (38 %) and 20 (63 %) who actually fell during the subsequent 6 months.

Simple logistic regression analyses of all available predictors and with falls as the dependent variable (Table 4) showed that near falls (AUC, 0.69) had the highest ability to distinguish between individuals with and without future falls. Rerunning these simple logistic regression analyses but with future falls and/or near falls as the dependent variable showed that a history of near falls and TG had the highest discriminant ability, both with an AUC (95 % CI) of 0.71 (0.62–0.80). Corresponding ORs (95 % CI) were 6.21 (2.91–13.25) for TG and 7.45 (3.32–16.70) for history of near falls (details available on request).

Multiple logistic regression analysis (backward method) using all available predictors as independent variables resulted in three significant predictors for the occurrence of future falls (Table 5): history of near falls, retropulsion (NRT), and comfortable gait speed <1.1 m/s, with an AUC (95 % CI) of 0.78 (0.70–0.86). Rerunning this analysis using falls and/or near falls as the dependent variable identified three predictors with an AUC (95 % CI) of 0.82 (0.75–0.89). The three predictors were (OR; 95 % CI): history of near falls (5.08; 2.04–12.66), retropulsion (NRT) (3.40; 1.26–9.14), and TG (4.41; 1.91–10.19) (sensitivity/specificity, 0.57/0.86, tolerance, ≥0.87 details available on request).

Table 3 External validation of the 3-step model for prediction of future falls, $n = 135$

Predictors	Wald	*P* value	OR (95 % CI)
History of falls[a]	7.26	0.007	3.34 (1.39–8.02)
History of FOG[b]	0.79	0.376	1.48 (0.62–3.49)
Comfortable gait speed <1.1 m/s (10MWT)	6.02	0.014	2.88 (1.24–6.72)

Multiple logistic regression analysis (enter method); Nagelkerke pseudo *R* square: 0.229; Hosmer and Lemeshow test: $P = 0.905$; tolerance: ≥0.81 Sensitivity/specificity, 0.37/0.92

CI, confidence interval; FOG, Freezing of Gait; FOGQsa, Freezing of Gait Questionnaire, self-administered version; OR, odds ratio; 10MWT, 10-Meter Walk test; m/s, meter per second

[a] Dichotomous question (Yes/No): *In the last 12 months, have you fallen in such a way that your body hit the ground?*

[b] Scores ≥1 on the FOGQsa, item 3 (*Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?*) were categorized as having FOG

Table 4 Simple logistic regression analysis: prediction of future falls, $n = 138$

	OR (95 % CI)	AUC (95 % CI)
History of falls[a]	5.44 (2.43–12.15)***	0.68 (0.57–0.78)
History of near falls[b]	5.14 (2.38–11.10)***	0.69 (0.59–0.79)
History of FOG[c], $n = 137$	3.1 (1.48–6.49)**	0.64 (0.54–0.74)
Comfortable gait speed <1.1 m/s (10MWT), $n = 136$	4.13 (1.92–8.85)***	0.67 (0.57–0.77)
Retropulsion (NRT)[d]	5.40 (2.39–12.20)***	0.67 (0.57–0.77)
Retropulsion (UPDRS item 30)[e]	2.52 (1.21–5.24)*	0.61 (0.51–0.71)
Abnormal tandem gait (TG)[f]	4.07 (1.81–9.17)**	0.66 (0.56–0.75)

AUC, area under the curve; CI, confidence interval; FOG, freezing of Gait; FOGQsa, freezing of Gait Questionnaire, self-administered version; NRT, Nutt Retropulsion test; OR, odds ratio; TG, Tandem gait; 10MWT, 10-Meter Walk test; m/s, meter per second; UPDRS item 30, Item 30 of unified Parkinson's Disease Rating Scale

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

[a] Dichotomous question (Yes/No): *In the last 12 months, have you fallen in such a way that your body hit the ground?*

[b] Dichotomous question (Yes/No): *Are you ever close to falling, but you manage to grab on to something/someone at the last minute so that your body does not hit the ground?*

[c] Scores ≥1 on the FOGQsa, item 3 (*Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?*) were categorized as having FOG

[d] Scores ≥1 on the NRT (unexpected shoulder pull) were categorized as having retropulsion

[e] Scores ≥1 on the UPDRS, item 30 (expected shoulder pull) were categorized as having retropulsion

[f] Scores ≥1 on the TG were categorized as abnormal

Discussion

In this prospective study of individuals with relatively mild PD we externally validated the accuracy of a previously suggested 3-step model for prediction of falls [18, 19]. We found the discriminant ability of this model to be lower but acceptable and overlapping (given the 95 % CIs of AUCs) compared to previous studies [18, 19]. Importantly, discriminant abilities of each single predictor were lower and below acceptable values. This supports the value of the 3-step model over reliance on single predictors.

Different study samples have revealed some differences regarding the contribution of each predictor in the 3-step model. For example, in the development study [18], FOG was significant and associated with more than a two-fold increased odds of falling, while it was not significant in the subsequent [19] or in our study despite similar percentages of individuals reporting FOG (41–46 %) in all three samples. These discrepancies may be due to methodological aspects, as FOG was not assessed uniformly across the studies; Paul et al. [18] specified a retrospective time frame of 1 month, whereas both Duncan et al. [19] and we used a dichotomized version of item 3 of the FOGQ, which does not specify the recall period. Furthermore, information on history of FOG does not take FOG severity into account [38]. Similarly, differences in observed ORs for history of falls may relate to different modes of data collection. Specifically, whereas we and Paul et al. [18] inquired about

Table 5 Extended multiple regression analysis: prediction of future falls, $n = 135$

Predictors[a]	Wald	*P* value	OR (95 % CI)
History of near falls[b]	6.33	0.012	3.03 (1.28–7.17)
Retropulsion (NRT)[c]	7.43	0.006	3.53 (1.43–8.72)
Comfortable gait speed <1.1 m/s (10MWT)	4.64	0.031	2.55 (1.09–5.98)

Multiple logistic regression analysis backward method (Wald); Nagelkerke pseudo *R* square: 0.299; Hosmer and Lemeshow test: $P = 0.903$; tolerance: ≥0.85

Sensitivity/specificity, 0.58/0.87

CI, confidence interval; FOGQsa, Freezing of Gait Questionnaire, self-administered version; NRT, Nutt Retropulsion test; OR, odds ratio; 10MWT, 10-Meter Walk test; m/s, meter per second

[a] Independent variables in the analysis were: history of falls past 12 months, history of near falls, history of FOG (FOGQsa item 3), comfortable gait speed <1.1 m/s (10MWT), retropulsion (NRT), retropulsion (UPDRS item 30), abnormal tandem gait (TG)

[b] Dichotomous question (Yes/No): *Are you ever close to falling, but you manage to grab on to something/someone at the last minute so that your body does not hit the ground?*

[c] Scores ≥1 on the NRT (unexpected shoulder pull) were categorized as having retropulsion

the presence or absence of falls during the past year, Duncan et al. [19] combined data from two time points 6 months apart, where a question with five response categories was used.

Regardless of the cause(s) for the observed discrepancies in ORs of individual predictors, this has implications for the suggested scoring weights and risk categories of the 3-step model. That is, the weights (scores) suggested by Paul et al. [18] were based on the observed ORs in that study, which have not been replicated either here or by Duncan et al. [19]. It can be noted that the percentages of individuals who actually fell in our study was 13, 38 and 63 % in the low, moderate and high risk categories, respectively. Corresponding values in the study by Duncan et al. were 9, 28 and 66 % [19]. This is in contrast to the expected probabilities suggested by Paul et al. (17, 51 and 85 %, respectively) [18]. This calls for caution regarding the use of the suggested weighted total score. Further studies are needed to firmly establish a scoring system and risk categories.

The contribution of gait speed was relatively similar here as compared to the study by Paul et al. [18], despite differences in motor status according to the UPDRS part III (12 vs. about 24). Thus, comfortable gait speed <1.1 m/s is associated with approximately a two-fold increase in odds of falling regardless of whether a 4- [18] or 10-meter walking distance was used. This suggests the possibility to adjust the walking distance according to practical circumstances. However, the need to calculate the mean value for two trials should be evaluated in order to explore the possibility to simplify the test.

According to current recommendations regarding improvement of prediction models [17, 19] we explored the addition of history of near falls, retropulsion, and TG to the 3-step model. This generated a new model including history of near falls, retropulsion (NRT) and gait speed. The discriminate ability of this new model as well as its sensitivity of prediction was somewhat better compared to the proposed 3-step model but the AUC 95 % CIs overlapped. Similarly, using falls and/or near falls as the dependent variable generated a model including history of near falls, retropulsion (NRT) and TG. These observations have important clinical implications. Near falls are more frequent than falls in PD [39, 40] and may occur also among those who do not experience falls [39, 41]. We previously found, in the same project, that history of near falls but not falls was a risk factor for future falls [12]. This is further supported here and suggests that information about near falls may be a useful predictor of future falls. Furthermore, since near falls may be seen as an early precursor of increased fall risk [42, 43], it is argued that prediction of falls and/or near falls has greater clinical value than prediction of falls alone. This is also in line with previous studies highlighting the importance of fall risk identification before the first fall has occurred, in order to optimize planning of interventions [9, 16]. From this perspective, our new model (history of near falls, TG and retropulsion according to the NRT) may be considered a promising alternative to the suggested 3-step model, at least among people with milder PD. Indeed, the use of TG and NRT has been recommended in the prediction of falls before [23, 24, 44]. However, this suggested new model needs further confirmation in additional studies.

NRT, but not UPDRS item 30 was identified as a predictor in both new models. UPDRS item 30 involves prior instructions, which does not mimic daily life circumstances where perturbations per definition are unexpected [44]. Accordingly, the unexpected pull test according to the NRT has been considered more relevant in the context of fall prediction [24], which is supported by our findings.

Limitations

This study involves people with relatively mild PD, excluding those with MMSE scores <24 or >80 years old. This limits the generalizability of findings, particularly regarding predictors explored in addition to the suggested 3-step model. Further studies are therefore needed to explore the external validity of these models in broader ranges of PD severities. Particularly, larger longitudinal studies addressing near falls and TG are needed to better understand these variables in the context of falls prediction.

Furthermore, we acknowledge that there might be other questions, questionnaires and clinical assessments that also may be of relevance in relation to fall prediction [9, 16, 45]. Finally, we did not consider the influence of the suggested 3-step model or other identified models on decision making, patient outcomes, or costs [17]. This will need to be addressed in specifically designed studies.

Conclusions

This study confirms the value of the 3-step model as a clinical fall prediction tool and illustrates that it outperforms the use of single predictors. However, further studies are needed to firmly establish a scoring system and risk categories based on this model, and to better understand the influence of methodological aspects of data collection regarding gait speed and history of falls and FOG. A new model for prediction of falls and near falls, including history of near falls, TG and retropulsion according to the NRT is considered a promising alternative to the 3-step model in milder PD, but needs to be tested in additional samples. Taken together, our observations provide important additions to the evidence base for clinical fall prediction in PD.

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Compliance with ethical standards

Conflicts of interest The authors have declared that no competing interests exist.

Ethical standards The study was approved by the institutional review board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Kan fallrisken hos personer med Parkinsons sjukdom identifieras tidigare och förebyggas effektivare än hittills? Vad kan jag som sjukgymnast göra för att effektivare än hittills förbygga fallrisk? Dessa var några av de många frågor som väcktes under mitt kliniska arbete i Rörelseteamet inom Neurologiverksamheten vid Skånes universitetssjukhus och vilka var driftkraften bakom detta avhandlingsarbete.

Nära samarbete mellan Region Skåne, Lunds Universitet och Högskolan Kristianstad samt stöd från finansiärer skapade förutsättningar för denna avhandling med det övergripande syftet att öka kunskapen på området med utgångspunkt från personer med relativt mild Parkinsons sjukdom.

Resultat avseende bidragande faktorer till fallrädsla, fall och nära fall tyder på att vardagsnära gångträning kan bidra till att minska fallrädslan, vilken i sin tur är den starkast bidragande faktorn till framtida fall och nära fall. Komplexiteten i sambanden mellan fallrädsla, fall och nära fall och dess bidragande faktorer, tyder dock på att inte enbart gången bör tränas. Det multiprofessionella teamet bör kopplas in tidigt i sjukdomsförloppet för optimalt omhändertagande av personer med Parkinsons sjukdom.

Vidare lyfts vikten av s.k. nära fall för tidig identifiering av fallrisken fram. Med nära fall menas händelser, när man håller på att falla men lyckas ta emot sig i sista stund genom att ta tag i en annan person, i ett föremål eller liknande. Andra betydelsefulla och kliniskt användbara riskfaktorer är nedsatt förmåga att klara yttre ”knuff”, nedsatt förmåga att gå med minskad understödsyta, erfarenhet av gångstopp och nedsatt gånghastighet.

Åtgärder som syftar till att påverka dessa faktorer kan således bidra till minskad fallrisk. Vi visar även att klinisk testning av gånghastighet kan förenklas, vilket kan minska bördan för patienten och spara tid i sjukvården. Förhoppningen är att resultaten från denna avhandling kan få betydelse för hur sjukvården framöver identifierar och hanterar fallrisken vid Parkinsons sjukdom.

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